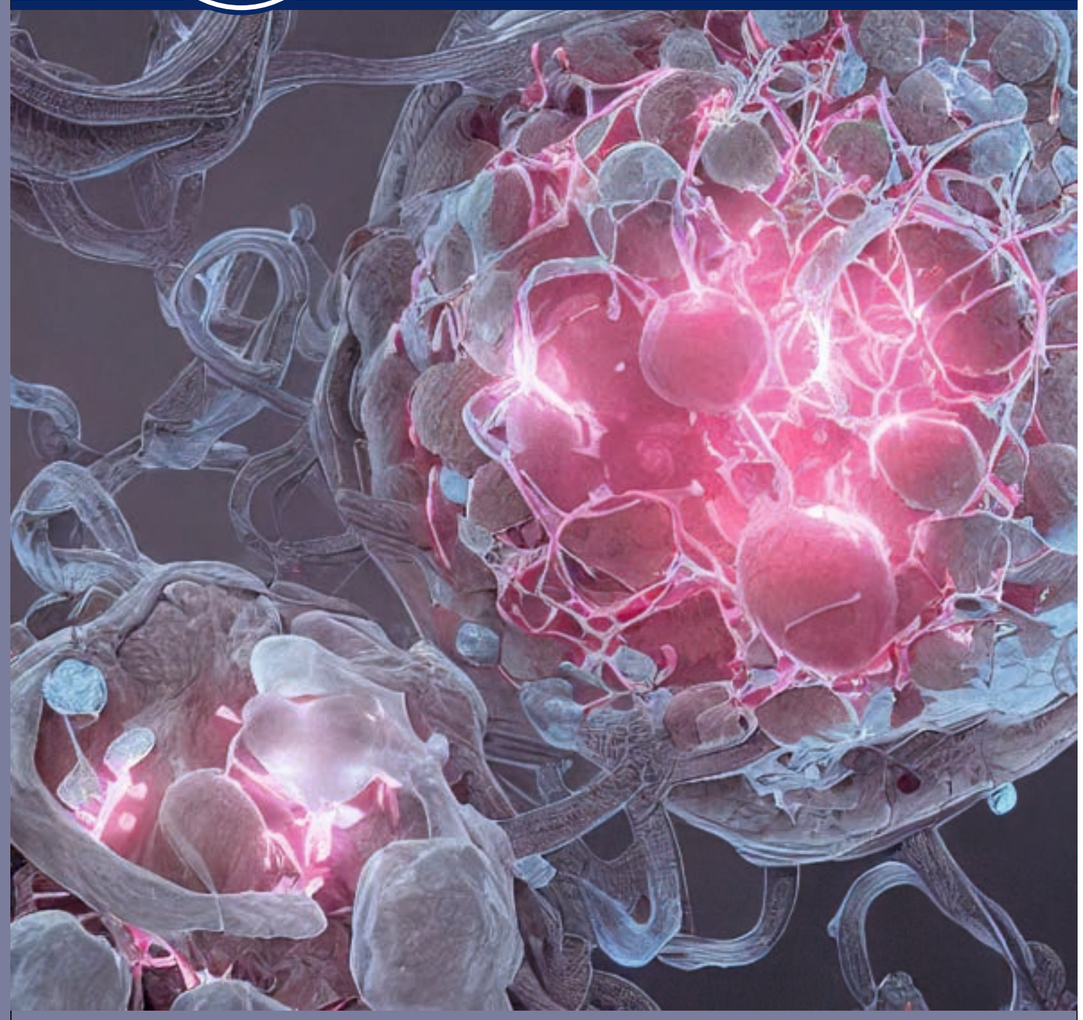
VOLUME 3 | APRIL 2024

THE WINGS

SCIENTIFIC NEWSLETTER



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MEDICAL DIRECTORS MESSAGE

Dear Colleagues,

Greetings from NCI !!

I would like to congratulate the editorial board of Wings 3 for bringing out this special issue covering research and publications done from our institute.

This contains case reports, reviews, abstracts, studies etc on variety of topics. There has been enthusiastic participation from different departments.

As all of you know that we would like define our institute as a Comprehensive Cancer Center and active research work is one essential component of this definition. I am pleased to see that we have taken significant steps in cancer research. This is just the beginning. Further research work should continue improve in quality and contribution in oncology. We had a successful brainstorming workshop on research with guidance from faculty from Rutgers Cancer Institute and Kearney recently. Our partnership with Rutgers will continue and evolve further.

The pace at which knowledge and discoveries are being made in oncology is tremendous and overwhelming. There is a huge opportunity here to do ground breaking research which will help us cure every and the last patient that comes to us for treatment.

Our chief patron Hon'ble Deputy CM *Mr Devendraji Fadnavis* wishes NCI to be the finest cancer research institute and has committed to unending support towards that cause. Additionally, the esteemed members of the Governing Board have assured full support to conduct research at NCI. With that I am sure all of you would be able to contribute to the cancer sciences. Let us make research as an activity of daily living. I would like to congratulate all the authors to take time out from day to day patient service and do original research.

I would like to appeal to rest of the faculty to join this research journey.

We all look forward to an annual research edition of the Wings from the editorial board in future.

Thank You!

Dr. Anand Pathak, MD

Medical Director

CONTENTS

National Cancer Institute
THE WINGS
VOLUME 3 | APRIL 2024

Dosimetric Evaluation Of FFF Photon Beam For Ca. Lung Stereotactic Body Radiotherapy (SBRT)

Mr. Mukesh Meshram, Dr. Manish Mathankar, Mr. Hemant Ghare, Doc. Prashantkumar Shinde, Mr. Parimal Patwe, Mr. Rameshwar Veer, Dr. Rahul Patil, Dr. Mahesh Upasani, Dr. Shruti Maheshwari, Dr. Alok Chand, Dr. Sameer Chandorkar.

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PURPOSE / OBJECTIVE

This study aims to analyse the dosimetric advantages of FFF beam of Varian linear accelerator for SBRT of Lung carcinoma patients over flattened beam.

MATERIALS / METHODS

Study group consisted of 9 patients with Lung Cancer who underwent SBRT treatment in Varian True beam linear accelerator. PTVs ranged between 13.5 to 100.6 cc. All the plans were generated using Eclipse Treatment planning system (v13.7). For each patient two different plans were optimized using 6MV and 6MV-FFF. All prescription doses, constraints parameter and beam setup were maintained same. The same normalization was used in both plans (80% isodose line covering 95% of the target volume). Both the optimized plan were evaluated and compared for the parameters as criteria defined by the RTOG 0915 protocol: We also analysed Plan total Mus and estimated Beam on time.

RESULTS

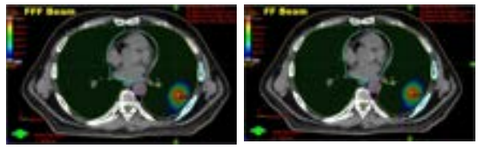
Dose heterogeneity index for the PTV between plans with flattened and unflattened beams were observed to be the same.

Similar comparable values were obtained for both conformity indices CI-100 (0.97-1.12 in FF vs 0.96-1.1 in FFF) and CI-50 (3.06-4.23 in FF vs 3.05-4.18 in FFF).

Avg.	FF Plan	FFF Plan
HI	1.054	1.059
CI 100	1.04	1.03
CI50	3.84	3.77
MUs	2293	2485
BOT	4.2min	2.0 min

FFF plans required on average 9.1% more MU than flattened plans but the average beam on time was reduced by 52.4% passing from about 4.2 min (with FF modality) to 2.0 min (with FFF modality).

The differences in the max dose in the PTV as well as the dose at 2cm from PTV were <1% between 6MV and 6MV-FFF plans. .



The volume of healthy lung receiving >20Gy was 5.6% for 6MVplans and 5.4% for 6MV-FFF plans.

OAR	FF Plan Avg. (Gy)	FFF Plan Avg. (Gy)
SC Dmax	10.3	10.2
SC (<0.35 cc)	8.8	8.7
SC (< 1.2 cc)	8.0	7.9
Brachial Plexus Dmax	0.4	0.4
Brachial Plexus (<3 cc)	0.2	0.2
Esophagus Dmax	17.3	17.3
Esophagus (< 5 cc)	8.6	8.4
Heart Dmax	15	15
Heart (<15 cc)	9.4	9.3
Great Vessels Dmax	18.5	18.4
Great Vessels (<10 cc)	10.6	10.3
Trachea Dmax	9.4	9.4
Trachea (< 4 cc)	6.2	6.1
Bronchus Dmax	13.7	13.5
Bronchus (<4cc)	8.4	8.2
Lung (1500 cc)	1.2	1.1
Lung (1000 cc)	3.0	2.7

In general 6MV-FFF plan didn't show any significant differences over standard 6MV plan in terms of dosimetric parameter with comparable PTV coverage and small differences in doses to organ at risk.

CONCLUSION

FFF modality yields dose distribution comparable to the standard flat beam in lung SBRT with very small absolute and clinically insignificant differences in OAR doses. Furthermore FFF requires significantly less beam on time which is associated with excellent patient comfort and reduces the risk of intra-fraction motion. It also increases the feasibility of breath hold and gating techniques in lung SBRT.

Thyroid Metastasis of Squamous Cell Carcinoma in an Unsuspected Patient

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ABSTRACT

Malignancies metastasizing to thyroid are a very rare phenomenon. Out of them all, diagnosis of metastatic squamous cell carcinoma in thyroid can be difficult to establish as in thyroid there can also be a primary thyroid squamous cell carcinoma SCC.

We herein report a rare case of a 28-year old man with metastasis of oral SCC the thyroid gland. He was operated six months back, took incomplete cycles of adjuvant chemo-radiotherapy. On FDG-PET CT was found to have metabolically active lesions in right lobe of thyroid along with right paratracheal and bilateral cervical nodes.

Fine needle aspiration cytology (FNAC) smears from thyroid showed malignant squamous cells. Considering various factors like previous history, histopathology, present FDG-PET scan findings and present cytology diagnosis was concluded to be metastatic over primary thyroid SCC.

It is necessary to differentiate between primary or metastatic SCC in thyroid as they are different in clinical and prognostic behaviour. Primary squamous cell carcinoma is very aggressive with a poor prognosis.

KEYWORDS: Thyroid; Squamous cell carcinoma; Immunohistochemistry;PAX8; FDG-PET CT scan

INTRODUCTION

Tumoral metastasis to the thyroid is a rare entity with only a few cases reported in literature till date [1-5]. Metastasis to thyroid is mostly discovered on autopsy with an incidence of 0.5-24% and most of these cases have widespread tumoral metastasis at the time of presentation. Of all these cases of thyroid metastasis, patients presenting with a palpable thyroid mass or deranged thyroid function tests are less than a quarter. Tumors causing thyroid metastasis are mostly from lungs followed by bones, liver, kidney, breast, pancreas, colon, ovary, bladder and malignant melanoma.

Out of all malignancies metastasizing to thyroid, squamous cell carcinoma has an incidence of 0.2-1.1%. A squamous cell carcinoma metastasizing to thyroid commonly originates from lung, esophagus, head and neck region and cervix whereas primary thyroid SCC is extremely rare [6]. Hence presence of malignant squamous cells in thyroid FNAC should prompt a first suspicion of metastasis from an occult primary over primary thyroid. We have reported a case of SCC tongue giving metastasis to thyroid which was picked up on FDG-PET CT scan and followed on by FNAC.

CASE REPORT

A 26-year-old male presented with. Pain and ulceration at right border of tongue. He was operated outside for right hemiglossectomy with modified neck dissection for carcinoma tongue, 6 months. Patient took incomplete adjuvant treatment, 4 cycles of chemotherapy and 17 cycles of radiotherapy, against 6 cycles of chemo and 30 cycles of radiotherapy as advised. He had left the treatment on his own.

Histopathology of previous hemiglossectomy was: Moderately differentiated squamous cell carcinoma with

focal sarcomatoid change. Tumor involving underlying muscle with perineural invasion and no lymphovascular emboli and a positive cervical node (1/29). Pathological stage was pT2pN1.

FDG-PET CT scan ordered for restaging, showed metabolically active lesions over right tongue border, bilateral cervical lymph nodes, one sub centimetric right paratracheal lymph node. Few hypodense nodules, largest measuring 1 X 1 cm in the enlarged right lobe of thyroid were seen with abnormal FDG uptake, (SUV max 14.32) as shown in Figure 1a-1d. Extrathyroidal extension was not seen. No other abnormal FDG uptake was seen elsewhere in the body.

USG guided FNAC was performed from thyroid and right paratracheal node.

Smears were stained using May - Grónwald Giemsa staining for air dried smears and Hematoxylin and eosin and Papanicolaou staining for smears wet fixed in 95% alcohol.

The smears showed many benign thyroid follicular cells, macrophages, and colloid along with atypical cells in clusters and occasional scattered cells as shown in Figure 2a. Cells are polygonal with dense, orangeophilic cytoplasm, few with cytoplasmic tails. Nuclei are hyperchromatic, pleomorphic. No atypical mitosis, necrosis, giant cells or papillary or follicular pattern are seen in Figure 2b and 2c. Few cells were elongated, having cytoplasmic tails and with spindly nuclei as shown in Figure 2d.

Similar tumor cells were also seen in smears from right paratracheal node. Considering previous history, histopathology, present FDG-PET scan findings and present cytology, a diagnosis of Metastatic squamous cell carcinoma-Bethesda VI was given.

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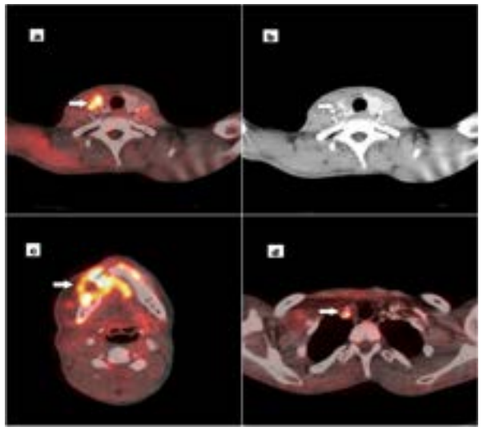

Figure 1: (a and b) FDG- PET CT scan showing metabolically active lesions in (a) right lobe of thyroid (arrow), (c) right border tongue(arrow) - previous wide

excision site, (d) right paratracheal node (arrow).

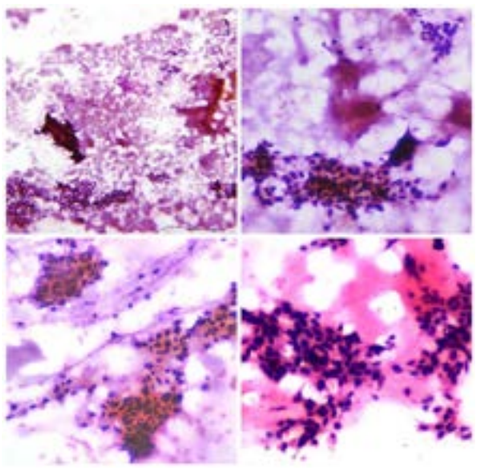

Figure 2: (a and b) Benign thyroid follicular cells, colloid and tumor cells in clusters (PAP, 40×), c) orangeophilic tumor cells (PAP,40×), (d) tumor cell with cytoplasmic tails (arrow) (PAP,40×).

Unfortunately, the patient was lost to follow up and could not be traced further.

DISCUSSION

Presence of squamous cells in thyroid is a very rare phenomenon. Incidence of Thyroid metastasis is more of an autopsy finding. Routes of thyroid involvement in head and neck SCC are lymphatic, hematogenous or local infiltration. Abundant, fast blood flow through the gland, high iodine content and hyperoxic environment, which prevent attachment and growth of tumor cell, are postulated to be the probable factors which inhibit the development of metastatic tumor cells in thyroid.

Clinically thyroid SCC - primary, metastatic or local infiltration, may present as a nodule, diffuse swelling, signs due to local infiltration like dysphonia, dyspnoea, dysphagia or cough, it could be silent without any significant change or just an incidental finding on work up (as in the present case).

Main differential diagnosis on cytology are squamous metaplasia of thyroid follicular epithelial cells, papillary thyroid carcinoma(PTC), follicular thyroid carcinoma(FTC) or anaplastic thyroid carcinoma(ATC) with squamous differentiation or primary SCC thyroid.

Presence of admixed normal thyroid follicular cells with tumor cells and absent papillary and follicular patterns favour metastasis on cytology.

However histopathology, along with immunohisto-chemistry is the best to form a definitive diagnosis. Immunohistochemical (IHC) analysis on FNAC material can be performed to give a diagnosis.

In identifying metastatic versus primary thyroid SCC, IHC plays a crucial and markers can be selected based on suspected origin of tumor.

Thyroid marker, TTF1, is positive in majority of differentiated thyroid malignancies like PTC/FTC and usually negative in ATC and primary thyroid SCC. Whereas PAX-8, another nuclear marker is found to be consistently positive in all thyroid malignancies including PTC, FTC, ATC or primary thyroid SCC as well as in squamous metaplasia of thyroid follicular cells. The reason for presence of PAX 8 in all differentiated and poorly differentiated thyroid malignancies is cited as being primitive in chronological emergence when compared to TTF-1 [7,8].

On other hand, SCC of lungs, larynx, thymus, and skin will be positive for p 63 and HMW-CK whereas they barely express PAX 8.

Some common SCCs metastasizing to thyroid, eg. SCC from lung might occasionally show TTF1 positivity, there will definitely be absence of PAX -8 whereas HPV related SCCs originating from cervix or head neck region will show p16 positivity and PAX8 negativity [7-9].

PAX8 is therefore useful in distinguishing primary thyroid SCC from extrathyroidal SCC.

In cases with malignant squamous cells, distinction between primary thyroid SCC or metastatic SCC is necessary as it has both prognostic and therapeutic significance.

Primary thyroid SCC mostly occurs in 5th or 6th decade with a rapidly growing anterior neck mass and/or dysphagia / dyspnoea. Also primary SCC thyroid is associated with rapid progression, poor response to radiotherapy, even radio-resistant in some cases and poor prognosis. Several theories have been postulated regarding its etiology:

• The embryonic nest theory suggests that the squamous cells are derived from the remnants of thyroglossal duct or the epithelium of the thymus.

• The metaplasia theory suggests that these cells present as a result of environmental stimuli (inflammation and Hashimoto's thyroiditis).

Also the de-differentiation theory suggests that existing papillary, follicular, medullary and anaplastic thyroid carcinoma de-differentiate into SCC.

Radioisotope scan [FDG-PET] makes a huge difference in cases of such hidden metastases. A focal thyroid lesion with significant uptake is more malignant as opposed diffuse uptake in other benign disorders like Graves disease, chronic thyroiditis, diffuse or multinodular goitre. Cytology is an easily available and accessible, non-invasive technique with a rapid turnaround time [10].

CONCLUSION

Incidence of metastatic SCC to thyroid is much more than primary thyroid SCC. So, history of any primary tumor elsewhere, clinical presentation, radiology findings and cyto / histomorphology along with ancillary techniques (wherever possible) is necessary before finalizing any diagnosis.

Hence, in presence of malignant squamous cells in thyroid, it is known that cases of metastasis or direct invasion of SCC into the thyroid gland are more common than primary thyroid SCC.

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Comparison of Continuous Epidural Analgesia and Intravenous Patient - Controlled Analgesia with Opioids in Terms of Postoperative Pain and Their Complications in Mega - Prosthesis Total Knee Arthroplasty for Bone Cancers

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Bhushan Katwale
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Aparna Chatterjee
Raghuveersingh P. Gehdoo (Nurse Educator, National Cancer Institute, Jamtha, Nagpur)

ABSTRACT

Total knee arthroplasty with mega-prosthesis in oncologic patients is a painful surgery and may be associated with nerve injury. Epidural analgesia (EA) with local anaesthetics (LA) is routinely used for pain relief in these patients. At our institute, we came across a high incidence of motor weakness in these patients compelling to shift to patient-controlled analgesia (PCA) with intravenous opioids. We retrospectively analysed our data to find the incidence and reasons for motor weakness and also to compare the efficacy of EA and PCA as analgesics. Over a period of 15 months, 68 patients were operated; out of these, 41 were in EA and 27 in PCA. Demographic details, level of epidural placement, drug used, pain scores, degree of motor weakness, measures taken to relieve the motor weakness and the improvement in symptoms after treatment were recorded. In the IV PCA group, details of drug used, dose of bolus, pain and sedation scores were analysed. Groups were comparable demographically. Motor weaknesses were present in 9 (22%) and 0 patients in EA and IV PCA groups respectively (p = 0.009). Average and maximum pain scores were significantly higher on day 1 in the IV PCA group (p of 0.00 and 0.001 respectively). Maximum pain scores were also significantly higher in the IV PCA group on day 2 (p = 0.010). Two patients out of 27 in IV PCA were found drowsy. Motor weakness is known with EA but can be managed effectively using a lower concentration of LA or by stopping the infusion of LA.

KEYWORDS

Analgesia . Arthroplasty . Epidural . Local . Patient-controlled

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INTRODUCTION

Patients undergoing bone cancer surgeries comprise special population. They suffer from pain extending from preoperative period and this sometimes becomes worst after surgery. Also, surgeries involving major bones are destructive so are very painful [1, 2]. These surgeries are sometimes associated with damage to nerves which also causes motor weakness which might lead to permanent damage. The most common major nerve complication associated with total knee arthroplasty (TKA) is peroneal nerve palsy which results in weakness of foot extensors and eventers causing a foot drop, sensory impairment of the anterolateral leg and dorsum of the foot. In our institute, the acute pain team found a high incidence of motor weakness in patients with EA. For this reason, we shifted to intravenous patient-controlled analgesia (IV PCA) with opioids as a modality for analgesia. We retrospectively analysed the data to statistically evaluate the incidence, causes of motor weakness and the role of EA with local anaesthesia (LA) and IV PCA with opioids for postoperative pain relief and associated complications in megaprosthesis TKA.

METHODS

This retrospective analysis of prospectively collected data was approved by Institutional Ethics Committee. We included data collected from electronic medical records of acute pain ser- vices of institute over the period of 15 months.

All patients above 18 years of age who had undergone TKA in our institute with either EA or IV PCA for pain relief postoperatively were included in this study. Patients who underwent bilateral TKA, required re-exploration or underwent a revision surgery, with preoperative motor weakness or the patients whose data was missing were excluded from the study.

Patients were divided into two categories, EA and IV PCA groups. All data pertaining to the patient in the form of demographic details, associated comorbidities, ASA physical status, level of epidural placement, drug solution used, pain scores, degree of motor weakness if present, measures taken to relieve the motor weakness and the improvement in symptoms after treatment were recorded. A modified Bromage score of 0–3 was used to assess motor weakness [3] and modified Bromage score > 1 was considered as motor weakness. Patients also received paraceta- mol, diclofenac and tramadol as per requirement, and total dose needed was also noted. Maximum pain score and average pain score on days 1, 2 and 3 of surgery were compared. For assessment purpose, pain score was labelled as mild (score 1–3), moderate (score 4–6) and severe (score 7–10). The drug used in PCA along with the dose of bolus set was recorded. Sedation score was measured on Pasero opioid-induced sedation scale (POSS) from 0 to 3 [4]. Primary outcome measure was motor weakness and secondary outcomes were pain scores and sedation score.

During the 15-month period, data of sixty-eight patients were collected and analysed. All the data was entered and analysed using SPSS software (version 20.0). The values were expressed as mean with standard deviations for numerical data and percentages for categorical data. Comparison of data between the groups was done using ANOVA with repeated measures, the frequency was compared by chi-square test and pain sores were compared by Mann-Whitney tests.

RESULTS

Out of 68 patients enrolled, 41patients were in EA and 27 patients in IV PCA group. Anaesthesia techniques were general anaesthesia with epidural analgesia in EA group and general anaesthesia only in IV PCA group. No patient was having any motor weakness in preoperative period. Groups were comparable pertaining to demographic data, ASA grading, side and approach of surgery with p values in correspondence to motor weakness. The most common site of epidural catheter insertion was L2–L3 interspace (22 patients, 53.7%) followed by L3–L4 (13, 31.7%) and L1–L2 (6, 14.6%). The 16 G Tuohy's needle was used in 28 patients whereas the 18 G was used in 13 patients. All the patients in both the groups were given round the clock non-opioid co-analgesics (nonsteroidal anti-inflammatory drugs and paracetamol), intravenously on postoperative day (POD) 1 and per-orally on POD 2 and 3.

In EA group, 9 (21.9%) out of 41 patients had neurological deficit; six amongst them had tingling and numbness. Three out of 9 patients with neurological deficit had bilateral motor weak- ness. None of the patients from the IV PCA group had motor weakness (Table 1). Out of 41 patients with epidural, 37 patients received bupivacaine infusion intraoperatively; the remaining 4 did not. None of the patients who developed motor weakness were applied a tourniquet. Twenty-one patients received 0.1% epidural bupivacaine, 10 received 0.0625% and 6 received 0.125% bupivacaine intraoperatively. As the concentration of local anaesthetic (bupivacaine) increased from 0.0625 to 0.125%, the number of patients having motor weakness also increased from 20 to 33% but this difference was not statistically significant (p = 0.70). All 41 patients were attached with a Fornia elastomeric pump (Royal Fornia Medical, China) for continuous infusion; out of these, 29 patients received 0.0625% and 12 patients received 0.05% bupivacaine infusion postoperatively and motor weakness was 24% and 16%, respectively, but this difference was not statistically significant. Eight out of 9 patients with motor blockade recovered with stopping of infusion, but one patient had prolonged block.

Twenty-seven patients received IV PCA (CADD-Legacy® PCA Pump from Smiths Medical, USA) in the postoperative period; out of these, 21 patients received fentanyl PCA with a demand dose of 15 or 20 mg and 6 patients received morphine with a demand dose of 1 or 2 mg.

Maximum and average pain scores (mean ± SD) are described in Table 2. Two (7.4%) patients out of 27 were found

TABLE 1

Groups	N	Motor weakness		p value
		Yes	No	
EA	41	9 (22%)	32 (78%)	0.009*
IV PCA	27	0	27 (100%)	

EA, epidural analgesia; IV PCA, intravenous patient-controlled analgesia

*Statistically significant

Table 2 Maximum and average pain scores (mean ± SD) in EA and IV PCA groups on days 1, 2, and 3 with p values of comparison for motor weakness

SD, standard deviation; EA, epidural analgesia; IV PCA, intravenous patient-controlled analgesia

*Statistically significant (Mann-Whitney test)

to be occasionally drowsy with a sedation score of 1; one was on fentany1 PCA and the other was on morphine. Sedation scores were comparable between fentany1 and morphine users. No other complication was noted in IV PCA group.

DISCUSSION

TKA for malignancy being a major and destructive surgery is associated with nerve injury. The problems with postoperative neurological deficit include the following: the surgeon may find it difficult to assess the results of surgery, sensory blockade may delay the identification of compartment syndrome, delayed mobilization and physiotherapy resulting in increased risk of pulmonary complications, venous thrombosis, patient discomfort, medico-legal problems leading to anxiety for the anaesthetist, need for additional imaging such as MRI of the spine with its resulting costs, radiation exposure and patient distress [5].

Although the patients who received a higher concentration of bupivacaine proportionately had higher motor block but this was not statistically significant. Time of mobilization was comparable in both groups receiving

Pain scores/days	Modality	Day 1	Day 2	Day 3
Average pain	EA	1.80 ± 0.67	1.46 ± 0.596	1.41 ± 0.74
score	IV PCA	2.74 ± 1.19	1.85 ± 0.94	1.48 ± 0.69
(mean ± SD)	p value	*0.00	0.105	0.628
Maximum pain	EA	3.46 ± 1.14	2.90 ± 0.94	2.95 ± 1.20
score	IV PCA	4.48 ± 1.39	3.74 ± 1.48	2.93 ± 0.99
(mean ± SD)	p value	*0.001	*0.010	0.764

epidural and IV PCA. No correlation was found between the level of insertion, attempts of insertion and neurological deficit. Although, Ahmed et al. state that the incidence of lower limb weaknesses was more in patients when the level of insertion was L2–L3

[6]. This may be because their comparison was between lumbar and thoracic epidurals whereas, in our study, only lumbar epidurals were inserted.

The limitation of our study is that patients in groups were unequal in number and there is also a small sample size of 68 patients.

CONCLUSION

In conclusion, neurological complications like motor weakness with EA are known and can impair motor assessment after surgery but this can be managed effectively by the vigilant acute pain service team and using a lower concentration of LA.

Compliance with Ethical Standards This retrospective analysis of prospectively collected data was approved by Institutional Ethics Committee.

Conflict of Interest The authors declare that they have no conflict of interest.

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Study of intranasal midazolam versus intranasal ketamine as a premedication in children undergoing surgical procedures

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ABSTRACT

Background: Usage of premedication in children undergoing surgery is almost imperative and various medications have been used with varying success. The present study was aimed at comparison of intranasal midazolam and intranasal ketamine as a premedication in children by assessing acceptability of the drug by patients, ease at parent separation, level of sedation at the time of induction and facilitation of intravenous cannulation.

Methods: In this comparative observational study, 60 eligible participants were randomly divided into two groups of 30 each on the basis of pre anaesthetic medication received: those intranasal midazolam group and intranasal ketamine group. At 30 minutes after intranasal dose, sedation, separation from parents and intravenous cannula acceptance was evaluated on four point score scale. Children were constantly observed for occurrence of possible adverse effects and the same were duly noted.

Results: The two groups were similar with respect to age, gender and body weight distribution. Twenty four patients (80%) in both ketamine and midazolam groups were observed to become drowsy, while 6 patients (20%) in ketamine group were asleep, compared to 0 patients in midazolam group (p=0.024). Thirteen (43.3%) patients from midazolam group had poor parenteral separation, as compared to 0 patients from ketamine group. And Comparison of intravenous cannula acceptance revealed the acceptance to be good in 26 (86.7%) patients in ketamine group as compared to 10 (33.3%) patients in midazolam group (p<0.001).

Conclusions: Ketamine when given in a dose of 5 mg/kg via intranasal route is better than midazolam given in a dose of 0.2mg/kg intranasally, as a premedication in children.

KEYWORDS:

Children, Intranasal ketamine, Intranasal midazolam, Pre-medication, Sedation, Induction

INTRODUCTION

The preoperative period is a stressful occurrence for most people undergoing surgery. Children in particular are more susceptible for obvious reasons, with fear and anxiety having been observed in nearly half of the children.[1] Symptoms like nightmares, enuresis and post operative behavioural regression along with physical signs like significant fluctuations in heart rate and blood pressure have all been reported. 2,3 To respond effectively to the scenario is imperative on the part of anesthesiologist.

The major objectives of pre-anaesthetic medication are to decrease the stress response with preservation of haemodynamic parameters, facilitate anaesthesia induction and produce amnesia. Adult patients can mostly be reasonably managed by psychological preparation. But a medicinal adjunct is advisable in children, considering immature age. Various medications like promethazine, ketamine, morphine, midazolam etc. have been used with varying success and they all come with their individual advantages/disadvantages.[4-6] The ideal pre-medicant in children should be readily acceptable and have a rapid and reliable onset of action along with sedative and anxiolytic effect with minimal side effects. Going by these criteria, ketamine and midazolam seem to be two agents fitting the bill.[7,8] Plus, both the drugs can be used intranasally as drugs for pre-medication, a route which is preferred in case of children.

Aim of the present study was to compare between intranasal midazolam and intranasal ketamine as a pre-medication in children by assessing acceptability of the drug by patients, ease at parent separation, level of sedation at the time of induction and facilitation of intravenous cannulation.

METHODS

This was a comparative observational study to determine the better drug between midazolam and ketamine, when given intranasally as premedication in children. The study was carried out at a tertiary care center in south India over the period of two years (August 2009 to July 2011).

After obtaining approval from Institutional Ethics Committee and written, informed consent from patient's parents, 60 patients fulfilling the selection criteria mentioned below were enrolled into the study.

Inclusion criteria

• American society of anesthesiologists (ASA) Grade I or II[9]

• Age of 1-6 years.

Exclusion criteria

• Emergency surgery cases

• Neurosurgery

• Nasal atresia

• History of recent nasal bleeding or discharge •

Refusal to consent.

The participants were randomly divided into two groups of 30 each on the basis of preanaesthetic medication they received:

• Group 1- Patients received intranasal midazolam (IM) (0.2mg/kg) (prepared from parenteral formulation of midazolam (1mg/ml) vial).

• Group 2- Patients received intranasal ketamine (IK) (5mg/kg) (prepared from parenteral formulation of ketamine (50mg/ml) vial).

All the participants were assessed thoroughly before surgery. Demographic data including age, gender, and weight were recorded. Children were allowed to have milk up to 4 hours prior to surgery, if breastfed. Otherwise, only plain water was allowed up to 2 hours prior to surgery. No pre-medication was given in the wards. Children were kept in holding area in comforting presence of their parents. A baseline heart rate and oxygen saturation were measured before pre-medication. Readings were taken at 5 minutes interval until 30 minutes, when child was separated from parents. Intranasal dose of the drug was given in presence of parents using a sterile dropper. Children were constantly observed for the possible side effects like nausea, vomiting and increased salivation. At 30 minutes after intranasal dose, sedation, ease of separation from parents and intravenous cannula acceptance was evaluated on a four point score scale as follows;[8]

Sedation score scale

1. Agitated

2. Awake

3. Drowsy

4. Asleep

Separation score

1. Poor (crying, clinging)

2. Fair (crying but not clinging)

3. Good (whimpers, easily reassured)

4. Excellent (easy separation).

Scores of 1 or 2 were considered as unsatisfactory sedation or separation while scores of 3 or 4 were considered as satisfactory sedation or separation from parents. In operation theatre, intravenous cannulation was done before induction of anaesthesia. A four point evaluation system was used to evaluate acceptance of intravenous cannula.

Intravenous cannula acceptance scale

1. Poor (terrified, crying)

2. Fair (fear of needle, not reassured)

3. Good (slight fear of needle, easily reassured) 4.

Excellent (unafraid, accepts intravenous cannula readily).

Scores of 1 or 2 were taken as unsatisfactory acceptance while scores of 3 or 4 were considered as satisfactory acceptance.

The statistical analysis was performed using SPSS (version 17) and Chi-square/ Fisher Exact test was used to find the significance of study parameters on categorical scale between the groups.

RESULTS

A total of 60 participants, divided in two groups formed on the basis of premedication received [intranasal midazolam (IM) and intranasal ketamine (IK), 30 participants each] were considered for final analysis. The two groups were similar with respect to age and gender. Majority of the children (56.7% in ketamine group and 60% children in midazolam group) were between 1 to 2 years old with 73.3% children in ketamine group being females as compared to 66.7% children in midazolam group. There was no difference with respect to weight of the children between the two groups, with 46.7% children in ketamine group having their weight between 7 and 10 kg as compared to 43.4% children in midazolam group (Table 1).

Table 1: Demographic details of the participants.

Demographic variable (n=30) Group IM (n=30) Group IK		
Age	**No. %**	**No. %**
1-2 years	18 60.0	17 56.7
3-4 years	930.0	826.7
5-6 years	310.0	516.7
Gender		
Male	1033.3	826.7
Female	2066.7	2273.3
Body weight		
5-6 kg	1136.7	826.7
7-10 kg	1343.3	1446.7
11-13 kg	620.0	826.7

A total of 53.3% children in ketamine group were in ASA grade I as compared to 56.7% children in midazolam group, and 46.7% children in ketamine group were in ASA grade II as compared to 43.3% children in midazolam group; the difference being statistically insignificant (p=0.795). As for the major indications for surgery, 53.3% children in midazolam group got operated for Patent Ductus Arteriosus (PDA) as compared to same number of children in ketamine group. Tetralogy of Fallot (TOF) (16.7% in midazolam group, 23.3% in ketamine group) and Ventral Septal Defect (VSD) (20% in midazolam group, 23.3% children in ketamine group) were the other common indications. One case each of total anomalous pulmonary venous connection (TAPVC), VSD+PDA and aorto-pulmonary window (AP window) were operated in the ketamine group during the study. There was no significant statistical difference (p=0.891) between the groups for the indications of surgery. Similarly, insignificant difference (p=0.862) was observed in the surgical procedures performed in the study, with ligation (53.3% in each group) and closure (23.3% in each group) being the commonest procedures performed in both the groups (Table 2). Twenty four patients (80%) in both ketamine and midazolam groups were observed to become drowsy, while 6 patients (20%) in ketamine group were asleep, compared to 0 patients in midazolam group who all remained awake. This difference was statistically significant (p=0.024), indicating relatively better sedation in ketamine group. Significant difference (p<0.001) was observed in parenteral separation assessment, with 13 (43.3%) patients from midazolam group having poor separation, as compared to 0 patients from ketamine group.

Table 2: Comparison of indications for surgery and procedures performed.

Group IM (N=30) Group IK (N=30)		
Surgery details	**No. %**	**No. %**
Indication for surgery		
PDA	16 53.3	16 53.3
TOF	7 23.3	5 16.6
VSD	7 23.3	6 20.0
TAPVC	0 0.0	1 3.3
VSD+PDA	0 0.0	1 3.3
AP window	0 0.0	1 3.3
Procedures performed		
Ligation	16 53.3	16 53.3
Closure	7 23.3	7 23.3
Left modified blalock taussig (LMBT) shunt	2 6.7	2 6.7
Intra-cardiac repair (ICR)		
for TOF	3 10.0	2 6.7
Repair	0 0.0	2 6.7
Right modified blalock taussig (RMBT) shunt	2 6.7	1 3.3

And Comparison of intravenous cannula acceptance revealed the acceptance to be good in 26 (86.7%) patients in ketamine group as compared to 10 (33.3%) patients in midazolam group, indicating significantly better acceptance in in ketamine group (p<0.001) (Table 3).

Table 3: sedation, parental separation and intravenous cannula acceptance scores (30 minutes after pre-medication).

Score Group IM (n=30) Group IK (n=30)		
Sedation score	**No. %**	**No. %**
Agitated	0 -	0 -
Awake	6 20.0	0 -
Drowsy	24 80.0	24 80.0
Asleep	0 -	6 20.0
Parenteral separation score		
Poor	13 43.3	0 -
Fair	14 46.7	16 53.3
Good	3 10.0	14 46.7
Excellent	0 -	0 -
Intravenous cannula acceptance scores		
Poor	6 20.0	0 -
Fair	14 46.7	2 6.7
Good	10 33.3	26 86.6
Excellent	0 -	2 6.7

Tachycardia and salivation were seen after ketamine while respiratory depression was seen after giving midazolam, with 6 (20%) patients having nystagmus and 10 (33.3%) patients having tachycardia, as compared to 0 and 1 patients from midazolam group respectively, while 3 patients developed respiratory depression following midazolam administration (Table 4).

Table 4: Adverse effect following pre-medication.

Adverse Group IM Group IK		
effect	(n=30)	(n=30) p value
Vomiting	2 (6.7%)	1 (3.3%) 1.000
Nystagmus	0 6 (20.0%)	0.024
Salivation	2 (6.7%)	3 (10.0%) 1.000
Tachycardia	1 (3.3%)	10 (33.3%) 0.006
Bradycardia	2 (6.7%)0	0.492
Respiratory depression	3 (10.0%)0	0.237

DISCUSSION

The purpose of using pre-anesthetic medication in paediatric patients, is the control of pain, fear and anxiety, thereby creating behaviour that will facilitate the provision of quality medical care. The search for a rapidly acting sedative tranquillizer, free of adverse effects and with short duration of action, however, is still on. Many drugs or combinations of drugs via various routes of administration have been studied by numerous researchers over years. Intranasal administration of sedatives/analgesics is lately being explored as a possible alternative route of promise.

With the present study, a comparative evaluation between intranasal midazolam and intranasal ketamine, using relevant parameters detailed above, was undertaken to determine which of the two drugs is better as a pre-medication in children. Sixty children were enrolled and distributed randomly between the two groups in equal numbers (30 each). Emergency cases were excluded; as in emergency cases, intranasal administration of the drugs in the stipulated time interval may not have been possible and emergency cases would have presented with full

stomach and thus could have resulted in increased incidences of peri-operative vomiting. Intranasal route was used for administration of pre-anesthetic drugs, similar to Henderson et al, and Wilton et al, believed to be the initial proponents of the method, who had studied the efficacy and safety of the route for pre-medication and found it to be effective and safe.[10] The intranasal route would not have been suitable in cases of neurosurgery or in patients with nasal atresia, history of recent nasal bleeding or discharge, and hence such cases were duly excluded.

Demographics of the participants were well matched between groups, strengthening validity of the observations. The preschool age group studied is common with previous similar studies.[8,10,11] There was no significant statistical difference between the two groups for the indications of surgery or the procedures performed as well.

The level of sedation, ease at parental separation and intravenous cannula acceptance were the parameters assessed in the present study. All the three studied parameters were in favour of the ketamine group and the differences were significant. Diaz et al, had compared the outcome of intranasal ketamine pre-medication with a placebo in paediatric outpatients and observed ketamine to help pleasant and rapid separation of children from their parents, acceptance of monitoring and mask inhalation induction, along with no delay in post operative recovery and discharge to home.[12] Gharde et al, in their strikingly similar study of efficacy of intranasal midazolam, ketamine and their mixture as premedication in children undergoing TOF repair, also reported ketamine to fair better, either alone or in mixture. Infact, the parameters used were also similar to the ones employed in the present study, adding further validity to the comparisons.8 Weksler et al, had also reported similar observations.[13]

There has been some conundrum over the dose of intranasal ketamine as premedication. In the present study, ketamine was used in a dose of 5 mg/kg body weight and the dose was observed to be adequate for required level of sedation. Weber et al, studied plasma concentration of ketamine after intranasal administration at a dose of 2 mg/kg and observed that rapid and high level drug absorption after nasal drug administration at that dose is possible without fluctuations in hemodynamic parameters. But the level of sedation was not monitored. 14 Weksler et al, (1993) studied intranasal ketamine in paediatric patients at a dose of 6 mg/kg and had found excellent sedation in significant number of patients. [13]

Tachycardia, nystagmus and salivation was seen more with ketamine while respiratory depression was seen after giving midazolam, findings corroborative of the observations of previous researchers.[5-7,10,12]

In conclusion, it can be said that ketamine when given in a dose of 5 mg/kg via intranasal route is better than midazolam given in a dose of 0.2mg/kg intranasally, as a premedication in children.

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Ethical approval: The study was approved by the

Institutional Ethics Committee

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Early metabolic changes in PET metrics over initial 8 weeks of treatment in patients with advanced head neck squamous cell carcinomas treated with chemotherapy

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BACKGROUND

Head and neck cancer is the most common cancer in India and the 6th most common malignant tumour worldwide. Around 60% of patients are diagnosed in advanced stage. No bio marker is available to assess the chemotherapy response.

How early to assess it is not established. So, it is of paramount to integrate molecular imaging into precision oncology care, exploring the potential of imaging as a biomarker.

METHODS

We conducted a prospective observational study at NCI, Nagpur, India; during 2019.The 102 advanced cases of SCC Head neck region were enrolled in study after ISC approval and informed consent. All patient's history, addictions, clinical examination were noted. Chemotherapy: Docetaxel-Cisplatin-5FU or Paclitaxel-Carboplatin.Imaging: Baseline PET-CT scans were done followed by response evaluation scan at 2 weeks interval. The pattern of PET metrics Tumour-SUVmax and Nodal-SUVmax analysed using PERCIST criteria. P<0.05 was considered statistically significant.

RESULTS

The mean age of study population was 48.96 yrs with male preponderance 70 (89.74%) males. The most common site involved were Buccal mucosa in 31 (39.74%) followed by tongue 20(25.64%). The 64 (82.05%) were tobacco chewer, 17 (21.79%) alcoholic and 21(26.92%) were smokers, all were in advanced stage, 6 (7.69%) stage III, 72(92%) in stage IV. The average(SD) PET-CT SUV max value of the primary tumour during baseline, first, second and third response evaluation were 16.17(6.03), 12.53(4.94),11.38(5.47) and 12.64(7.57) respectively.As compared to baseline the change/decrease in PET-CT SUV max values during subsequent response evaluation at 2weeks interval during chemotherapy for primary tumour and regional lymph node were statistically significant with p<0.00001.

CONCLUSIONS

PET-CT metrics SUV max detects metabolic response in the primary tumour and regional lymph nodes in advance head and neck squamous cell carcinoma during chemotherapy as early as 2 week with clinical correlation. It has a potential role as surrogate marker for treatment response evaluation and tailoring of the management of squamous cell carcinoma of head neck region.

LEGAL ENTITY RESPONSIBLE FOR THE STUDY

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A predictive and prognostic biomarker profile of carcinoma breast

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ABSTRACT

Context: The immunohistochemical (IHC 4) biomarker profile is part of the standard histopathology report of all newly diagnosed and recurrent cases of carcinoma Breast. This profile is the basis for all neoadjuvant and adjuvant treatment planning in these cases.

Aims: 1. To study the IHC4 biomarker profile of Carcinoma Breast cases at our Institute.

2. To study the correlation of the five types of molecular subgroups with various clinical and histological parameters.

Settings and Design: 271 cases of carcinoma breast diagnosed and treated at our Institute, during the period 1st July 2017 till 30th June 2018. This is a prospective, observational study.

Materials and Methods: All the cases of biopsy proven carcinoma Breast were subjected to immunohistochemical staining for four markers- ER, PR, Her 2, and Ki 67.

Formalin Fixed Paraffin Embedded tumor tissue was stained for 4 biomarkers and scored with appropriate method. (Interpretive Guide: ASCO - CAP Test Guidelines Recommendations 2013)

Manual method of staining was employed, using commercially available reagents.

The cases were classified into five molecular subtypes.

Results: Triple negative breast carcinoma was the most frequent subgroup, followed by the luminal B and A types and the Her2 enriched cases were lowest in number.

A few cases showed triple positive staining pattern.

Conclusions: The IHC 4 biomarker findings in every case of carcinoma has a direct impact on the treatment decision making and also on risk stratification of the patients.

1. INTRODUCTION

Carcinoma of the breast is one of the leading sites of cancer all over the world.[1] In India it is the top ranked cancer in females with age adjusted rate as high as 25.8 per 100000 women.[2] Breast cancer is recognised as a heterogenous disease, with different biological properties across the different subtypes. Accordingly, the standard of care includes the immunohistochemical staining for every case, to classify it into different subtypes based upon the scoring for at least three biomarkers- Estrogen receptor, Progesterone receptor and Her 2 neu. These are called as predictive biomarkers because the neoadjuvant or adjuvant therapy of carcinoma breast is decided by the particular subtype. Additionally Her2 neu is also a prognostic biomarker which has bearing on the disease free survival as well as overall survival of the patient.

The hormone receptor profile of carcinoma Breast cases in India has been studied by many authors, but very few reports exist about the profile of patients from Central India.[3–11]

Genetic tests like Oncotype DX or Mammaprint are validated tests to predict the recurrence of disease. But the cost is beyond the reach of a majority of patients. Ki 67 is a surrogate predictive biomarker which is much more economical as compared to the genetic tests.[12]

With this background, the study was conducted to profile all the patients of carcinoma breast diagnosed at our institute.

2. MATERIALS AND METHODS

271 newly diagnosed and recurrent cases of carcinoma breast registered from 1st July 2017 till 30th June 2018 form the subject material of the study.

All the cases were clinically examined and staged after radiological evaluation.

As per the NCCN guidelines, all Stage I, IIa, IIb, IIIa cases were subjected to FNAC and if necessary to a core needle biopsy to document the tissue diagnosis of Carcinoma Breast. All these cases underwent surgery as the first modality of treatment. The surgical specimens were processed, tissue sections studied and the appropriate sections were subjected to immunohistochemical staing for the biomarkers to help plan the adjuvant therapy.

In cases of locally advanced breast cancer (IIIa, IIIb, IIIc - LABC), the patients underwent a core needle biopsy to document the disease as well as to determine the molecular subtype by immunohistochemstry for biomarkers to plan the neoadjuvant therapy.

In every case, Formalin fixed paraffin embedded sections were stained by the manual method for the four biomarkers-ER, PR, Her2 neu and Ki67.

The standard clones were used for the primary antibodies.

All the cases were typed into five subtypes (St Gallen (Vienna) 2013 consensus classification)13

1. Luminal A – ER positive, HER2 negative, Ki-67 < 15%, and PR high;

2. Luminal B (HER2 negative) – ER positive, HER2 negative, and either Ki-67 high or PR low;

3. Luminal B-like (HER2 positive) – ER positive, HER2 over expressed or amplified, any Ki-67, and any PR;

4. HER2 enriched – HER2 over-expressed or amplified, ER and PR absent;

5. Triple negative – ER and PR absent and HER2 negative.

3. RESULTS

The majority of cases w ere seen in female breast (267), only four cases were found in male breasts (four). The pre and post menopausal age group distribution did not show significant difference. Infiltrating Duct Carcinoma-Not otherwise specified- was the most frequent histological type (263) and other variants like Infiltrating Lobular Carcinoma (three), Papillary Carcinoma (one), Medullary Carcinoma (one), Metaplastic Carcinoma (three) were very few. (Figure 1)

Triple Negative Breast Cancer was the most frequent molecular subtype, followed closely by Luminal A type.

Only Her2 positive was the least frequent. (Figure 2) Of the triple negative group, significant number of cases were having T size 2 and 3 with N1 status and so more likely to show higher p stages. Table 1

The luminal A subgroup also showed T2 as the most frequent T size, but the node status was more likely to be N0 and thus showed a lower p stage. Table 2

Both the luminal B types and the Her 2 enriched subtype showed similar associations as the Luminal A subtype. Tables 3, 4 and 5

Most interesting was The Ki67 score which showed a significant concentration at different values between the subtypes, Luminal A showing the lowest score and TNBC the highest. Table 6

Table 1: Correlation of TNBC with T size, N status and p Stage

T size		
T1	1.11	
T2	17.71	Significant
T3	9.96	Significant
T4	1.48	
N Status		
N0	4.80	
N1	17.34	Significant
N2	7.01	
N3	0.37	
Stage		
I	1.48	
IIa,IIb	12.38	Significant
IIIa	8.12	Significant
LABC	8.49	Significant

Table 2: Correlation of Luminal A with T size, N status and p Stage

T size		
T1	2.21	
T2	21.40	Significant
T3	1.11	
T4	0.74	
N Status		
N0	18.45	Significant
N1	5.17	
N2	0.37	
N3	1.48	
Stage		
I	2.21	
IIa,IIb	20.30	Significant
IIIa	0	
LABC	2.95	

Table 3: Correlation of Luminal B (Her2 Negative) with T size, N status and p Stage		
T size		
T1	0.37	
T2	14.02	Significant
T3	4.30	
T4	0.37	
N Status		
N0	9.59	Significant
N1	7.38	
N2	1.85	
N3	1.11	
Stage		
I	0.37	
IIa,IIb	13.65	Significant
IIIa	4.06	
LABC	1.11	

Table 4: Correlation of Luminal B -like(Her2 Positive) with Tsize, N status and p Stage		
T size		
T1	0	
T2	11.07	Significant
T3	1.85	
T4	0	
N Status		
N0	5.90	Significant
N1	6.27	Significant
N2	0.37	
N3	0.37	
Stage		
I	0	
IIa,IIb	10.33	Significant
IIIa	1.85	
LABC	0.74	

Table 5: Correlation of Her 2 enriched group with T size, N status and p Stage		
T size		
T1	0.37	
T2	9.59	Significant
T3	1.85	
T4	0.37	
N Status		
N0	3.69	
N1	6.64	Significant
N2	1.48	
N3	0.37	
Stage		
I	0.37	
IIa,IIb	8.86	Significant
IIIa	1.48	
LABC	1.48	

4. DISCUSSION

Triple negative Breast cancer is the most frequent subtype (30%) found in this study. This observation is similar to that reported previously.[11] Since all three receptors are not expressed by this tumor subtype, these patients do not benefit from hormonal treatment, they have to be managed by chemotherapy. The reported prognosis of this group is poorer as compared to the hormone receptor positive subtype.[14,15]

The Ki 67 score in this study group was found to be the highest, prompting a close follow up to assess recurrence and progression.

Luminal A (26%) was the next most frequent group. Since these tumors express the hormone receptors, they respond to hormonal treatment directed against these targets. Consequently this group as a whole is reported to have a better prognosis.[15] The Ki 67 scores in this group was the lowest, which also predicts a better outcome as compared to other subtypes.

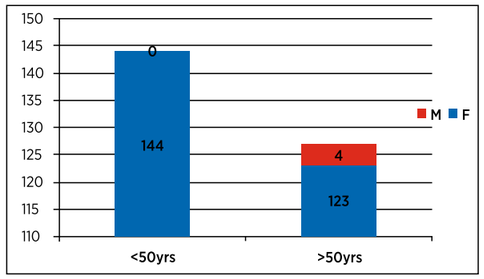

Fig. 1: Age group and sex distribution of carcinoma Breast cases

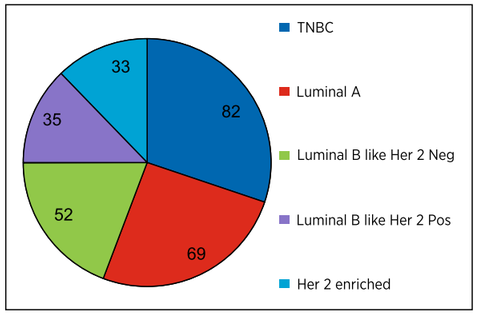

Fig. 2: Frequency of molecular subtypes of carcinoma Breast cases

The two Luminal B subtypes were the next in frequency (Her2 negative 19% and Her2 Positive13%). Amongst these subtypes, the luminal B/HER2-is reported to have had higher risk of mortality than the luminal B/HER2+.15

The Ki 67 scores in both these groups were low, without much statistical difference which predict a better outcome as compared to TNBC and Her 2 enriched subtypes.

The least number of cases were of the Her2 enriched subtype. This group of patients benefit by targeted therapy in the form of Herceptin. However, the Ki67 score of this group was found to be high, again prompting a close follow up to detect early recurrence.

The Ki 67 scores of different molecular types show interesting findings. The Luminal A cases show the lowest proliferation index whereas the TNBC type shows the highest Proliferation index. These findings will have to be correlated with the disease free survival rates in follow up.

Table 6: Correlation of Ki67 score - a significant concentration at different values between the subtypes, Luminal A showing the lowest score and TNBC the highest.

Ki 67 score										
S.No.	**Molecular type**	**0-15**	**16-25**	**26-35**	**36-45**	**45 onwards**	**Total**	**P value**	**Significance**	**Observations significantly concentrate at**
1	Luminal A	69	0	0	0	0	69	0	Significant	0-15
2	Luminal B HN	8	21	8	9	6	52	0.0074	Significant	16-25
3	Luminal B HP	8	15	2	4	6	35	0.0226	Significant	16-25
4	Her 2 enriched	3	3	17	5	5	33	0.0006	Significant	26-35
5	TNBC	8	9	20	17	28	82	0.0023	Significant	>45

5. CONCLUSION

Indian data on breast cancer is being published from different geographical regions of the country and gradually a clearer picture is emerging regarding the distribution of different molecular types of carcinoma breast. As more and more patients get tested and typed for the hormonal markers, and long term survival data emerges, we will have a better idea about the challenge of treating Breast cancer in our country.

6. SOURCE OF FUNDING

None.

7. CONFLICT OF INTEREST

None.

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Ball in the Wall: Mesenteric Fibromatosis—a Rare Case Report

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ABSTRACT

Introduction Mesenteric fibromatosis-desmoid tumor of mesentery is a rare benign soft tissue tumor of mesentery. On CT, it mimics gastrointestinal stromal tumor (GIST).

Case Report A 44-year-old female with small intestinal mass, preoperatively diagnosed radiologically and pathologically as GIST.

Conclusion Mesenteric fibromatosis is a rare tumor often mistaken for GIST. Histopathology and immunohistochemistry is the key as management of both the tumors differs.

KEYWORDS

Mesenteric fibromatosis . GIST . Desmoid tumor of mesentery

INTRODUCTION

Mesenteric fibromatosis, also known as desmoid tumor of mesentery is a rare benign soft tissue proliferative tumor having its origin in the mesenteric tissue. It is a locally aggressive tumor. Though it lacks malignant potential, recurrences have been documented in the literature. It is important to differentiate mesenteric fibromatosis from GIST (gastrointestinal stromal tumor) as it is its closest differential on radiology as well as on histopathology. The management of both tumors is completely different. Mesenteric fibromatosis is treated by surgical resection. R0 resection minimizes the chances of local recurrence. Treatment of GIST is surgery along with Tyrosine Kinase inhibitors. Misdiagnosis can lead to hazardous therapeutic management.

We report a case of 44-year-old female presenting with small intestinal tumor preoperatively suspected as GIST.

CASE REPORT

A 44-year-old female presented to us with history of vague abdominal discomfort. She was previously operated for total abdominal hysterectomy for multiple fibroids and was on regular follow up. On follow up ultrasonography, the radiologist reported small intestinal soft tissue lesion and histopathological correlation was suggested. Transabdominal CT-guided biopsy was done and was reported as benign spindle cell neoplasm suspicious of GIST and was advised for immunohistochemistry (IHC) for confirmation of diagnosis. However, patient being unaffordable IHC was not performed and the patient was directly referred to us. The CECT reported the same radiological finding as that of ultrasonography revealing small intestinal soft tissue mass, well-circumscribed homogenously hypoechoic measuring approximately 11 × 7.5 × 6 cm probably originating from intestinal wall suspicious of GIST(Figs. 1 and 2).

The patient underwent exploratory laparotomy. Intraoperatively to our surprise, there were multiple soft tissue masses, largest dumbbell-shaped mass measuring approximately 11 × 7.5 × 6 cm attached to the wall of small intestine and invading the surrounding mesentery. The tumor was close to the root of mesentery; however, no gross invasion was seen. Also, there were two small nodules similar in appearance at separate sites in the same intestinal segment. For attaining R0 resection, a large segment of small intestine had to be resected measuring approximately 60 cm. Intraoperative and postoperative period was uneventful, and the specimen was sent for histopathological examination.

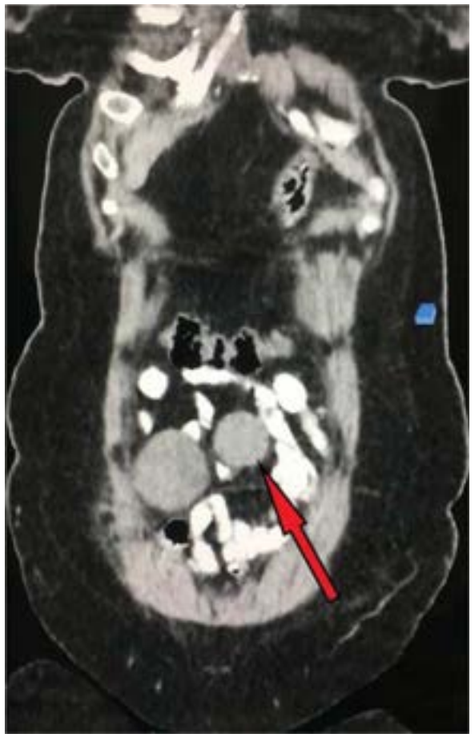

Fig. 1 CT scan image shows a dumbbell-shaped tumor (marked by red arrow) attached to the small intestine

On gross examination the intestinal segment measured approximately 60 cm in length, with a dumbbell-shaped tumor measuring approximately 11 × 7.5 × 6 cm arising from the intestinal wall and extending deep into the surrounding mesentery (Fig. 3). Another 2 smaller lesions were also identified largest measuring 1.5 × 1 × 1 cm embedded in the mesenteric tissue. The proximal resection margin was 14 cm away from the main tumor, and distal resection margin was 30 cm away from the main tumor. However, two smaller nodules closest being 8 cm from the distal resection margin were identified which were not reported on pre-operative CT. The two smaller nodules were approximately 20 cm away from the main tumor.

The tumor was well circumscribed, and the cut surface showed a solid, homogenous mass with whirling pattern without areas of hemorrhage or necrosis. Representative sections were taken for histopathological diagnosis.

On microscopy, the sections showed well circumscribed benign spindle cell tumor arising from the serosa with cytologically bland spindle cells, stellate-shaped cells forming fascicles and storiform pattern. Prominent sclerosed blood vessels were seen with collagenized fibers. Intestinal mucosa, submucosa, muscularis propria, and subserosal fat were unremarkable (Figs. 4 and 5).

For confirmation of diagnosis, IHC was performed which showed immunoreactivity for nuclear beta catenin, vimentin, and variable SMA positivity while tumor cells were negative for CD-117, DOG-1,CD-34, and ALK-1 ruling out the differentials of GIST and inflammatory myofibroblastic tumor (IMFT). MIB 1 labeling index was 1%.

Follow up Immediately after 2 months of surgery, the patient presented with diarrhea because of short bowel syndrome and was managed symptomatically. The patient is post 1 year of surgery and on regular follow up with the operating surgeon and presently asymptomatic.

The patient underwent colonoscopy for evaluation of familial adenomatous polyposis (FAP); however, it was unremarkable.

DISCUSSION

Mesenteric fibromatosis is a benign tumor arising from the fibroblasts of mesentery. It is postulated that its occurrence may be due to previous surgical trauma,

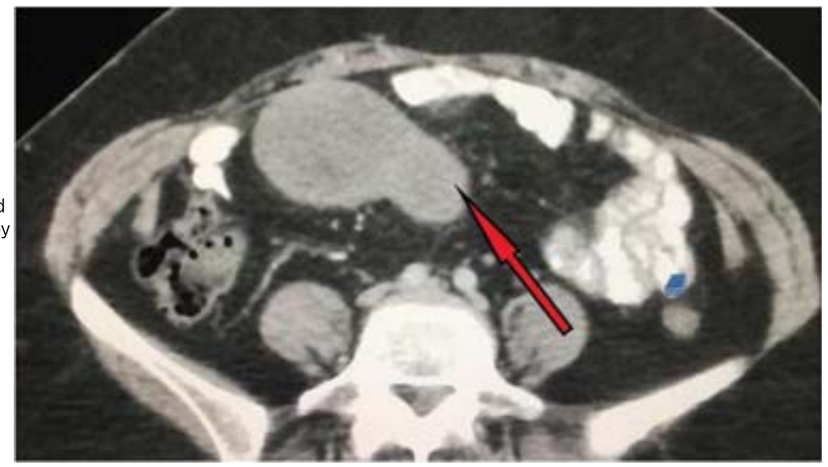

Fig. 2 CT scan sagittal section image shows a dumbbell-shaped tumor (marked by red arrow) attached to the small intestine

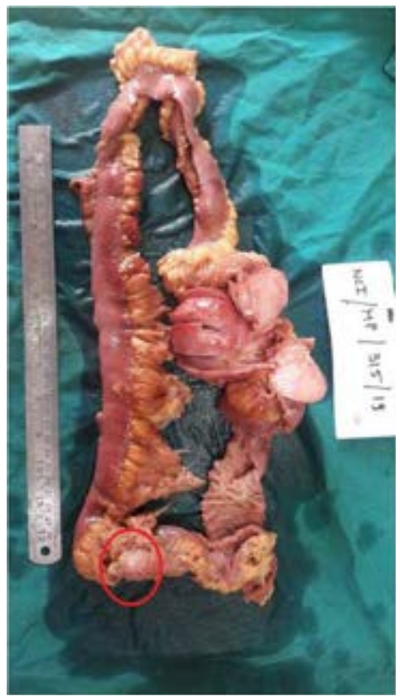

Fig. 3 Gross of the resectedspecimen showing a dumbbellshaped tumor, cut section solid white whirling seen.
A smaller tumormarked by red circle is seen separately

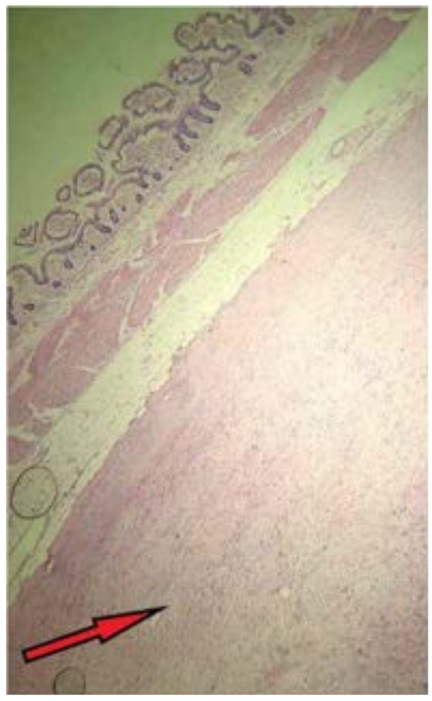

Fig. 4 Microscopy (× 10) shows a spindle-shaped neoplasm arising from serosa. Muscularis propria and subserosa is unremarkable

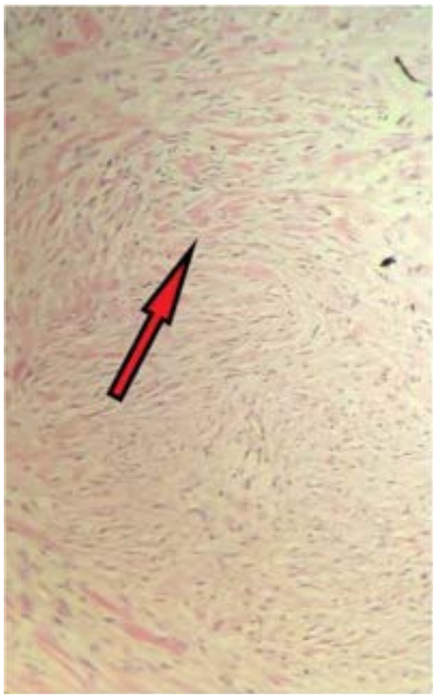

Fig. 5 Microscopy (× 40) shows spindle cells arranged in whorls and storiform pattern.
Collagenized fibers are also seen.
Mitosis is not seen

Table 1 Characteristics of studies

Studies	Number of patients	Presentation	Past history	Family history	Treatment given	Outcome/follow up, recommendation
Marek Wronski et al., 2011 [7]	One (44-year-old female)	Epigastric pain	Arterial hypertension, Hashimoto thyroiditis, hypercholesterolemia History of previous cesarean section	Not significant	Elective laparotomy	No recurrence (1 year follow up)
Mukut D et al., 2014 [8]	One (29-year-old male)	Swelling on the right side of the umbilicus for 6 months and dull aching pain for 2 months	Not significant	Not significant	Exploratory laparotomy	No recurrence (3 years follow up)
Rodriguez et al., 2004 [9]	25 cases	Varied presentation depending on the organ of involvement, stomach, duodenum, ileum, jejunum, and colon. Mistaken for GIST in majority of patients.	Six patients had history of abdominal surgery in the past	Not significant in any case	Elective laparotomy	Not mentioned
Jian Li et al., 2019 [10]	One case (18-year-old female)	Acute abdomen for 10 h (abdominal	Appendectomy 2 years back pain, nausea, and vomiting)	Not significant	Exploratory	No recurrence (17 laparotomy months follow up)
Anandaravi BN et al., 2015 [11]	One case (24-year-old female)	Progressive abdominal distention associated with dull aching pain laparotomy	Not significant	Not significant	Elective	Postoperative period uneventful. Follow up not mentioned
Haibin Ji et al., 2019 [12]	One case (26-year-old male)	Abdominal distention and loss of appetite. On examination, lump in abdomen	Not significant	Not significant	Exploratory laparotomy	No recurrence (18 months follow up)
Present study, 2019	One case (44-year-old female)	Vague abdominal discomfort	Underwent total abdominal hysterectomy for multiple fibroids	Not significant	Elective laparotomy	No recurrence (1 year follow up)

handling of the intestine and also is often related to hormonal influence. Familial adenomatous polyposis (FAP) and Gardner syndrome patients are often at risk of developing mesenteric fibromatosis.

Approximately 10% of patients develop mesenteric desmoids. FAP associated fibromatosis have an aggressive clinical course with increased rate of recurrences. APC (adenomatous polyposis coli) gene mutations in FAP lead to over expression of nuclear beta catenin [1–4].

Clinical course of mesenteric fibromatosis is usually uneventful after surgical resection. Rate of recurrence in sporadic cases is very low.

However, large tumors not resected for long can often cause intestinal obstruction or can lead to mesenteric ischemia. Treatment modality of mesenteric desmoids is individualized, with surgical resection done only in well circumscribed tumors and tumors which do not invade the root of mesentery. Fifty-three to 67% of mesenteric desmoids are resectable [5].

Radiation and chemotherapy is not found useful in cases of R0 resection and patients with sporadic desmoids. Doxorubicin is given in cases of recurrent tumors and tumors with genetic mutation. Tumors which are resistant to doxorubicin have been tried with imatinib, which is most commonly useful in cases of GIST; however, its utility has not been proven in large studies (Table 1) [6].

CONCLUSION

The present case report documents an unusual case of mesenteric fibromatosis.

IHC-proven histopathological diagnosis is mandatory for mesenteric fibromatosis as other closest differentials have a completely different surgical and therapeutic management. MRI is a preferred modality of diagnosis than CT. Usually, mesenteric fibromatosis is diagnosed as GIST on radiology and tissue diagnosis followed by IHC is mandatory.

R0 resection is vital to prevent recurrences.

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Head Neck Squamous Cell Cancer Genomics: Oncogenes, Tumor Suppressor Genes and Clinical Implications

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ABSTRACT

Head Neck Squamous Cell Cancer is genomically heterogenous. Common somatic mutations involve TP53, CDKN2A, FAT1, NOTCH1, PIK3CA, KMT2D and NSD1, less frequently others. Epigenetic changes also contribute to HNSCC biology. Alterations in tumor suppressor genes is a major oncogenic event in HNSCC. Genomic heterogeneity exists between different subsites within head neck region and also between the primary and metastatic disease. Intratumor heterogeneity has also been recognized. Based on key genomic alterations, four major molecular subtypes have been identified. Multi-omics analysis has provided further insights into HNSCC biology and shed light on EGFR pathway and immunogenomics. Corelative genomics of tumor cells, stromal cells and immune cells have led to emergence of distinct immune molecular subtypes of HNSCC. Major tumor suppressor genes and oncogenes have a correlation with prognosis, survival and treatment resistance. EGFR pathway is in focus for renewed understanding of resistance to EGFR targeted treatments and novel ways to target EGFR pathways. Increasingly genomic data is being leveraged towards clinical use including HNSCC prevention, prediction of metastases, survival and prognostication, fine tuning use of surgery, chemotherapy and radiation therapy, identifying patients for using immunotherapy, predicting drug resistance and gaining new information from radiological studies. Several novel targeted therapies are being pursued in clinical trials. Molecular co targeting strategies are being developed. Understanding the way tumor suppressor genes and oncogenes shape HNSCC biology and clinical behaviour is bringing the much-needed therapeutic breakthrough in this tough to treat disease.

KEYWORDS: Head Neck, Squamous, genomics, clinical, profiling, applications

1. INTRODUCTION

Head neck squamous cell carcinomas (HNSCC) include cancers arising in the mucosa of oral cavity, pharynx, larynx, hypopharynx. According to GLOBOCAN 2020 report, worldwide head neck cancer statistics indicate that there are 1,518,133 cases of head neck cancers per year, resulting in approximately 510,771 deaths per year. In Asia there are 944,946 cases of head neck cancers per year, resulting in approximately 347,870 deaths per year. High incidence rates have been reported from developing countries including India, Pakistan, Bangladesh, Taiwan, and Sri Lanka [1].

Treatment of HNSCC is guided uniformly by anatomic location, tumor size, presence or absence of nodal and distant metastases. Oral cavity cancers are primary treated with surgery followed by adjuvant radiation or chemo-radiation based on pathological features. Cancers in the oropharynx, larynx and hypopharynx are primary treated with chemo-radiation with function preservation as the main goal of therapy. Neo-adjuvant chemotherapy is used in locally advanced tumors to improve resectability. EGFR targeting drugs afatinib, Cetuximab and immune check point inhibitors pembrolizumab, nivolumab are the only FDA approved biological treatments today.

Clinicians managing HNSCC face number of challenges today. Some of these include.

• High mortality in spite of optimal use of currently existing therapeutics.

• Lack of clinically meaningful biological classifier of HNSCC other than HPV status.

• Continued emergence of treatment resistance.

• Great variability in clinical outcome despite uniformity in approach.

• Continued reliance on anatomical factors (TNM) to guide treatment.

• High morbidity and poor quality of life after conventional treatments

• Lack of robust biomarkers to select EGFR targeted therapy which seems to be the only existing targeted therapy for HNSCC.

• Lack of effective systemic adjuvant systemic therapies in high-risk patients.

• Lack of genomically directed therapies similar to other oncogene addicted cancers.

• Lack of effective later lines of therapies

• Low response rates to currently approved immune check point inhibitors

• Lack of robust biomarkers to predict nodal, distant metastases and recurrence

• And even lack of predictive biomarkers for selection of conventional treatments, not to mention lack of robust biomarkers for prognosis.

Considerable work has been done on deciphering HNSCC at genomic level. Major alterations in tumor suppressor genes and oncogenes in HNSCC have been identified. Multi-omics studies have shed considerable light on how genomic alterations shape HNSCC biology and clinical behavior. Number of studies are addressing how knowledge about HNSCC genomics/multi-omics can leveraged to address some of the challenges faced by clinicians managing HNSCC. The need to break the ground in HNSCC prevention and therapy has never been so urgent.

This chapter attempts to review key alterations in tumor suppressor genes and oncogenes in HPV negative HNSCC and the potential clinical implications of these alterations. Key insights gained from multi-omics studies will also be highlighted. This review also quotes some of the novel targeting therapies and novel strategies. Specifically, insights gained in EGFR targeting and immune therapies will also be discussed in the context of genomics. Since the amount of literature being published is so large, it is beyond the scope of this review to provide exhaustive coverage on each aspect of head neck cancer genomics. Hence few indicative studies are quoted to elaborate each point to give the reader a basic orientation. This review will focus on HPV- HNSCC.

2. HEAD NECK SQUAMOUS CELL CANCER (HNSCC): ONCOGENES AND TUMOR SUPPRESSOR GENES

The Cancer Genome Atlas (TCGA) provided landscape of somatic genomic alterations by profiling 279 head neck squamous cell carcinomas. Tobacco related head neck squamous cell cancers showed loss of function mutations of TP53, CDKN2A inactivation, Copy number alterations of 3q26/28, 11q13/22. Few subgroups showed alterations in NSD1, WNT pathway genes AJUBA and FAT1, NFE2L2 [2]. HPV positive cases showed mutations of PIK3CA, loss of TRAF3 and amplification of cell cycle gene E2F1.Whole exome sequencing and microarray data showed unstable HNSCC genome showing high copy number alterations including copy number loss and copy number gains. Co amplifications of CCND1, FADD and CTTN and BIRC2 and YAP1 were found. Focal deletions were found in NSD1 and tumor suppressor genes including FAT1, NOTCH1, SMAD4, CDKN2A. Focal amplifications were found in receptor tyrosine kinases (RTKs) like EGFR, ERBB2, FGFR1. There was a small subset of oral cavity cancer characterized by activating mutations in HRAS, inactivating mutations in CASP8 and wild type TP53. This subset has been labeled as 'M' class which is driven by mutations rather than copy number alterations with tumorigenesis involving RAS, cell death pathway and NFkB. Fusion oncogenes like ALK, ROS or RET were not observed. MET exon 14 skipping mutation was uncommon. Loss of tumor suppressor function was more common than protein coding fusion events.

TCGA identified genes which can be grouped into (1) genes responsible for cell survival and proliferation (TP53, HRAS, EGFR, PIK3CA), (2) cell cycle control genes (CDKN2A AND CCND1), (3) cellular differentiation (NOTCH1) and (4) adhesion and invasion signaling (FAT1). Out of the most commonly mutated genes, TP53, CDKN2A, CASP8 AND NSD1 are differentially mutated across anatomic sites in the head neck region.

Frequency wise the common mutations in HNSCC are listed in Table 1. More than 70% of HNSCC harbor mutations in the tumor suppressor p53 (TP53). TP53 mutations have been characterized in several ways. These mutations could be somatic or missense mutations, functional, partially functional or non-functional, and based on the alteration of DNA binding, as disruptive and non-disruptive.

TP53 mutations influence cell cycle, genomic integrity causing aberrant proliferation, disrupted apoptosis and defective DNA repair. TP53 mutation is probably the main actor in HNSCC pathogenesis and occur early in carcinoma. These mutations are also very high in metastatic HNSCC. Mutation rates of TP53 vary across different subsites in head neck. Larynx and hypopharynx have the highest TP53 mutation rate (83.5%), oral cavity and tongue 75.6%. oropharynx including tonsils and base of tongue have the lowest mutation rate 28.6% [3].

CDKN2A is the second most commonly altered gene in HNSCC CDKN2A encodes a CDK4/CDK6 kinase inhibitor which constrains cells from progressing through G1 restriction point. CDKN2A mutations are rare in HPV+ HNSCC [3]. Mutations involving NOTCH gene are third most common in HNSCC [3, 4]. NOTCH family members are transmembrane proteins (NOTCH 1-4) and two family of ligands the Jagged and the Delta-like proteins, involved in cell to cell communication and regulations of squamous differentiation.

CCND1 encodes cyclin D1 and regulates G1-to-S phase transition by formation of complexes with cyclin dependent kinases like CDK4 and CDK6. CCND1 is amplified in 30-40% of HNSCC with cyclin D1 overexpression [3]. AJUBA regulates cell division, vertebrate ciliogenesis and left–right axis determination. NSD1 is a tumor suppressor gene. Mutations in KMT2D and HLA-A contribute to a defective immunosurveillance. EGFR is commonly overexpressed in HNSCC and has been explored as a therapeutic target. PIK3CA alterations are common in HNSCC especially in HPV+ cancers. PIK3CA are seen in patients with advanced HNSCC harboring multiple PI3K pathway mutations [3]. MET is a Hepatocyte Growth Factor (HGF) receptor which regulates cancer cell plasticity through reversible programming of epithelia-mesenchymal transition (EMT) [3]. MET over expression leads to MET/ HGF pathway activation and corelates with worse outcome.

Table 1. Somatic mutations (TCGA findings).

Molecular Mechanisms in Cancer	
Mutations	**Percentage**
TP53	72
CDKN2A	22
FAT1	23
NOTCH1	19
PIK3CA	21
KMT2D	18
NSD1	10
CASP8	9
NFE2L2	6
FBXW7	5
TGFBR2	4
HRAS	4
CUL3	4
RB1	3
HLA-A	3
PTEN	2
TRAF3	1

2.1 Epigenetics in HNSCC

Epigenetic changes such as DNA methylation, histone acetylation and expression of small non coding RNAs affect gene expression. There is some evidence of importance of epigenetic changes in HNSCC. Global hypomethylation has been linked to poor prognosis. Epigenetic changes is one major method for tumor resistance. Many tumor suppressor genes like CDKN2A, CDH1, MGME, RASSF1A show promoter hypermethylation [5].

2.2 Key oncogenic events in HNSCC

In terms of key driver oncogenic events in HNSCC can be summarized as follows; (Table 2). In the TCGA dataset, most of the tumors that were sequenced were from early-stage surgical samples. The genomic profile of recurrent/metastatic HNSCC could be different. The American Association for Cancer Research has undertaken a project Genomic Evidence Neoplasia Information Exchange (GENIE) which is an international data sharing project allowing multiple international institutions to share their data of cancer sequencing. This combined dataset includes 700 patients with HNSCC, 40% representing patients with metastases. The frequency of common mutations in HNSCC in the three datasets TCGA, AACR GENIE and COSMIC are found comparable and has paved the way for developing targeted therapies [6].

2.3 Genomic heterogeneity of HNSCC at different subsites and between primary and recurrent metastatic tumor

iIn addition to HPV status as one important biological differential, different subsites of HNSCC seem to harbor differences at genomic level. TP53 mutations are most frequent in Laryngeal/hypopharyngeal sites followed by oral cavity followed by oropharynx [3]. David Vossena et al. did DNA sequencing on 111 HPV negative HNSCC, 55 oral and 56 laryngeal/pharyngeal cancers and identified somatic point mutations and copy number alterations. They also included sample data from TCGA to expand analysis. Mutational profiles of oral and laryngeal pharyngeal squamous cell carcinoma showed many similarities. However, oral squamous cell carcinoma was significantly enriched for CASP8 and HRAS mutations. Laryngeal/pharyngeal squamous cell cancers were enriched in LAMA and NSD1. Overall, oral squamous cell carcinoma had fewer somatic point mutations and copy number alterations. Laryngeal/pharyngeal squamous cancer scored higher on mutational and genomic scar signatures associated with homologous recombination DNA repair defects explaining differential response to chemoradiation [7].

Table 2. Oncogenic events in HNSCC.

Function	Gene	Event
Tumor Suppressor	TP53	Loss of function mutation
Tumor suppressor	CDKN2A	Mutation, homozygous
		deletion, protein down
		regulation
Tumor suppressor	NF1	Mutation, amplification
PI(3)K	PIK3CA	Amplification, mutation
PI(3)K	PTEN	Mutation, protein down
		regulation
PI(3)K	PIK3R1	mutation
Oncogenes	CCND1	amplification
Oncogenes	MYC	Amplification
Oncogenes	HRAS	Mutation
Receptor Tyrosine	EGFR	Amplification, mutation,
Kinases (RTKs)		protein up regulation
RTKs	FGFR1	Mostly amplification, rarely
		mutation
RTKs	ERBB2	Amplification, protein up
		regulation, mutation
RTKs	IGF1R	Amplification, mutation
RTKs	EPHA2	Mutation
RTKs	DDR2	Amplification, mutation
RTKs	FGFR2	Amplification, mutation
RTKs	FGFR3	Amplification, mutation
RTKs	MET	Amplification, exon 14
		skipping mutation

Recurrent and metastatic HNSCC do share driver mutations with their primaries in addition to accumulating new mutations. High rates of TERT promoter mutations are found in recurrent or metastatic HPV- HNSCC. HPV+ HNSCC may also start exhibiting mutational landscape of HPV- negative tumors after recurrence and metastases. Recurrent HPV+ positive tumors may get enriched in TP53 mutations and lack PIK3CA mutations as compared to primary HPV+ primary tumors [8].

As noted earlier, head neck mucosal squamous cell carcinoma occurs at several subsites. Clinical behavior heterogeneity in terms of response to therapy, metastatic rate is commonly observed. Clinical heterogeneity is

observed even within a single subsite. Tumor cells are known to accumulate genetic alterations over time. Some of these are driver mutations and some are passenger mutations. Heterogenic cell clones undergo selection leading to development of aggressive clones with growth advantage. This is one main reason for development of resistance to chemotherapy and radiation therapy. High degree of intratumor heterogeneity leads to tumor progression, inferior treatment outcome and reduced survival. Whole genome analysis of 74 cases of HNSCC used to calculate Mutant Allele Tumor Heterogeneity (MATH) can be a genetic biomarker of high-risk disease. High MATH has been found to have shorter overall survival [9, 10]. Targeted monotherapies are unlikely to be major breakthrough in HNSCC. Rational combination of two or several therapies or effective co-targeting seems to be the way forward.

2.4 Molecular subtypes of HNSCC cancers based on gene expression profiles

Chung et al. and Walter et al. described four distinct molecular classes in HNSCC based on gene expression patterns: basal, mesenchymal, atypical, and classical (Table 3) [11, 12]. The basal subtype is characterized by over-expression of genes functioning in cell adhesion including COL17A1, and growth factor and receptor TGFA and EGFR, high expression of transcription factor TP63. The mesenchymal subtype shows over expression of genes involved in immune response and genes associated with epithelial to mesenchymal transition including vimentin, desmin, TWIST1, and HGF. The classical subtype is shows over-expression of genes related to oxidative stress response and xenobiotic metabolism. The atypical subtype shows elevated expression of CDKN2A, LIG1, and RPA2, low expression of EGFR.

2.5 Multi-omics analysis of HNSCC and novel insights

Huang et al. did proteogenomic study on 108 HPV negative HNSCCs in order to gain biological insights and novel treatment strategies [13]. They found correlation between 263 proteins, 173 phosphoproteins and overall survival.Poor prognosis associated proteins / phosphoproteins were enriched in pathways for somatic copy number alteration drivers, DNA replication, cell cycle and RNA processing. They also found poor prognosis associated with FAT1 truncation or 11q13.3 amplification. Analysis of Rb pathway showed interesting observations. CDKN2A and CCND1 alterations do not always result in increased CCND1 protein and CDK4/6 activity. Rb status was found more effective indicator of CDK4/6 dependent cell cycle activity than genomic or transcriptomic markers.

Similarly, novel insight was obtained in EGFR pathway. EGFR amplification activates EGFR in a ligand independent manner. The EGFR monoclonal antibody works by binding to the extracellular domain of EGFR to prevent ligand induced activity. Therefore, EGFR ligand abundance is more important to activity of anti EGFR moAbs than EGFR amplification or overexpression.

Immune-proteogenomic analysis revealed immunosuppressive somatic copy number alterations. Higher immune cell infiltration was linked to low clinical stage, less smoking and better prognosis. Immune hot tumors showed both cytotoxic immune enzymes and immunosuppressive proteins. This explains why the response to immune check point inhibitors in PD L1 positive HNSCC patients is modest. In immune cold tumors, the low immune infiltration was not driven by lack of tumor antigen sources but deficient Antigen Presentation Machinery (APM) pathway.

Table 3. Molecular subtypes of HNSCC and key features.

Molecular subtype	Key features
Classical	TP53 mutation
	CDKN2A loss
	3q amplification
	Alterations in oxidative stress genes like KEAP1, NFE2L2, CUL3,
	Smoking history
	Laryngeal subsite
Basal	NOTCH1 inactivation
	Decreased SOX2 expression
	HRAS-CASP8 co-mutation
	Co-amplified 11q13/q22
Atypical	Lack of chromosome 7 amplification
	Activating exon 9 mutations (PIK3CA domain)
Mesenchymal	Alterations in innate immunity genes,
	High expression of CD56
	Low frequency of HLA class I mutations

Further Huang et al. divided HNSCC tumors into three clusters using multiomics data. Cluster I was associated with laryngeal site, strong smoking and high chromosome instability (CIN). Proteomic data suggested linkage between aberrant epigenetic activity, smoking and high CIN. This cluster had the worst prognosis. Cluster II showed elevation of several basal factors and high translational activity. Cluster III showed tumors with weak smoking history, higher immune scores and higher stromal scores. So, cluster I, II and III were CIN, Basal and Immune subtypes respectively. In terms of treatment selection, CIN subtype was associated with frequent aberrations of CCND1, CDKN2A and Rb hyperphosphorylation indicating potential for CDK 4/6 inhibitors. Basal subtype was associated with high EGFR ligand activity suggesting a potential role for anti- EGFR mAbs. The immune subtype could be appropriate for immune checkpoint blockade. Frequency of high level of biomarkers were 32% in CIN tumors, 62% in Basal tumors and 83% in Immune tumors emphasizing the tremendous potential to select appropriate therapy.

New targets for therapy were also identified including KIT, ECER1G, PLAU, SERPINE1, TOP2A, MMPs, several cell cycle and DNA damage related kinases. Multiple C/T and neoantigens were also found in their analysis which could be potential immunotherapy targets.

2.6 Immunogenomics

Thorsson et al. and Tamborero et al. did extensive immunogenomic analysis of many tumors and came out with six molecular immune subtypes: wound healing (C1), IFN gamma dominant (C2), inflammatory (C3), lymphocyte depleted (C4), immunologically quiet (C5) and TGF-beta dominant (C6) [14, 15]. In the TCGA HNSCC cohort, most tumors were C1 with elevated expression of angiogenic genes, high proliferation rate and a Th2 cell bias to the adaptive immune infiltrate or C2 with the highest M1/M2 macrophage polarization, a strong CD8 signal and prominent TCR diversity.

Genomic and neoantigen evolution from primary to first metastases was studied by Charles Schutt et al. between 23 paired primary and recurrent HNSCC tumors [16]. They found 6 genes which predicted neoantigens in 4 or more patients. Neoantigens in shared genes had increased CD3+ and CD8+ T cell infiltration and duration of survival with disease.

Yao Yao et al. in a study involving 5 HNSCC tumors and normal tissue found four immune related genes, PVR, TNFRSF12A, IL21R, SOCS1 to be significantly associated with overall survival [17]. They tried to integrate these four genes with pathological N stage to better predict overall survival. High expression of PVR AND TNFRSF12A indicated poor overall survival whereas high expression of IL21R and SOCS1 indicated better overall survival.

Chen et al. characterized the immune landscape of HNSC by their tumor and stromal compartments to identify novel immune molecular subgroups [18]. In their study, a training cohort of 522 HNSC samples from the Cancer Genome Atlas profiled by RNA sequencing was analyzed. Gene patterns from tumor, stromal, and immune cell genes were separated. Correlations were studied between the expression patterns with a set of immune related gene signatures, potential immune biomarkers, and clinicopathological features. Validation was done with six independent datasets containing 838 HNSC samples.

Approximately 40% of HNSCs were labeled as immune class based on enriched inflammatory response, enhanced cytolytic activity, and active interferon-c signaling. Within this, some samples had markers of exhausted immune response and some had markers of active immune response. The Exhausted Immune Class was characterized by enrichment of activated stroma and anti-inflammatory M2 macrophage signatures, WNT/transforming growth factor-b signaling pathway activation and poor survival. Active immune class showed enriched proinflammatory M1 macrophage signature, enhanced cytolytic activity, abundant tumor-infiltrating lymphocytes, high human papillomavirus (HPV) infection, and favorable prognosis. Such a subgrouping might help in tailoring immune therapies to appropriate subsets of patients.

Several genomic features may influence response to immune check point inhibitors [19]. High tumor mutational burden is associated with neoepitope presentation and immune hot phenotype leading to enhanced benefit with immune check point inhibitors. NSD1 inactivating mutations, global DNA hypomethylation, aneuploidy, may lead to impaired chemokine signaling and immune effector response leading to an immune cold phenotype and low benefit from immune checkpoint inhibitors. Groups led by Many HNSCC specific studies tried to subtype patients as immune molecular subtypes. Considerable work is also being done to understand immune events occurring in the areas of field cancerization around an oral premalignant lesion raising the hope for using immunotherapy as immunoprevention. Integrated omics studies are also being pursued to understand occurrence of immune related adverse events and development of immune resistance.

3. HEAD NECK CANCER GENOMICS : CLINICAL IMPLICATIONS

3.1 Clinical and therapeutic implications of major tumor suppressor genes and oncogenes in HNSCC

TP53 mutation which is common in HNSCC has predictive value for disease free and overall survival. There is a correlation between TP53 mutations and resistance to chemotherapy drugs like cisplatin, doxorubicin, paclitaxel also leading to lower rates of pathological complete responses to neoadjuvant chemotherapy. Absence of TP53 mutated DNA in the surgical margins has been found to improve local recurrence free survival. Patients with no TP53 mutated DNA in the surgical margins may be spared post-operative radiation therapy. Disruptive TP53 mutations predict locoregional recurrence.

Mutant TP53 could be targeted in several ways; (1) introduction of wild type TP53 inside the cancer cells, (2) reactivation of some function of wild type TP53 in mutant cancer cells, (3) degradation of mutant TP53, or (4) targeting coexisting genetic alterations such as CDKN2A deletions or PIK3CA activation to induce synthetic lethality.

CDKN2A It is associated with worse survival in recurrent metastatic HNSCC. Frequent alterations of PI3K-AKT- m TOR pathway has raised the hope for therapeutic targets. However, the results with PI3K/AKT/m TOR pathway targeting have been inconsistent.

There could be a scope for combination of PI3K inhibition with chemotherapy and/or radiation. Currently there are trials underway combining buparlisib, copanlisib and alpelisib in combination with radiation, cisplatin and/or cetuximab. mTOR inhibitors sirolimus, everolimus and temsirolimus have limited efficacy in HNSCC. Further work is needed in this area to develop effective strategies. Activated PI3K/Akt also confers resistance to MET inhibition. Therefore, combining MET/PI3K inhibition might be a good strategy. CCND1 amplification has been associated with recurrence and metastases. It may also confer resistance to cisplatin and EGFR inhibitors. CDK4/6 inhibitors abemaciclib and palbocilib are being tested in combination with cetuximab and IMRT in locally advanced HNSCC. Oral squamous cell carcinoma patients with NOTCH pathway mutations are three times more likely to die with recurrent disease. NOTCH1 mutation may sever as biomarker for identification of HNSCC with higher sensitivity to radiotherapy and chemotherapy. Activated NOTCH1 also contributes to resistance of PI3K inhibitors. NOTCH1 inhibition may enhance efficacy of conventional chemotherapeutic agents by targeting head neck cancer stem cells. Exposure to chemotherapeutic agents may lead to selection of recurrent tumors enriched in cancer stem cells. NOTCH1 inhibition may attenuate such an effect [4].

EGFR is commonly overexpressed in HNSCC [20]. It is associated with resistance to radiation therapy and chemotherapy and worse locoregional and disease-free

survival. Two agents Cetuximab a monoclonal antibody binding to the extracellular domain of EGFR and Afatinib a small anti molecule tyrosine kinase inhibitor have been approved by FDA [21, 22]. However, currently there is no biomarker to select patients for these drugs. Considerable work has been done to understand resistance mechanisms to anti-EGFR monoclonal antibodies and EGFR tyrosine kinase inhibitors. These include (1) Metabolic pathways, (2) cross talk with other signaling pathways, (3) dysregulation of EGFR pathway, (4) epithelial mesenchymal transition and nuclear translocation of EGFR. This understanding will help in overcoming EGFR resistance.

There could be several ways to augment EGFR targeting such as (1) combination of EGFR Mab and EGFR TKi, (2) Horizontal targeting multiple HER receptors, (3) Vertical targeting with inhibition of EGFR and other RTKs involved in nuclear translocation of EGFR.

MET alterations are low but important in terms of serving as a target for therapy. Several drugs are available such as tivantinib, cabozantinib, crizotinib to target MET. MET mutations are also associated with EGFR inhibitor resistance and reduced sensitivity to VEGFR TKIs. Dual VEGFR/c-MET inhibition or dual blockade of MET/EGFR could enhance efficacy.

3.2 Genomic data to improve head neck cancer prevention

We know that progression from normal epithelium to fully developed squamous cell cancer occurs through a multistep process often involving a stage of premalignant lesions. It has been found that these stages of normal epithelium, premalignant lesions and malignant lesions are not only different histologically, but are different in terms of genomics. Some earlier studies using Affymetrix Gene Chips found that progression from normal epithelium to pre-malignant lesions are associated with more transcriptional alterations than progression from pre-malignant lesions to malignant lesions. Moreover, the normal, pre-malignant and malignant lesions cluster differently. Based on this, there could be potential to classify premalignant lesions into low risk and high risk with appropriate treatment approach of aggressive treatment of high- risk lesions to prevent occurrence of HNSCC [23].

3.3 Prediction of metastases based on genomic profiling

Currently, presence or absence of neck nodal metastases is the only robust predictor of recurrence and metastases. Therefore, in most cases clinical N0 necks are addressed with surgical neck dissection. This often means treating a great majority of patients with unnecessary surgery. Currently, there is no single gene mutation or genomic profile which can predict recurrence and metastases as effectively as neck nodal status. This could be due to the fact that occurrence of metastases involves multiple genetic, molecular and metabolic pathways in addition to influence of host immune system. Genomic changes necessary for metastases may exist in majority of primary tumor at diagnosis paving the way to develop a robust metastatic gene signature.

Cromer et al. studied patients with hypopharyngeal squamous cell cancers using gene expression and found metastatic prediction accuracy of 92% using 168 gene targets [24].

Roepman et al. studied expression profiles of 82 primary oral cavity and oropharynx squamous cell cancers using 102 genes as predictors and observed predictive accuracy of 86% in comparison to clinical staging accuracy of 68% [25].

In view of the different lymphatic drainage patterns of different anatomical subsites, probably each anatomic subsite will need different genetic signature to predict nodal metastases.

Karpothiou et al. studied 18 HNSCC and corresponding node metastases and non-neoplastic tissue for RT-qPCR for EGFR, VEGF, Claudin7, Maspin, Survivin and SCCA [26]. They found differential gene expression levels in node metastases compared to the primary tumor and some correlation with prognosis.

Zevallos et al. did a retrospective study applying four molecular subtypes of HNSCC namely Basal (BA), Mesenchymal (MS), Atypical (AT) and Classical (CL) to oral cavity and laryngeal squamous cell cancers [27]. They found that early-stage oral cavity cancer with MS subtype was associated with high risk of nodal metastases. In laryngeal cancer, CL subtype was associated with worse overall survival. Oral cavity squamous cell cancers were predominantly BA and MS whereas laryngeal cancers were predominantly CL and AT subtype.

Ribeiro et al. used array comparative genomic hybridization data from HNSCC patients to develop a model to predict HNSCC recurrence/metastasis [28]. In their study of 104 HNSCC patients, this predictive model showed a good accuracy (>80%). Validation was done in an independent population from TCGA data portal. The genomic model included chromosomal regions from 5p, 6p, 8p, 9p, 11q, 12q, 15q and 17p, containing many upstream and downstream signaling pathways associated with cell proliferation and invasion. This model will need further large-scale study and has the potential to individualize clinical management and also identify potential therapeutic targets.

3.4 Survival and prognostication

There is considerable heterogeneity in the outcome of HNSCC patients with similar TNM stage. Number of studies are addressing this question. Investigators from China came out with a six gene signature (PEX11A, NLRP2, SERPINE1, UPK, CTTN, D2HGDH) using bioinformatics analysis of TCGA dataset, as a new prognostic marker for predicting survival of HNSCC patients [29]. They also did Gene Set Enrichment Analysis and found some pathways significantly enriched between high risk and low risk groups. Clinical trials testing such signature will be helpful. Reddy et al. in a meta-analysis approach identified respective differentials (tongue: 3508, laryngopharynx: 4893, oropharynx: 2386) [30]; validation in TCGA revealed markers with high incidence (altered in >10% of patients) in tongue (n = 331), laryngopharynx (n = 701) and oropharynx (n = 404). Assessment of these genes in clinical sub-cohorts of TCGA indicated that early stage tongue (MTFR1, C8ORF33, OTUD6B) and laryngeal cancers (TWISTNB, KLHL13 and UBE2Q1) were defined by distinct prognosticators. Similarly, correlation with perineural/angio-lymphatic invasion, identified discrete marker panels with survival impact (tongue: NUDCD1, PRKC1; laryngopharynx: SLC4A1AP, PIK3CA, AP2M1). Alterations in ANO1, NUDCD1, PIK3CA defined survival in tongue cancer patients with nodal metastasis (node+ ECS-), while EPS8 is a significant differential in node+ ECS- laryngopharyngeal cancers.

3.5 Genomics and surgery in HNSCC

Goal of head neck cancer surgery includes wide resection of the primary tumor, neck dissection in clinically selected patients with the goal of obtaining adequate negative margins and acceptable functional outcome. Adjuvant therapy depends upon presence or absence of certain histopathological findings like positive margins, angiolymphatic space invasion, perineural invasion, nodal metastases, nodal metastatic burden, extracapsular extension in the involved nodes. How can HNSCC genomics help in precision surgery [31]?

1. Refining indications for surgery: There is often a dilemma in early - stage oral cavity cancers that are clinically N0, whether to do elective neck node dissection. Here genomic characterization of the primary tumor might help in prediction of nodal metastases and help in selection of patients for neck dissection [32]. Similarly, negative predictive value of transcriptomic signature in early - stage oral cavity cancer might help in avoiding unnecessary neck dissection [33].

2. Surgery for pre-malignant lesions. Some premalignant lesions progress to malignant lesions. Molecular genomic studies might help to identify such lesions so that they can be resected immediately [34].

3. Some patients with oligometastatic cancer with indolent behavior might be surgical candidates. Genomic studies on tumor dormancy might help identify such patients who could benefit by metastasectomy [35].

4. Genomic prediction of radiosensitivity (discussed below) might help avoid surgery in such patients.

5. Markers of aggressiveness: Genomics might predict for occurrence of extracapsular spread in involved and hence help allocate patients for adjuvant chemoradiation [36].

6. Perineural invasion is a known pathological marker of aggressiveness. Genomic expression profile of perineural invasion indicating aggressiveness might help triage patients for appropriate adjuvant therapies after surgery [37].

7. Genomic analysis of surgical margins. In-spite of clear surgical margins about 15% patients do recur after surgery. Molecular analysis of the surgical margins might identify such patients and improve surgical resectability [38–41].

8. Many oral cavity cancers involve mandible. Mandibular resections add considerable morbidity and impair quality of life. Genomic studies might help in deciding extent of mandibular resections based on tumor tropism to involve bone [42].

9. Neoadjuvant immunotherapy is being increasing pursued in clinical trials with it's potential to real down stage the tumor and prevent metastases. This might redefine approach to surgery in near future [43–46].

10. Follow up of patients after cancer surgery: Functional genomics might help in optimizing follow of patients after curative surgical resection by identifying markers of aggressiveness. Genomic profile identification of perineural invasion might help in enhanced surveillance of such patients [47]. Patients with intratumor heterogeneity might be at risk of recurrence. Such patients can be identified prospectively [48]. Genomics may also help in prediction of loco-regional relapse. Group led by Davide Gissi analyzed DNA methylation for the following genes: ZAP70, ITGA4, KIF1A, PARP15, EPHX3, NTM, LRRTM1, FLI1, MIR193, LINC00599, MIR296, TERT, and GP1BB in the brushings from the tumor area at diagnosis and from the regenerating area 6 months after surgery in 49 consecutive patients [49]. As per a predefined cut-off value, sample was labeled as positive or negative. At diagnosis 47 out of 49 specimens were found positive. 16 out of 49 patients had positive scores at six months after resection. 7 patients relapsed and out of these 6 patients had a positive score in the regenerative area after surgery. The presence of a positive score after oral cancer treatment was the most powerful variable related to the appearance of locoregional relapse. The authors concluded that 13-gene DNA methylation analysis by oral brushing may have a clinical application as a prognostic non-invasive tool in the follow-up of patients surgically treated for oral cavity squamous cancers.

3.6 Genomics to help using radiation therapy in HNSCC

Radiation therapy is mainstay of therapy in majority of HNSCC either as an adjuvant after surgery in oral cavity cancers, as principal treatment with or without chemotherapy in non-oral cavity cancers, as palliative or salvage therapy. Currently, radiation therapy strategies are same across anatomic sites based purely on TNM stage. There are no robust biomarkers of prediction of response, resistance and outcome in HPV- HNSCC.

Genomics have the potential to guide radiation response/resistance and predict toxicities. SF2, survival fraction at 2Gy in cell lines was published by Torres-Roca et al [50].

Pramana et al. also found potential to use gene expression profiling to predict outcome after chemo-radiation in head neck cancer [51].

Radiosensitivity index has been shown to predict clinical outcome in HNSCC patients treated with chemo-radiation in clinical trials, with 2 year survival of 86% in radiation sensitive signature versus 61% in resistant signature [52].

Concept of GARD (Genomic adjusted radiation dose) was developed by Jacob Scott et al., using a gene expression based radiation-sensitivity index and linear quadratic model to derive GARD. GARD based clinical module potentially can allow individualization of radiation therapy and guide new design for genomically guided clinical trials [53].

Tumor hypoxia is known to lead to radiation resistance. Work has been to develop genomic signature to predict tumor hypoxia so that appropriate intervention strategies targeting tumor hypoxia can be developed [54].

Along the same lines immunogenomics might be used to predict outcome of radiation and immune therapies given

in different combinations. Biology based radiation adaptation trials are already going in HPV positive HNSCC.

Gene alterations can also predict radiation induced toxicity and identify patients who are super sensitive to radiation therapy. Whitney Sumner et al. analyzed 37 HNSCC patients and found that genetic alterations in RCA2, ERBB3, NOTCH1, and CCND1 were associated with higher mean grad radiation toxicity [55]. Alterations in TNFAIP3, HNF1A, SPTA1 and CASP8 were found in radiation supersensitive patients. Such an approach will help in improving therapeutic index of radiation therapy in HNSCC.

Overexpression of FOXC2, MDR1, MRP2, ERCC1. PDGF-C, NRG1, survivin are linked to treatment resistance. Amongst the miRNAs, overexpression of miR- 371a-p, miR- 34c-50, miR-1323 and downregulation of miR-324 3p, miR-93-3p, miR-4501 has been linked to radio resistance in nasopharyngeal carcinoma [56].

3.7 Genomics and chemotherapy in HNSCC

Cisplatin remains the most common chemotherapy drug used in HNSCC. However, resistance to cisplatin is common. Number of genomic correlates of cisplatin response/resistance have been identified. Sanne et al. employed an array of 21,121 pools of siRNAs targeting unique human genes in the NCBI RefSeq database and performed in vitro genome-wide functional geneticscreen to identify genes that influence the response to cisplatin in HNSCC cells [57]. By siRNA mediated knockdown, Fanconi anemia/BRCA pathway emerged as the predominant pathway for cisplatin response in HNSCC cells. Goretti Duran et al. investigated thirty-six selected single nucleotide polymorphisms (SNPs) in 29 genes in 110 patients treated with cisplatin based chemoradiotherapy and found that genetic polymorphisms with activity in intracellular detoxification (GSTP1), DNA repair (ERCC1, ERCC4, ERCC5, RAD51), and multidrug resistance-associated protein (ABCB1, ABCC1, ABCC2) affect drug toxicity in patients with head and neck who received platinumbased CRT [58]. Gene variants and haplotypes of ERCC1 were associated with the risk of developing hematologic toxicity.

Hiroyuki Shimomura et al. examined Non-SMC Condensin I Complex Subunit H (NCAPH) expression in OSCC and performed a functional analysis of human Oral Squamous Carcinoma Cells (OSCC) and found that resistance to cisplatin, carboplatin, and nedaplatin was enhanced by NCAPH in OSCC cells. NCAPH silencing combined with platinum decreased multidrug resistance [59]. There was no association between NCAPH and resistance to paclitaxel, docetaxel, and 5-fluorouracil.

Lot of studies arelooking at potential of using circulating tumor cells and circulating tumor DNA to monitor for recurrence and evolution of treatment resistance.

3.8 Genomics and immunotherapies in HNSCC

Immunotherapy is a promising approach and seems to have added a new paradigm to several cancers including HNSCC. However, with currently available immune checkpoint inhibitors, the response rate is low, very few patients derive benefit, many patients fail to respond, some patients develop hyper-progressive disease and patients may develop immune related adverse events in an unpredicted fashion.

In 2016, FDA approved anti PD1 antibodies pembrolizumab and nivolumab [60, 61]. With establishment of nivolumab and pembrolizumab in the treatment of recurrent metastatic HNSCC, there are several studies looking at different ways to combine them with established treatments like surgery, radiation therapy and chemotherapy including cetuximab. These molecules are being tested in the neoadjuvant, concurrent and adjuvant therapeutic spaces in HNSCC. pilimumab an anti- CTLA-4 antibody which works well has been shown to reverse resistance to treatment in HNSCC. Ipilimumab given after cetuximab has been shown to reverse resistance to cetuximab. It has been observed that there is increased infiltration with Treg cells following exposure to cetuximab. Ipilimumab eliminates these Treg cells. Several trials are underway looking at combinations of ipilimumab, radiation and nivolumab.

Several genomic features may influence response to immune check point inhibitors [19]. High tumor mutational burden is associated with neoepitope presentation and immune hot phenotype leading to enhanced benefit with immune check point inhibitors. NSD1 inactivating mutations, global DNA hypomethylation, aneuploidy, may lead to impaired chemokine signaling and immune effector response leading to an immune cold phenotype and low benefit from immune checkpoint inhibitors.

3.9 Genomics and drug resistance

3.9.1 Co-relation between genomic alterations and drug resistance

Several studies have found association of drug resistance and genomic alterations listed below. This knowledge might help in selecting appropriate patients for chemotherapy/drugs including targeted drugs and avoiding un-necessary treatment in those who may not benefit from it [3].

Genomic marker	Therapy resistance
TP53	Cisplatin resistance
EGFR	Radiation resistance
CCND1	Gefitinib resistance
NOTCH1	PI3K inhibitor
MET	Resistance to Cetuximab, Erlotinib
PIK3CA	Bio-radiation with cetuximab, PI3K inhibitors MET inhibitors

3.10 Genomics and radiomics

Imaging including contrast enhanced CT scan, MRI scans and recently PET scans are commonly used to accurately stage the patient at diagnosis and also to monitor response and recurrence. Radiomics based on image texture analysis has the potential to provide valuable real ime information about tumor biology and response/resistance to treatment. Studies are looking at correlation between radiomics and genomics. Group led by Kerstin Zwirner at Eberhard Karls university in Germany looked at genetic tumor profiles and radiomic features in 20 HNSCC patients treated with primary radio chemotherapy [62]. They did NGS of the tumor and corresponding normal tissue and analyzed 327 genes. TP53, FAT1 and KMT2D were the most frequently mutated driver genes in their cohort. They found good correlation between reduced radiomic intra-tumor heterogeneity and somatic mutations in FAT1 with small tumor volumes. Radiomic features of heterogeneity did not corelate with omatic mutations in TP53 or KMT2D. Radiomics and genomics remain work under progress.

4. HEAD NECK CANCER GENOMICS AND NEWER TARGETS, DRUGS AND STRATEGIES IN HNSCC

4.1 New targets, ways and drugs in HNSCC

In addition to focusing on common mutations, there are rare mutations with druggable targets worth exploring [6].

1. Rearrangement of Neutrotrophic Tropomyosin Receptor Kinase (NTRK) gene. NTRK 1,2 and 3 fusions are found in 3%, 1.6% and 3% of HNSCC in the AACR GENIE data set. Pan TRK inhibitor Larotrectinib is being tested in these patients.

2. HRAS is a farnesyl transferase substrate depending exclusively on farnesylation. HRAS mutations have been found in 4% of HNSCC patients in the GENIE data set. Tipifarnib which is highly selective inhibitor of farnesyl transferase is being tested in HRAS mutated HNSCC.

3. Antibody Drug Conjugate (ADC) are monoclonal antibodies conjugated to cytotoxic agents. Antibody targets a particular cell surface protein and the drug payload is delivered inside the cell. Several ADCs are being tested in HNSCC including ABBV-221, AVID100 which target EGFR, BAY1129980 targeting C4.4a, IMMU-132 which targets TROP-2 antigen and tisotumab vedotin targeting human tissue factor.

4. DNA damage repair. DNA damage response (DDR) pathway is a druggable target. The most glaring example is PARP inhibitors in BRCA1/2 mutated cancers. About 8% of HNSCC cases have alterations in the DDR related genes. There are several DDR pathway inhibitors targeting DNA damage signaling proteins like ATM, ATR, DNA-PK, WEE1, CHK1 and 2.

5. Tumor Mutational Burden (TMB). High tumor mutational burden is associated with increased expression of tumor specific antigens on the cancer cell surface making the cancer more immunogenic. About 25% HNSCC patients have high TMB having >20 mutations per mega-base of DNA making them susceptible to immunotherapy.

6. Dynamic Monitoring of tumor using ctDNA. As the cancer clinically evolves, it's genomic and molecular landscape changes. ctDNA are short fragments ofdouble stranded DNA shed in the blood by the tumor undergoing necrosis andapoptosis. ctDNA may have mutational profile not seen in the normal cells and could represent the changing genomic landscape of tumor in vivo. Serial monitoring of ctDNA could help in detecting early relapse and help appropriately matched therapies to be delivered in real time.

7. FGFR2 and FGFR3 fusion occurs in 1-3% of HNSCC. These patients might benefit by FGFR inhibitors. Several targeted drugs are being tested in clinical trials. Exhaustive review of these are beyond the scope of this chapter.

4.2 Molecular co-targeting strategies

HNSCC are genetically highly heterogenous. Monotherapies with targeted therapies yield modest benefit with eventual development of resistance. So, combining two or more molecularly targeted agents might emerge as effective therapy.

There could be several ways to do this; (1) targeting molecules within convergent signaling pathways, (2) targeting molecules with non-overlapping mechanisms of action, (3) targeting anti-tumorigenic molecules working synergistically with conventional chemotherapy or radiation therapy. Several clinical trials evaluating this strategy are listed below (Table 4) [5].

4.3 Molecular tumor boards in HNSCC

Most HNSCC will have complex genomes making it difficult to select therapy. This might not be corelating with traditional risk factors. There could be multiple driver mutations in a case or part of a tumor. E. g. a patient might be NOTCH1/ PIK3CA double mutant. The question could be should this patient receive a WNT pathway inhibitor or PIK3CA inhibitor or both? The treating Head neck cancer clinician will have to document the genomic data, use of targeted drugs and record longitudinal follow up of each case to further develop use of NGS data in the clinic.

Multidisciplinary involvement of head neck surgeons, geneticists, medicaloncologists, radiation oncologists, translational biologists will be integral to formulate personalized treatment approaches in head neck cancers.

Table 4. Clinical trials evaluating molecular co-targeting strategies.

Clinical trial	Intervention
NCT02124850	Cetuximab + motolimod + Nivolumab
NCT01218048	cetuximab + surgical resection + adjuvant cisplatin, carboplatin, radiation
NCT02277197	ficlatuzumab + Cetuximab
NCT 0957853	Cetuximab + anti IgG1 antibody + surgical resection
NCT 3153982	Ruxolitinib + Surgical resection
NCT02035527	Raf inhibitor + Doectaxel + cisplatin
NCT01051791	Everolimus
NCT01588431	Bevacizumab + Cetuximab
	+ Docetaxel + Cisplatin followed by radiation/surgical resection
NCT02769520	Pembrolizumab
NCT01316757	Erlotinib + Cetuximab + paclitaxel + carboplatin
NCT01016769	Temsirolimus + Paclitaxel + Carboplatin
NCT02741570	nivolumab + ipilimumab + cetuximab + cisplatin + carboplatin +5fluracil
NCT02952586	Avelumab + cisplatin + radiation
NCT02499120	Cetuximab + Palbociclib

European Society for Medical Oncology (ESMO) has a designed a scale (ESCAT) to guide the clinician to select a

novel targeted drug with highest potential of efficacy in an HNSCC patient. The most Accordingly, compelling actionable molecular alterations in HNSCC included HRAS activating mutations (tipifarnib, farnesyl transferase inhibitor), MSI, high TMB (for immune check point inhibitors), NTRK fusions (TRK tyrosine kinase inhibitors), CDKN2A inactivating alterations (CDK 4/6 inhibitors) and EGFR amplification (afatinib) [63].

4.4 Big data in HNSCC

Big data approach is being explored in head neck oncology integrating data generated from genomic studies, radiomic data generated from CT, MRI and PET scans, data generated from clinical evaluation and optical imaging, data generated from radiation therapy response and toxicity and integration of all other nongenetic data such as epidemiology, diet, habits, stress, socioeconomic factors etc. There is a multicentric study BD2Decide (Big Data Models for personalized head neck cancer decision support) going on to explore Big Data approach. Three main goals for Big Data in HNSCC will be 1) support and augment clinical decisions, 2) generate new knowledge, 3) develop guidelines for HNSCC prevention and management [64].

5. CONCLUSIONS

HNSCC is genomically unstable. TCGA has identified key alterations in tumor suppressor genes and oncogenes in HNSCC. TP53 alteration is a key player in HNSCC tumorigenesis and biology. Principally loss of tumor suppressor drives tumorigenesis than oncogene addiction in HNSCC, however, a small subset of oral cavity cancer may be driven by mutations rather than loss of tumor suppressor gene function. Tumor heterogeneity is prominent in HNSCC and is a major challenge in developing effective therapies. Biologic classifier of HNSCC remains to be implemented in the clinic. Clustering of HNSCC according to multi-omics studies may be more clinically meaningful. Immune therapy is a major treatment paradigm in oncology in general including HNSCC. Corelative genomics and immune contexture will help realize the full potential of this approach. Sufficient indication exists linking major genomic alterations in HNSCC and clinical behavior including performance of conventional treatments. Opportunity exists to leverage this knowledge to fine tune currently existing surgical, radiation and chemotherapeutic approaches. EGFR targeting remains important in HNSCC in spite of lack of predictive biomarker and eventual treatment resistance. Mutli-omics studies have shed light on resistance to EGFR targeting and novel ways to target EGFR axis. Several studies are addressing genomically targeted monotherapies, molecular co targeting strategies and ways to escalate and deescalate treatment intensity based on biology. Time has come to implement molecular tumor boards in HNSCC regularly. BIG data approach will certainly help design multi-pronged approach to control HNSCC globally. Tissue repositories, participation in clinical trials and multi-institutional collaboration remains critical to further progress.

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Analysis Of Delay in initiation of Chemotherapy after Admission to Day Care Unit of Tertiary Cancer Institute

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ABSTRACT

Patients & Methodology: A survey of those patients admitted for elective chemotherapy was conducted for three months from 01 Jan 2021 to 31 Mar 2021 in day care chemotherapy units in National Cancer Institute, Nagpur. Time taken for various processes from the time of patient's arrival in the ward till the time of initiation of chemotherapy was noted. The difference in time between processes was analyzed. Findings: 16% of the chemotherapy were started within one hour of admission, 37% within 2 hrs, 25% within 3 hrs., and 22% chemotherapy was initiated after 3 hrs. of admission. 78% of the chemotherapy in the institute was started within the institutional benchmark of 3 hrs. CONCLUSION: Reducing waiting time between patient admission and initiation of chemotherapy is a big challenge in any cancer institute due to involvement of multiple processes, departments, and people. It directly affects operations, bed occupancy and turnaround time in daycare center, and ultimately patient satisfaction. Identifying the causes for delay and application of lean techniques will optimize the time taken for initiation of chemotherapy and improve patient satisfaction.

KEYWORDS : Chemotherapy, Daycare Unit, Delay in initiation of Chemotherapy

INTRODUCTION

Chemotherapy is an integral part of comprehensive cancer treatment. Cancer patients often experience delays in starting scheduled inpatient chemotherapy after admission in the day care centers . This compromises the quality, patient satisfaction and has a negative impact on reputation of the treating hospital.

The advantages of day care chemotherapy are compelling for the bulk of patients and the advantages of day care chemotherapy far out weighs the disadvantages. Day care chemotherapy centers are designed and equipped for patients who require short therapies or procedures that does not warrant over-night stay in the hospital. The advantages are [2] Drugs can be administered safely and easily Patients wish to avoid admission to hospital is respected. When not admitted overnight the patients feel safe and it strengthens their physical and psychological well-being. The treating Oncologist supervises and controls the administration of chemotherapy. Hospitalization expenses and overnight stay can be avoided. Chemotherapy is administered at patient's convenience.

Other advantages include: - Routine activities of a patient and their families remain mostly undisrupted.

1. There is easy availability of highly trained oncologists, pain & palliative care specialists, and other oncology trained medical and paramedical staff including onconurses, rehabilitation specialists, dieticians, and pharmacist to attend to the patients.

2. There is no need for boarding and lodging for those coming with the patient from faraway places, patients can be sent home on the same day.

3. Day c are also minimizes the chance of Hospital Acquired Infections (HAIs) and the patients can remain with their near and dear ones while undergoing chemotherapy.

Disadvantages of day care chemotherapy are mainly related to patient condition.

1. Hospitalized chemotherapy will be ideal in cases of patients requiring very high dose Cisplatin or Methotrexate protocols, specialized procedure chemotherapy, Acute Leukemia Induction Therapy, high dose chemotherapy with or without stem cell or bone marrow transplantation, chemotherapy with severe emesis, therapy with Ifosfamide, treatment involving combination of radiation and chemotherapy regimens, patients with medical comorbidities, complex chemotherapy regimens, chemotherapy scheduled during hospitalization for an unrelated illness, administration of drugs with complex side effects, intraperitoneal chemotherapy, certain investigational treatment protocols, and when chemotherapy is mandatory with medical conditions that would ordinarily post pone chemotherapy .

2. Cancer patients reporting for chemotherapy regularly experience long waiting in initiation of scheduled inpatient chemotherapy after arrival to the hospital day care unit. These delays have the potential to impair the quality of care, increase the burden of resource utilization on the hospital and ultimately leads to suboptimal patient satisfaction.

3. Chemotherapies are generally protocol based and are repeated in cyclic intervals. Delays in initiation of chemotherapy in day care centre are not liked by the patients and the relatives in general as it goes against their planning for the day. Hence, it is pertinent that, there is a great responsibility on the part of the day care centre to provide safe and timely chemotherapy to the admitted patients.

4. Reducing waiting time between patient admission and initiation of chemotherapy is a big challenge in any cancer institute due to involvement of multiple processes, departments, and people. It directly affects operations, bed occupancy and turn-around in a day care center and eventually patient satisfaction. Prolonged hospital length of stay (LOS) is also associated with increased risk of HAIs

5. Once the treating oncologist takes the decision for chemotherapy, the patient reports to the hospital at a scheduled date and time. The operations often encounter planning problems when there is a steady increase in the new patients with existing patients for chemo therapy

Every step in this process involves expert and intensive involvement of trained manpower and has the potential for delay due to their involvement in other activities. There are also situations when the condition of the patient does not allow them to undertake the chemotherapy, which is likely to affect the patient's health adversely.

These processes, if not monitored and intervened timely are likely to delay the initiation of chemotherapy post admission to the day care unit, resulting in prolonged waiting time and also adversely affecting patient satisfaction.

A careful analysis of these processes will ascertain wasteful moves and paves the way for lean thinking. Lean doctrine emphasizes that, regardless of the number of attempts made to improve a process, there will be further scope for improvement. Small changes that occur due to incremental steps taken for improvement of an existing process slowly leads to perfection. The plan do-study-act cycle when used suitably does help in any effort towards perfection.

Our institute is a highly advanced cancer center, which caters for cancer patients of a vast area in Central India. It offers chemotherapy, immunotherapy, hormonal therapy, radiotherapy, and surgery as treatment for cancer patients of all age group. Decreasing the length of stay is of top-priority objective for all health care establishments. Even though there is no benchmark available, literature suggests that a chemotherapy regimen should be initiated within 4 hours of admission.

This survey is to audit and identify the causes for delay in initiation of chemotherapy post- admission to a day care unit in a tertiary cancer hospital and determine the avoidable delays in post-admission processes and discuss the application of appropriate lean methods to reduce this delay in initiation of chemotherapy after admission as well as to improve patient satisfaction.

OBJECTIVE.

The objective of the project is to perform a survey to identify the causes for delay in initiation of chemotherapy after admission in a day care unit at National Cancer Institute, Nagpur.

This included:

1. Study of the process of chemotherapy administration

2. Audit of the timeline from admission to administration of chemotherapy and timeline of all the in between processes from ward records.

3. Identification of all possible causes of delays. Determining the possible interventions to avoid / reduce delay in initiation of chemotherapy.

4. Application of lean methods to reduce delay in initiation of chemotherapy after admission to a day care unit to improve patient satisfaction.

MATERIALS & METHODS.

Adult patients admitted for chemotherapy in the hospital day care center and chemotherapy ward were included in the study. Paediatric patients, and those admitted for surgery, long chemotherapy (>12 hrs.), supportive care or ICU were not included in the study.

On admission to the hospital for chemotherapy, the Operations executive of the ward filled in a chemotherapy tracker form designed for this purpose and was loaded on to an MS Excel sheet for data analysis.

Five hundred such records of patients those who had undergone chemotherapy in day care units w.e.f 01 Jan 2021 to 31 Mar 2021 were randomly selected with the help of RAND function in MS Excel and audited.

The data was cleaned and formatted. Name of the patient, date & time of admission, time of patient arrival in the ward, time of initiation of chemotherapy were noted. The differences in time between various processes starting from admission till initiation of chemotherapy were analyzed. We set an institutional standard reference time) for each process, based on evidence from literature and practice and calculated the variation from the set standards. Reasons for delay were divided into various categories.

The difference between the time of initiation of chemotherapy and the time of patient arrival in the ward was calculated. 3 hours was taken as the institutional benchmark Initiation of chemotherapy after 3 hours of patient's arrival in the ward was considered as delay in commencement of chemotherapy.

Common causes for delay in initiation were identified, and lean methods to improve the processes that contribute to the delay are discussed.

FINDINGS.

1. Timing for various processes from admission to initiation of chemotherapy was documented by the nurse / operations executive in the day care wards.

2. The average duration of chemotherapy was 4 hrs. and 19 mins, and the most frequent chemo infusion duration was 2 hrs.

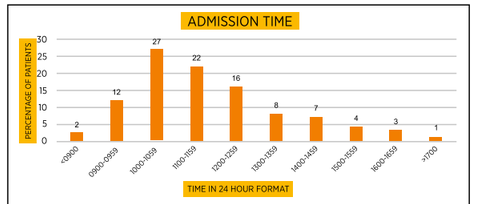

Fig 2. Admission Time In Daycare Wards - 77% of admission were between 0900-1300 hrs.

3. The average time for various processes after admission to the day care centre are as Follows

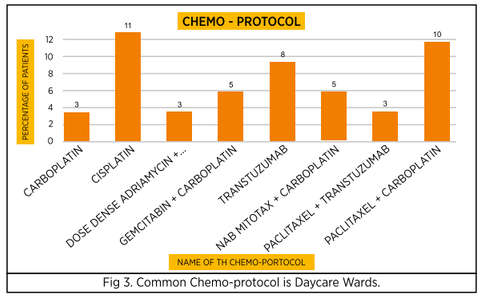

Fig 3. Common Chemo-protocol is Daycare Wards.

4. Average time between admission and finalization of lab reports was 1 hour and 34 minutes.

5. Average time between admission and preparation of chemo protocol was 1 hour and 25 minutes.

6.Average time between protocol preparation and pharmacy indenting was 45 minutes

7. Average time between pharmacy indenting and arrival of drugs 46 minutes.

8. Average time between arrival of drugs and initiation of chemotherapy was 44 minutes.

9. Average time from admission to hospital and initiation of chemotherapy was 2 hrs. and 11 minutes.

10. It was found that 39% percent of the admissions took place between 9 – 11 a.m. and 61% admissions to daycare units occurred by 12 noon

11. It was also found that 48% of the chemotherapy drugs consisted of Cisplatin, Paclitaxel, Carboplatin, Transtuzumab and Gemcitabin, either as a single drug or in combination

12. The relevant lab reports to start the chemotherapy in day care was already available with 78% of the patients. Of the remaining, 20% of them got their blood investigations done on the day of admission on daycare basis. 2% patient's data was not available

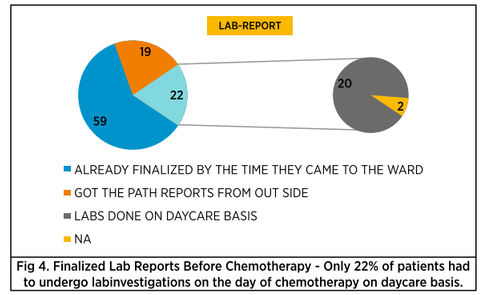

Fig 4. Finalized Lab Reports Before Chemotherapy - Only 22% of patients had to undergo labinvestigations on the day of chemotherapy on daycare basis.

13. Of the 20% patients whose investigations were done on daycare basis, 37% reports were made available between 1200 – 1300 hours daily and 90% of the reports were made available before 1400 hours on the day of admission.

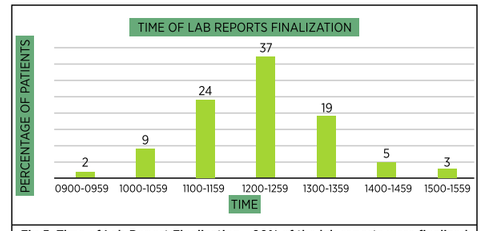

Fig 5. Time of Lab Report Finalization - 80% of the lab reports were finalized between 1100 - 1440 hrs.

14. Almost 66% of the patient's chemotherapy infusion duration was between 2-6 hrs.

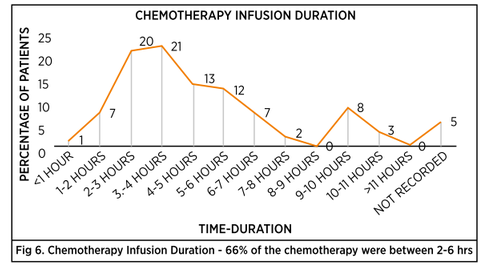

Fig 6. Chemotherapy Infusion Duration - 66% of the chemotherapy were between 2-6 hrs

15. About 55% of the indents were placed between 1000 – 1200 hrs.

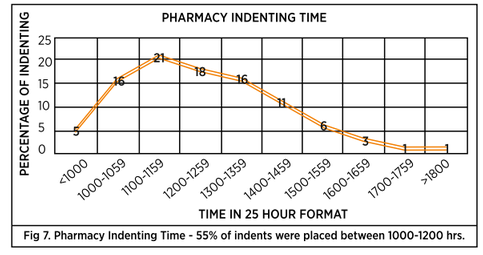

Fig 7. Pharmacy Indenting Time - 55% of indents were placed between 1000-1200 hrs.

16. Chemo protocol was already available with 51% of the patients and about 37% of the remaining patient's protocol was prepared between 1200 – 1400 hrs.

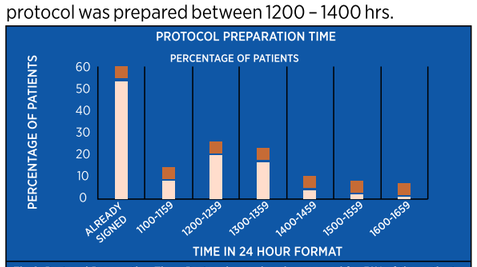

Fig 8. Protocol Preparation Time. Protocol was already prepared for 51% of the patients.

17. 60% of the ward pharmacy indent was received between 1200 – 1500 hr.

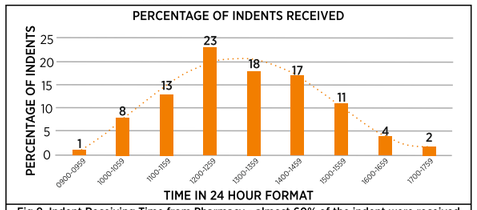

Fig 9. Indent Receiving Time from Pharmacy - almost 60% of the indent were received between 1200-1500 hrs.

18. Chemotherapy was initiated in 50% of the patients before 1400 hrs. and the rest of the 50% after 1400 hrs. Less than 5% chemotherapy was stated before 1100 hrs. and after 1700 hrs. 82% of the chemotherapy started between 1200 – 1700 hrs.

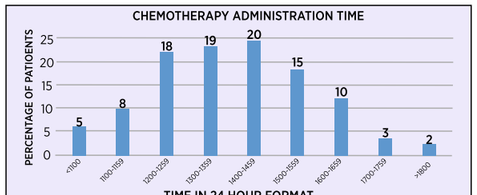

Fig 10.Chemotherapy Administration Time - 82% of the chemotherapy were administrated between 1200-1700 hrs.

19. Sixteen percent (16%) of the chemotherapy were started within one hour of admission and about 22 % chemotherapy was initiated after 3 hrs. of admission. 37% were administered chemotherapy within 2 hrs. of admission and 25% within 3 hrs.

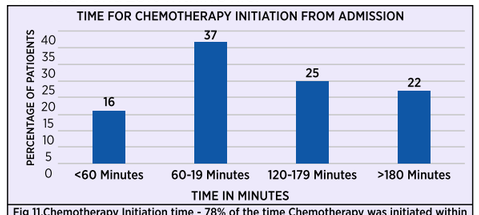

Fig 11.Chemotherapy Initiation time - 78% of the time Chemotherapy was initiated within the institutional benchmark which available international timings.

20. Out of 110 patients whose chemotherapy was delayed more than 3 hrs., 80 patient's reason for delay was available in the records. Out of them 24% of the time the delay was due to delay in preparation & availability of protocol and 16% of the time the delay was related to establishment of Intravenous access. Out of the 16%, dificulty in accessing a peripheral line was 5% of the time, 5% of the time the delay was due to requirement of central venous access and another 6% of the time the delay was due to want of insertion of chemo port or a Peripherally Inserted Central Line (PICC).

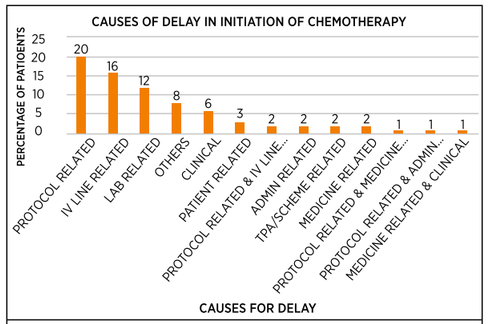

Fig 12.Common causes for delay in initiation of chemotherapy.Most common causes of delay was related to protocol preperation and signing followed by establishment of intravenous access.

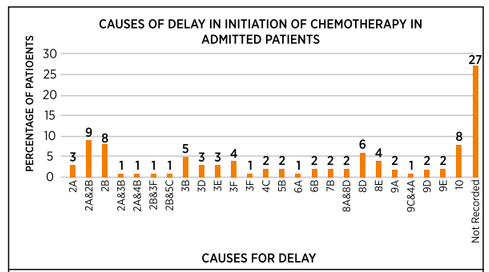

Fig 13. Common causes for delay in initiation of chemotherapy. Out of 110 recorded delays (More than 3 hrs. of delay), causes were in 80 patients. The numbers assigned are various reasons related to the causes of delay (Table 2)

Table 1: Benchmark - Institutional Standard Reference Time for Various Processes in Chemotherapy administration

Process Time	Benchmark-Institutional Reference Time (in Minutes)
Time between admission and finalization of lab reports.	Within 60 minutes after admission
Time between admission and preparation of chemo protocol	Within 45 minutes after admission
Time between protocol preparation and pharmacy indenting	Within 15 minutes after preparation of protocol
Time between pharmacy indenting and arrival of drugs	Within 45 minutes after indenting
Time between arrival of drugs and initiation of chemotherapy	Within 15 minutes after receiving the drugs from pharmacy
Total time from admission to hospital and initiation of chemotherapy	Within 180 minutes after admission to day care ward

Table 2: Causes for Delay in Initiation of Chemotherapy

Assigned Number	Causes for Delay	Related Reasons
1	Nurse Related	a. Bed not prepared b. Nurse busy with an emergency/another patient
2	Protocol related	a. Not prepared b. Not Signed c. Wrong Protocol
3	IV line related	a. Waiting for anesthetist/surgeon b. Difficult to get IV line c. PICC/Chemo port/Central line dressing d. PICC line insertion e. Chemo port insertion f. Central line insertion
4	Medicine related	a. Delay in indenting b. Delay in supply c. Medicines Not Available
5	Admin related	a. Patient Care Attendant (PCA) Not available b. Waiting for old documents from Medical Records Department (MRD) c. Consent not obtained
6	Patient related	a. Patient not on bed b. Patient having meals
7	TPA/SCHEME related	a.MJPJAY/PMJAY (State/Central Govt Schemes) b. MPKAY (Departmental Scheme) c. CGHS (Central Govt Employees Scheme)
8	Lab related	a. Abnormal CBC b. Abnormal Creatinine c. Abnormal SGOT/SGPT d. Reports not made ready e. Reports Not available
9	Clinical	a. High BP b. Low 8P c. Low RBS d. High RBS e. Vitals not stable
10	Others (Specify)	Any other reason not covered in the above list

Table 3: Chemotherapy Infusion Duration

Sample Size (n)	476
Mean	4 hrs, 19 mins
Median	3 hrs, 30 mins
Mode	2 hrs
Standard Deviation	2 hrs, 28 mins
Minimum	20 mins
Maximum	12 hrs, 50 mins
Range	12 hrs, 30 mins

Table 4: Descriptive Statistics of Time Measures of Various Processes in Chemotherapy. This is compared with Institutional Benchmark.

Statistic	Time between admission and finalization of lab-reports	Time between admission and preparation of chemo protocol	Time between protocol preparation and pharmacy indenting	Time between and pharmacy Indenting arrival of drugs	Time between arrival of drugs and Initiation of chemotherapy	Total time from admission to hospital and initiation of chemotherapy
Sample Size (n)	97	244	492	495	488	500
Institutional Benchmark	1 hr	45 mins	15 mins	45 mins	15 mins	3 hrs
Mean	1 hr 34 mins	1 hr 25 mins	45 mins	46 mins	44 mins	2 hrs & 11 mins
Median	1 hr.& 29 mins	1 hr & 17 mins	22 mins	43 mins	20 mins	1 hr & 52 mins
Standard Deviation	50 mins	1 hr & 3 mins	53 mins	25 mins	1 ht & 8 mins	1 hr & 25 mins
Minimum	8 mins	1 min	O mins	0 mins	2 mins	10 mins
Maximum	5 his & 9 mins	5 hrs & 30 mins	6 hrs & 10 mins	3 hrs & 52 mins	13 hrs & 30 mins	14 hrs & 10 mins
Range	5 hrs & 1 min	5 hrs & 29 mins	6 hrs & 10 mins	3 hrs & 52 mins	13 hrs & 28 mins	14 hrs

Table 5: Benchmark - Institutional Standard Reference Time for Various Processes in Chemotherapy administration

Process Time	Benchmark	Average	Min	Max
Time between admission and finalization of lab reports.	1 hr	1 hr, 34 mins	8 mins	5 hrs, 9 mins
Time between admission and preparation of chemo protocol	45 mits	1 hr, 25 mins	1 min	5 hrs, 30 mins
Time between protocol preparation and pharmacy indenting	15 mins	45 mins	0 min	6 hrs, 10 mins
Time between pharmacy indenting and arrival of drugs	45 mins	46 mins	0 min	3 hrs, 52 mins
Time between arrival of drugs and initiation of chemotherapy	15 mins	44 mins	2 mins	13 hrs, 30 mins
Total time from admission to hospital and initiation of chemotherapy	3 hrs	2 hrs,11 mins	10 mins	14 hr, 10 mins

Table 6: Outliers in the Data Set

Process Time	Sample Size	Q1	Q3	IQR of Outliers	Upper Limit of Outliers	Number	Percentage
Time between admission and finalization of lab reports	97	1 hr, 6 mins	1 hr, 53 mins	47 mins	3 hrs, 3 mins	5	5%
Time between admission and preparation of chemo protocol	244	32 mins	2 hrs, 4 mins	1 hr,32 mins	4 hrs, 22 mins	4	2%
Time between protocol preparation and pharmacy indenting	492	13 mins	57 mins	44 mins	2 hrs, 3 mins	47	10%
Time between pharmacy indenting and arrival of drugs	495	29 mins	1 hr	31 mins	1 hr, 46 mins	11	2%
Time between arrival of drugs and initiation of chemotherapy	488	13 mins	50 mins	37 mins	1 hr, 45 mins	51	10%
Total time from admission to hospital and initiation of chemotherapy	500	1 hr, 13 mins	2 hrs, 50 mins	1 hr,37 mins	5 hrs, 15 mins	14	3%

Table 7: Time for Chemotherapy if Outliers (3%) were to be not considered

Statistic	Total time from admission to hospital and initiation of chemotherapy	Total time from admission to hospital and initiation of chemotherapy
Outliers Present	Yes	No
Sample Size (n)	500	486
Institutional Benchmark	3hrs	3hrs
Mean	2hrs & 11mins	2hrs & 3mins
Median	1hrs & 52mins	1hrs & 5mins
Standard Deviation	1hrs & 25 mins	1 hrs & 5mins
Minimum	10 mins	10 mins
Maximum	14 hrs & 10 mins	5 hrs & 15 mins
Range	14 hrs	5hrs & 5mins

Table 8 : Chemotherapy Processes, Stakeholders, Departments, Equipment		
Process	**People**	**Department & Equipment**
Blood Sample collection	Phlebotomist	Lab
Blood Sample Transportation to Lab	Office Assistant/PCA	IPD
Height, Weight, Vitals Checking	Nurse	IPD-Weighing Machine, BP Apparatus, Stethoscope, Thermometer, Stadiometer, Pulse Oximeter
Consultation & Protocol Preparation	Oncologist	OPD/IPD
Admission/Discharge	Data Entry Operators/Operations Executive	Front Desk, Operations - Computers, HIMS, IT Dept
Allotment of Beds	Ward/Floor Executives	Operations
Patient Examination	RMO/Registrar	IPD-Stethoscope, BP Apparatus, Pulse Oximeter
IV Access	Nurse/Anaesthesiologist/Surgeon	IPD/OT-Chem-port / PICC Line / CVP Line/ USG Machine
Placement of Indent	Nurse	Computers (HIMS) / IT Dept
Supply of Medicines	Pharmacist	Central Drug Store, HIMS, IT Dept
Arrival of Medicines	Office Assistant/PCA	Central Drug Store/IPD
Administration of Drugs	Nurse	IPD
Patient Help	PCA/House Keeping	IPD
Fetching Patient's Old File	Office Assistant/PCA	Medical Records Department
Insurance/Govt Schemes	Front Desk & Billing Executives	TPA/Billing Dept
Patient Food & Beverages	F & B Executives	F & B Dept

SUMMARY & RECOMMENDATIONS.

In summary, reducing waiting time between patient admission and initiation of chemotherapy is a big challenge in any cancer institute due to involvement of multiple processes, departments, and people. It directly affects operations, bed occupancy and turnaround time in day care center and ultimately patient satisfaction. Identifying the causes for delay can be accomplished by dividing the processes involved in chemotherapy administration and by tracking the time taken for each of the processes.

Recommendations:-

The following lean methods will help in reducing the time taken to initiate chemotherapy after admission to day care centre.

- Establishing a satellite lab near the daycare centre to improve TAT.
- Finalization of protocol before scheduling patients, authorizing the Registrars to initiate chemotherapy based on oncologists notes and advice.
- Discouraging unscheduled chemotherapy.
- Dedicated indenting nurse.
- Dedicated chemo drugs dispensing team in central drug store / pharmacy will ensure fast and safe dispensing of medicines.
- Adequate stocking of relevant chemo and adjuvant drugs, having them as ward stock and replenishing them as and when they get expended.
- Dedicated chemo drug administration nurse or pharmacist.
- Dedicated Chemo-Officer, preferably an oncologist to be in-charge for all the protocolized chemotherapies of the day. These recommendations can be of immense benefit in an institutional setup and can avoid delays and dissatisfactions.

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A study to assess the effectiveness of Structured teaching program on Knowledge regarding prevention of Breast cancer and cervical cancer among Staff nurses in National Cancer Institute, Jamtha, Nagpur

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ABSTRACT

Introduction: Breast and cervical cancers are the two most common women's cancers worldwide. Countries have invested for decades in early detection programs for breast and cervical cancer through screening, community education, and opportunistic case detection by health professionals. However, effectiveness in low- and middle-income countries has been limited due to low coverage, insufficient laboratory capacities for diagnosis, health information systems that are not designed to track patients or monitor program performance, barriers that inhibit women's uptake of services, and inadequate treatment options.

Aim: The aim of the study is to assess the effectiveness of structured teaching program on knowledge regarding prevention of breast cancer and cervical cancer among staff nurses in National Cancer Institute (NCI), Jamtha, Nagpur.

Objectives: The objectives of the study were to assess the pre-test knowledge regarding prevention of breast cancer and cervical cancer, to assess the effectiveness of structured teaching program on knowledge regarding prevention of breast cancer and cervical cancer, to assess the post-test knowledge regarding prevention of breast cancer and cervical cancer, and association of knowledge score with selected demographic variables.

Material and Method: The research design used in this study is experimental design. One-group pre-test post-test design is used; the samples were 150 staff nurses which fulfill the inclusion criteria. Setting of the study was NCI, Jamtha, Nagpur.

Conclusion: There was a significant increase in the knowledge of staff nurses after the introduction of structured teaching programme on knowledge regarding prevention of breast cancer and cervical cancer among staff nurses "t"-value was applied and "t"-value was calculated; post-test score was significant higher at 0.05 level than that of pre-test score. Thus, it was concluded that structured teaching program on prevention of breast cancer and cervical cancer was found effective. Hence, based on the above cited findings, it is clear that the structured teaching programme helped the staff nurses to improve their knowledge regarding prevention of breast cancer and cervical cancer.

KEYWORDS: Assess, breast cancer, cervical cancer, staff nurses

INTRODUCTION

Breast and cervical cancers are the two most common women's cancers worldwide. Countries have invested for decades in early detection programs for breast and cervical cancer through screening, community education, and opportunistic case detection by health professionals. However, effectiveness in low- and middle-income countries has been limited due to low coverage, insufficient laboratory capacities for diagnosis, health information systems that are not designed to track patients or monitor program performance, barriers that inhibit women's uptake of services, and inadequate treatment options. Even where some screening activities exist, there has not been sufficient attention to ensuring completion of appropriate diagnosis and treatment after women receive a positive screening test result or report symptoms suggesting cervical or breast cancer. Because of this failure to provide adequate follow-up care, these women miss the potential benefit from early detection and have a higher than average risk to develop cancer or progress to more advanced cancer stages that could have been avoided.[1]

Cervical cancer is a deadly disease once it reaches the invasive stages, but out of all the female genital tract cancers, it is the only preventable cancer if detected at its early stages. Population-based screening with Pap smear is an important secondary preventive measure for cervical cancer that leads to a high cure rate among cervical cancer patients. The facilities to carry out Pap smear are available in the institute where the study has been carried out. Furthermore, under the National Cancer Control Programme, screening camps for early detection of cervical cancer are organized in various regions of Gujarat at regular intervals by the Gujarat Cancer Research Institute which is one of the regional cancer care institutes of India.[2]

PROBLEM STATEMENT

"A study to assess the effectiveness of structured teaching program on knowledge regarding prevention of breast cancer and cervical cancer among staff nurses in National Cancer Institute (NCI), Jamtha, Nagpur."

OBJECTIVES

The objectives of the study were as follows:

• To assess the pre-test knowledge regarding prevention of breast cancer and cervical cancer

• To assess the effectiveness of structured teaching program on knowledge regarding prevention of breast cancer and cervical cancer

• To assess the post-test knowledge regarding prevention of breast cancer and cervical cancer

• Association of knowledge score with selected demographic variables.

HYPOTHESIS

• H0 – There will be no significant difference in pre-test and post-test knowledge score regarding prevention of breast cancer and cervical cancer among staff nurses

• H1 – There will be a significant difference in pre-test and post-test knowledge score regarding prevention of breast cancer and cervical cancer among staff nurses.

METHODOLOGY

In this study, descriptive research design was used. The samples were 150 staff nurses. Setting of the study was surgical NCI, Jamtha, Nagpur, and sampling technique was non-probability convenience sampling technique. Inclusion criterions staff nurses present at the time of data collection. Exclusion criteria, staff nurses those who are absent were excluded from the study. Structured questionnaire was used to assess the knowledge of staff nurses in NCI. For this study, we have used structured teaching program[3].

RESULTS

The present study has been taken up to the knowledge of the staff nurses in prevention of breast cancer and cervical cancer. Analysis and interpretation are based on the objectives of the study. A structured questionnaire used for data collection.

• According to Table 1, the age in years reveals that majority of the finding 98 (65.33%) were belonging to the 20–30 years and it followed by 34 (22.66%) were belonging to the 31–40 years, 12 (8%) were belonging to the 41–50 years, and 6 (4%) were belonging to the 50 years and above.

• According to Table 1, the gender reveals that majority of the finding 136 (90.66%) belonging to the female and followed by minority of the male 14 (9.33%)

• According to Table 1, the qualification status reveals that majority of the finding 80 (53.33%) were GNM/RGNM and it followed by 44 (29.33%) were ANM nursing, 23 (15.33%) were B.Sc./PBBSc nursing, and 3 (2%) were MSc (Nursing).

• According to Table 1, the marital status reveals that majority of the finding 89 (59.33%) were married and it followed by 57 (38%) were unmarried, 4 (2.66%) were widow/widower, and 0 (0%) divorced and separated.

• According to Table 1, the residence reveals that majority of the finding 59 (39.33%) were semi-urban, it followed by 46 (33.66%) were rural and it followed by 45 (30%) were urban

• According to Table 1, the year of clinical experience at NCI reveals that majority of the finding 61 (40.66%) were belonging to the 3–4 years, and it followed by 57 (38%) were belonging to the 1–2 years, 17 (11.33%) were belonging to the more than 4 years, and 15 (10%) were belonging to the <1 years.

• According to Table 1, the religion reveals that majority of the finding 89 (59.33%) were Hindu, and it followed by 59 (39.33%) were Buddhist, 2 (1.33%) were Christian, and 0 (0%) were Muslim 0 (0%) were others.

• According to Table 1, the type of family reveals that the majority of the finding 81 (54%) were nuclear family, followed by 63 (42%) were joint family and 6 (4%) were extended family[4].

• According to Table 2 and Figure 1, the findings show that majority of the staff nurses 78 (52%) had average knowledge, and 52 (34.66%) had poor knowledge, 20 (13.33%) of staff nurses had good knowledge, and none of the sample 0 (0%) had very good or excellent knowledge. The mean pre-test score was 15.86 and SD was 3.66.

• The findings show that majority of the staff nurses 75 (50%) had very good knowledge, 59 (39.33%) had excellent knowledge, 16 (10.66%) had good knowledge, and 0 (0%) had poor knowledge and average knowledge. The mean post-test score was 39.98 and SD was 2.47[4].

Table 1: Percentage wise distribution of staff nurses according to their demographic characteristics

Demographic variables	Frequency (n)	Percentage (%)
Age in years		
20–30 years	98	65.33
31–40 years	34	22.66
41–50 years	12	8
50 years and above	6	4
Gender		
Male	14	9.33
Female	136	90.66
Qualification		
ANM	44	29.33
GNM	80	53.33
B.BSC/PBB.SC nursing	23	15.33
M.Sc. nursing	3	2
Marital status		
Married	89	59.33
Unmarried	57	38
Widow	4	2.66
Divorcee	0	0
Separated	0	0
Residential area		
Urban	45	30
Semi-urban	59	39.33
Rural	46	30.66
Years of experience at NCI		
<1 year	15	10
1–2 years	57	38
3–4 years	61	40.66
More than 4 years	17	11.33
Religion		
Hindu	89	59.33
Muslim	0	0
Buddhist	59	39.33
Christian	2	1.33
Other	0	0
Types of family		
Nuclear	81	54
Joint	63	42
Extended	6	4

Significance of difference between knowledge scores in pre- and post-test of staff nurses in relation to the prevention of breast cancer and cervical cancer.

According to Table 3, the overall mean knowledge scores of pre-test and post-test reveal that post-test mean knowledge score was higher 39.98 with SD of ±2.47 when compared with pre-test mean knowledge score value which was 15.86 with SD of ±3.66.

The statistical Student's paired t-test implies that the difference in the pre-test and post-test knowledge score found to be 54.53 statistically significant at 0.05% level. Hence, it is statistically interpreted that structured teaching program on knowledge regarding prevention of breast cancer and cervical cancer was effective. Thus, H1 is accepted and H0 is rejected.

From Table 4, qualification of staff nurses has significant effect on awareness regarding prevention of breast cancer and cervical cancer[4].

All other demographic variables have no significant association of knowledge score of staff nurses in relation to prevention of breast cancer and cervical cancer.

Table 2: Assessment of pre-test and post-test knowledge of staff nurses regarding prevention of breast cancer and cervical cancer

Knowledge score	Score range	Pre-test F (n)	%	SD	Post-test F (n)	%	SD
Poor	0-10	52	34.66		0	0	
Average	11-20	78	52	3.66	0	0	
Good	21-30	20	13.33	16	10.66		
Very good	31-40	0	0		75	50	2.47
Excellent	41-50	0	0		59	39.33	

Table 3: Analysis of effectiveness of structured teaching program on knowledge regarding prevention of breast cancer and cervical cancer among staff nurses, n=150

Overall	Mean	SD	Mean percentage	t-value	P-value
Pre-test	15.86	3.66	31.66	54.53	0.0001*HS
Post-test	39.98	2.47	79.96		p<0.05

Table 4: Association of post-test knowledge regarding prevention of breast cancer and cervical cancer among staff nurses with selected demographic variables, n=150

Demographic variables	Df	Chi-square	Level of significance	Significance
Age	6	5.76	P=0.45 P>0.05	NS
Gender	2	0.002	P=0.99 P>0.05	NS
Qualification	8	15.25	P=0.50 P<0.05	Significant
Marital status	6	5.39	P=0.49 P>0.05	NS
Residential area	6	6.55	P=0.36 P>0.05	NS
Years of experience at NCI	6	10.74	P=0.60 P>0.05	NS
Religion	8	6.34	P=0.60 P>0.05	NS
Family type	6	6.35	P=0.38 P>0.05	NS

In the study, qualification of staff nurses has significant effect on awareness of disease.

DISCUSSION

Finding of the study was based on the objective of the

study qualification of staff nurses has significant effect on awareness regarding prevention of breast cancer and cervical cancer. All other demographic variables have no significant association of knowledge score of staff nurses in relation to prevention of breast cancer and cervical cancer. In the study, qualification of staff nurses has significant effect on awareness of disease. Mean standard deviation and mean score percentage values are compared and t-test is applied at 5% level of significance. The tabulated value for n = 150

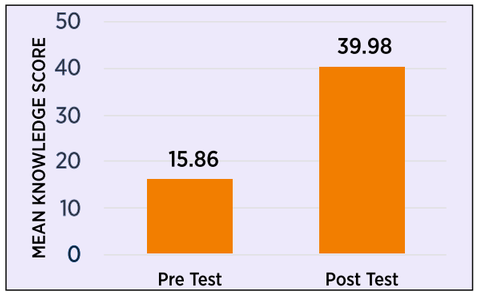

Figure 1: Bar diagram showing significance of difference between knowledge scores in pre- and post-test of staff nurses in relation to the prevention of breast cancer and cervical cancer

−1, that is, 59° of freedom was 8.00. The calculated value was respectively for the knowledge regarding prevention of breast cancer and cervical cancer; the calculated "t" value is much higher than the tabulated value at 5% level of significance which is statistically acceptable level of significance in addition; the calculated "P" value for all the areas of knowledge regarding prevention of breast cancer and cervical cancer was 0.000 which is ideal for any population. Hence, it is statistically interpreted that the structured teaching program regarding prevention of breast cancer and cervical cancer was effective. Thus, the H0 is rejected and H1 is accepted that there is a significant difference between pre-test and post-test knowledge score of staff nurses regarding prevention of breast cancer and cervical cancer which is measured by structured questioner at level of significance, P < 0.05.[4]

CONCLUSION

After the detailed analysis, this study leads to the following conclusion:

There was a significant increase in the knowledge of staff nurses after the introduction of structured teaching programme on knowledge regarding prevention of breast cancer and cervical cancer among staff nurses "t"-value was applied and "t"-value was calculated; post-test score was significant higher at 0.05 level than that of pre-test score. Thus, it was concluded that structured teaching program on prevention of breast cancer and cervical cancer was found effective.

Hence, based on the above-cited findings, it is clear that the structured teaching program helped the staff nurses to improve their knowledge regarding prevention of breast cancer and cervical cancer[5].

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Magic box – not only flesh but also with a fatal bone: A rare case of extraskeletal intra-abdominal osteogenic sarcoma

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ABSTRACT

Extraskeletal osteogenic sarcoma is a rare tumor with a poor prognosis. It is histologically characterized by the formation of malignant osteoid, however, there is no association with the axial or appendicular skeleton. It comprises less than 2% of the soft-tissue sarcomas.

Postulated risk factors for the development of extraskeletal osteogenic sarcoma are middle and elderly aged patients, history of radiation in the past, and trauma. Here, we report a rare case of extraskeletal intra-abdominal osteogenic sarcoma in a 56-year-old female who presented with a complaint of on and off abdominal pain for the past month. The patient presented with a large retroperitoneal soft-tissue mass with areas of calcifications on CT. Positron emission tomography-CT revealed a large mass with diffuse fluorodeoxyglucose uptake with noother lesion elsewhere in the body. A CT-guided tru-cut biopsy was taken and immunohistochemistry was done on the same. This was proven as osteogenic sarcoma on immunohistochemistry. The patient was started on palliative chemotherapy as the mass was not resectable.

Key words: Conventional osteogenic sarcoma, Extraskeletal osteogenic sarcoma, Retroperitoneal sarcoma

Extraskeletal intra-abdominal osteogenic sarcoma is a rare malignant mesenchymal tumor not in continuation with the appendicular or axial skeleton. To date, less than 300 cases have been reported [1]. Extraskeletal osteogenic sarcomas are rare tumors with a prevalence of 4% of osteogenic sarcoma and 1% of all soft-tissue sarcomas [2]. Here, we present a rare case of intra-abdominal osteogenic sarcoma in a 56-year-old female who presented at our institute. In view of this rarity and difficult location, this case needs a mention in the literature.

CASE REPORT

A 56-year-old female presented at our hospital complaining of on and off abdominal pain for the past 1 month. She also had associated nausea, generalized weakness, loss of appetite, history of weight loss, and decreased frequency of micturition for the past 1–2 months. She was a known diabetic and hypertensive for the past 10 years and was on regular medication for that.

On examination, the patient was European Cooperative Oncology Group status 1. Her vitals were stable. She had a

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significant history of weight loss of approximately 20 kg from the past 1–2 months.

Her routine blood investigations revealed increased serum creatinine and serum urea levels (serum creatinine 52 mg/dl and serum urea 2.30 mg/dl). Serum sodium was low (129 mmol/L).

The other blood investigations were within normal limits.

Fluorodeoxyglucose-positron emission tomography computed tomography (PET/CT) showed a hypermetabolic irregular mass lesion with calcification in the retroperitoneum predominantly in the left para-aortic region encasing the left mid ureter with the left hydronephrosis and with indistinct fat planes with the aorta, forth part of the duodenum, and proximal jejunum. Hypermetabolic mesenteric and omental nodularities with surrounding fat stranding were noted with minimal ascites with low-grade metabolic activity (Fig. 1). For a definite diagnosis, the patient was planned for a CT-guided biopsy.

A CT-guided biopsy was performed from the retroperitoneal mass. Two-three tiny linear cores were obtained. Histopathology showed two-three linear cores infiltrated by poorly differentiated cells invading the adjacent fibrocollagenous tissue. Areas of necrosis were noted. No areas containing osteoid were seen. It was reported as poorly differentiated malignancy (Fig. 2).

Immunohistochemistry was advised for definitive subtyping and diagnosis.

Immunohistochemistry showed neoplastic cells showing diffuse and strong immunoreactivity for Vimentin and moderate and diffuse immunoreactivity for SATB-2 (Fig. 3a) while they were immunonegative for MDM-2, SMA, and desmin (Fig. 3b-d).

Thus, a diagnosis of extraskeletal osteogenic sarcoma was made.

In view of her extensive disease and comorbidities, the patient was advised palliative chemotherapy. The patient is on palliative chemotherapy with stable disease.

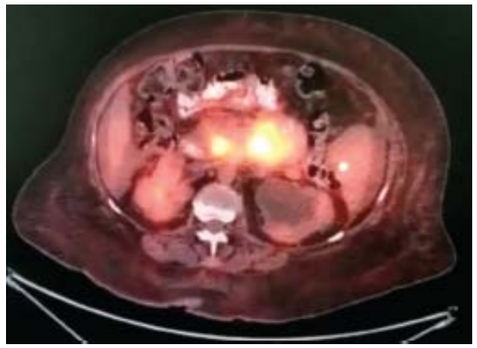

Figure 1: Positron emission tomography image shows large fluorodeoxyglucose avid retroperitoneal mass measuring approximately 10 Ã— 8 Ã— 6 cm

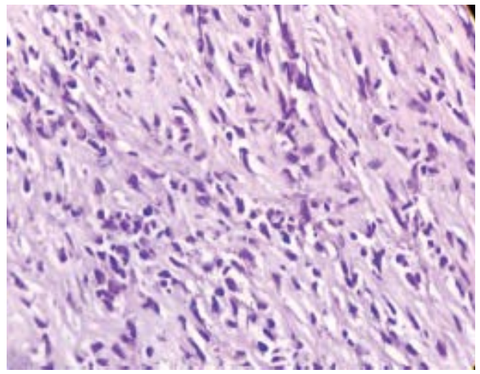

Figure 2: H & E section shows malignant mesenchymal cells, spindeloid in shape with nuclear pleomorphism, and atypia (Ã—40)

DISCUSSION

The overall incidence of retroperitoneal sarcoma is less. The most common retroperitoneal sarcomas are the liposarcomas followed by leiomyosarcomas. Extraskeletal intra-abdominal osteogenic sarcoma is an extremely rare entity comprising only 4% of osteogenic sarcomas and 1.2% of all soft-tissue sarcomas [2-4]. Extra skeletal osteogenic sarcoma most commonly occurs in the thigh followed by the upper limb. Retroperitoneum is a very uncommon site as reviewed in the literature [5,6]. Other than the above-mentioned sites, the incidence of extraskeletal osteogenic sarcoma has been reported in the larynx, kidney, esophagus, small intestine, liver, heart, urinary bladder, parotid gland, and breast [3]. Until now, only two cases of intra-abdominal osteogenic sarcoma have been reported [1,7]. The incidence of conventional osteogenic sarcoma has been mostly related to the bones of the appendicular skeleton and axial skeleton occurring in the first two decades of life. The patients with extraskeletal osteogenic sarcoma usually belong to the fourth and fifth decade [3-5]. Even our patient was 56 years old.

The etiopathogenesis of extraskeletal osteogenic sarcoma remains unknown. Few have postulated the exposure to radiation and trauma as the causative factors, however generally, the cause remains unknown [8,9]. Our patient did not have any of the above histories.

The diagnosis is often challenging because a majority of the patients present with very vague symptoms or at times no symptoms at all. Typically, the patients present with advanced disease because of late presentation at the time of diagnosis. One-third of the patients present with intra-abdominal mass associated with a vague pain. Renal function tests might be obliterated, just like in this case if the mass is compromising renal functions. Usually, the rest of the blood parameters are within normal limits [10]. In this case, PET-CT showed a large intra-abdominal mass with areas of calcification along with omental and mesenteric metastasis.

Histomorphology showed sheets of malignant mesenchymal cells along with areas of necrosis. The differentials to be considered in this case are leiomyosarcoma, liposarcoma, and osteogenic sarcoma. Osteoid was not documented in the submitted biopsy; hence, the diagnosis of osteogenic sarcoma was made after immunohistochemistry.

Immunohistochemistry shows diffuse and strong immunoreactivity for Vimentin and SATB-2 while the tumor cells are immunonegative for AE1/AE3, CD-45, desmin, SMA, and MDM2 ruling out other differentials of retroperitoneal malignancies such as high-grade lymphoma, metastatic deposits of epithelial malignancy, leiomyosarcoma, and liposarcoma.

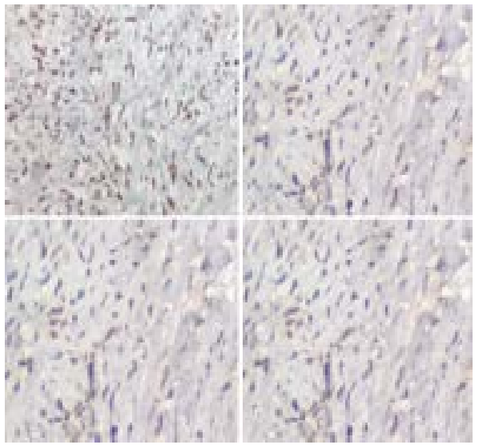

Figure 3: (a) Section shows diffuse and moderate immunoreactivity of tumor cells to SATB2. Tumor cells are immunonegative for (a) desmin, (c) MDM2, and (d) SMA

The overall survival of extraskeletal osteogenic sarcoma is poor with a cause-specific survival rate at 5 years less than 25% [11]. Resection of the tumor is best to have local disease control and to reduce the symptoms, however, it does take care of the metastasis and overall survival [12].

Systemic chemotherapy is the treatment of choice, however, its efficacy has not been proven by clinical trials due to the rarity of this entity. Radiotherapy is opted to achieve temporary palliation [12]. Goldstein-Jackson et al. in their article have proposed the use of multiagent aggressive chemotherapy [12]. The patient is on palliative chemotherapy with stable disease. More information needs to be obtained concerning the clinical outcome for appropriate management, planning, and prognostic estimation.

CONCLUSION

Here, we report an extremely rare case of extraskeletal intra-abdominal osteogenic sarcoma arising in the retroperitoneum with extensive omental and mesenteric metastasis. A suspicion of this entity is advised when an intra-abdominal soft-tissue tumor with abundant areas of intratumoral calcification or ossification is seen.

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Breast Cancer Diagnosis And Management

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INTRODUCTION

Cancer begins when healthy cells in the breast change and grow out of control, forming a mass or sheet of cells called a tumor. A tumor can be cancerous or benign. A cancerous tumor is malignant, meaning it can grow and spread to other parts of the body. A benign tumor means the tumor can grow but will not spread. Breast cancer spreads when the cancer grows into adjacent organs or other parts of the body or when breast cancer cells move to other parts of the body through the blood vessels and/or lymph vessels. This is called a metastasis. Although breast cancer most commonly spreads to nearby lymph nodes, it can also spread further through the body to areas such as the bones, lungs, liver, and brain. This is called metastatic or stage IV breast cancer and is the most advanced type of breast cancer. However, the involvement of lymph nodes alone is generally not stage IV breast cancer. If breast cancer comes back after initial treatment, it can recur locally, meaning in the same breast and/or regional lymph nodes. It can also recur elsewhere in the body, called a distant recurrence or metastatic recurrence.

DEFINITION OF BREAST CANCER

Cancer that forms in tissues of the breast. The most common type of breast cancer is ductal carcinoma, which begins in the lining of the milk ducts(thin tubes that carry milk from the lobules of the breast to the nipple

RISK FACTORS

A risk factor is anything that increases a person's chance of developing cancer. Although risk factors often influence the development of cancer, most do not directly cause cancer. Some people with several risk factors never develop cancer, while others with no known risk factors do.

The following factors may raise a woman's risk of developing breast cancer:

Age. The risk of developing breast cancer increases as a woman ages, with most cancers developing in women older than 50.

Personal history of breast cancer. A woman who has had breast cancer in 1 breast has a higher risk of developing a new cancer in either breast.

Family history of breast cancer. Breast cancer may run in the family in any of these situations:

•1 or more women are diagnosed with breast cancer at age 45 or younger

•1 or more women are diagnosed with breast cancer before age 50 with an additional family history of cancer, such as ovarian cancer, metastatic prostate cancer, and pancreatic cancer

•There are breast and/or ovarian cancers in multiple generations on one side of the family, such as having both a grandmother and an aunt on the father's side of the family who were both diagnosed with 1 of these cancers

•A woman in the family is diagnosed with a second breast cancer in the same or the other breast or has both breast and ovarian cancer.

•A male relative is diagnosed with breast cancer

•There is at least 1 close relative who was diagnosed with breast cancer at age 50 or younger, or ovarian cancer, prostate cancer, and/or pancreatic cancer

GENETIC TESTING

- Early menstruation and late menopause
- Timing of pregnancy
- Hormone replacement therapy after menopause
- Oral contraceptives or birth control pills
- Race and ethnicity
- Lifestyle factors
- Weight
- Physical activity
- Alcohol
- Food
- Socioeconomic factors
- Radiation exposure at a young age

SIGN & SYMPTOMS

The majority of women with breast cancer do not have any body changes (signs) or symptoms when they are first diagnosed with breast cancer.

•A lump that feels like a hard knot or a thickening in the breast or under the arm. It is important to feel the same area in the other breast to make sure the change is not a part of healthy breast tissue in that area.

•Change in the size or shape of the breast

•Nipple discharge that occurs suddenly, is bloody, or occurs in only 1 breast

•Physical changes, such as a nipple turned inward or a sore located in the nipple area

•Skin irritation or changes, such as puckering, dimpling, scaliness, or new creases

•A warm, red, swollen breast with or without a rash with dimpling resembling the skin of an orange, called "peaud'orange"

•Pain in the breast, particularly breast pain that does not go away. Pain is not usually a symptom of breast cancer, but it should be reported to a doctor.

DIAGNOSIS

For most types of cancer, a biopsy is the only sure way for the doctor to know if an area of the body has cancer. Biopsy is done where a small sample of tissue is sent for testing in a laboratory

The following tests may be used to diagnose breast cancer or for follow-up testing after a breast cancer diagnosis.

Imaging tests

• **Diagnostic mammography.** Diagnostic mammography is similar to screening mammography except that more pictures of the breast are taken. It is often used when a woman is experiencing signs, such as a new lump or nipple discharge.

• **Ultrasound.** An ultrasound uses sound waves to create a picture of the breast tissue. An ultrasound can distinguish between a solid mass, which may be cancer, and a fluid-filled cyst, which is usually not cancer.

• **MRI.** An MRI uses magnetic fields, not x-rays, to produce detailed images of the body. A special dye called a contrast medium is given before the scan to help create a clear picture of the possible cancer. This dye is injected into the patient's vein. A breast MRI may be used after a woman has been diagnosed with cancer to find out how much the disease has grown throughout the breast or to check the other breast for cancer.

Biopsy

A biopsy is the removal of a small amount of tissue for examination under a microscope. Other tests can suggest that cancer is present, but only a biopsy can make a definite diagnosis. Sample is analyzed for evaluating cells, tissues, and organs to diagnose the disease. There are different types of biopsies, classified by the technique and/or size of needle used to collect the tissue sample.

• **Fine needle aspiration biopsy.** This type of biopsy uses a thin needle to remove a small sample of cells.

• **Core needle biopsy.** This type of biopsy uses a wider needle to remove a larger sample of tissue.

• **Surgical biopsy.** This type of biopsy removes the largest amount of tissue.

• **Image-guided biopsy.** During this procedure, a needle is guided to the location of the mass or calcifications with the help of an imaging technique, such as mammography, ultrasound, or MRI.

• **Sentinel lymph node biopsy.** When cancer spreads through the lymphatic system, the lymph node or group of lymph nodes the cancer reaches first is called the "sentinel" lymph node.

Blood tests

These tests may be done before or after surgery.

• **Complete blood count**. A complete blood count (CBC) is used to measure the number of different types of cells, such as red blood cells and white blood cells, in a sample of a person's blood. It is done to make sure that your bone marrow is functioning well.

• **Blood chemistry**. This test evaluates how well your liver and kidneys are working.

• **Hepatitis tests**. While not currently the standard of care, these tests are occasionally used to check for evidence of prior exposure to hepatitis B and/or hepatitis C. If you have evidence of an active hepatitis B infection, you may need to take a special medication to suppress the virus before you receive chemotherapy.

Treatment

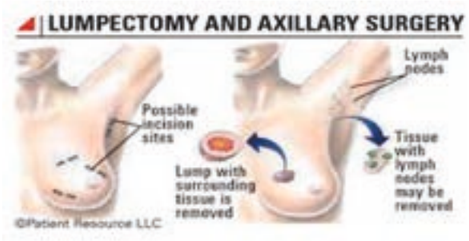
For cancer treatment such as surgery, radiation oncology, and medical oncologist work together with radiologists and pathologists to create a patient's overall treatment plan that combines different types of treatments. This is called a multidisciplinary team, sits in Tumor Board where the decision is taken related to further treatment planning.

Surgery

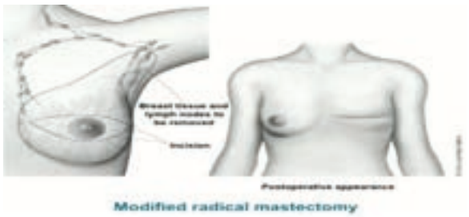
Surgery is the removal of the tumor and some surrounding healthy tissue during an operation. Surgery is also used to examine the nearby axillary lymph nodes, which are under the arm. The types of surgery for breast cancer include the following:

• **Lumpectomy.** This is the removal of the tumor and a small, cancer-free margin of healthy tissue around the tumor. Most of the breast remains. A lumpectomy may also be called breast-conserving surgery, a partial

mastectomy, quadrantectomy, or a segmental mastectomy.



• **Mastectomy.** This is the surgical removal of the entire breast. There are several types of mastectomies. The skin can be preserved, called a skin-sparing mastectomy, or whether the nipple can be preserved, called a nipple-sparing mastectomy or total skin-sparing mastectomy.



Lymph node removal, analysis, and treatment

Cancer cells can be found in the Axiliary lymph nodes in some cancers. Knowing whether any of the lymph nodes near the breast contain cancer can provide useful information to determine treatment and prognosis.

• **Sentinel lymph node biopsy**:- In a sentinel lymph node biopsy (also called a sentinel node biopsy or SNB), the surgeon finds and removes 1 to 3 or more lymph nodes from under the arm that receive lymph drainage from the breast. The smaller lymph node procedure helps lower the risk of several possible side effects. Those side effects include swelling of the arm called lymphedema, numbness, and arm movement and range of motion problems with the shoulder.

• **Axillary lymph node dissection**:- In an axillary lymph node dissection, the surgeon removes many lymph nodes from under the arm. These are then examined for cancer cells by a pathologist. The actual number of lymph nodes removed varies from person to person.

Reconstructive (plastic) surgery

Women who have a mastectomy or lumpectomy may want to consider breast reconstruction. This is surgery to recreate a breast using either tissue taken from another part of the body or synthetic implants. Reconstruction is usually performed by a plastic surgeon. A person may be able to have reconstruction at the same time as the mastectomy, called immediate reconstruction.

The techniques discussed below are typically used to shape a new breast.

• **Implants**:-A breast implant uses saline-filled or silicone gel-filled forms to reshape the breast. The outside of a saline-filled implant is made up of silicone, and it is filled with sterile saline, which is salt water. Silicone gel-filled implants are filled with silicone instead of saline. They were thought to cause connective tissue disorders, but clear evidence of this has not been found. Before having permanent implants, a woman may temporarily have a tissue expander placed that will create the correct sized pocket for the implant. Implants can be placed above or below the pectoralis muscle.

External breast forms (prostheses)

An external breast prosthesis or artificial breast form provides an option for women who plan to delay or not have reconstructive surgery. These can be made of silicone or soft material, and they fit into a mastectomy bra. Breast prostheses can be made to provide a good fit and natural appearance for each woman.

Radiation therapy

Radiation therapy is the use of high-energy x-rays or other particles to destroy cancer cells. A doctor who specializes in giving radiation therapy to treat cancer is called a radiation oncologist. There are several different types of radiation therapy:

• **External-beam radiation therapy**. This is the most common type of radiation treatment and is given from a machine outside the body. This includes whole breast radiation therapy and partial breast radiation therapy, as well as accelerated breast radiation therapy, which can be several days instead of several weeks.

• **Intra-operative radiation therapy.** This is when radiation treatment is given using a probe in the operating room.

• **Brachytherapy**. This type of radiation therapy is given by placing radioactive sources into the tumor.

Radiation therapy may be given after or before surgery:

• **Adjuvant radiation therapy** is given after surgery. Most commonly, it is given after a lumpectomy, and sometimes, chemotherapy. Patients who have a mastectomy may or may not need radiation therapy, depending on the features of the tumor. Radiation therapy may be recommended after mastectomy if a patient has a larger tumor, cancer in the lymph nodes, cancer cells outside of the capsule of the lymph node, or cancer that has grown into the skin or chest wall, as well as for other reasons.

• **Neoadjuvant radiation therapy** is radiation therapy given before surgery to shrink a large tumor, which makes it easier to remove. This approach is uncommon and is usually only considered when a tumor cannot be removed with surgery.

Radiation therapy schedule

Radiation therapy is usually given daily for a set number of weeks.

• **After a lumpectomy**. Radiation therapy after a lumpectomy is external-beam radiation therapy given Monday through Friday for 3 to 4 weeks if the cancer is not in the lymph nodes. If the cancer is in the lymph nodes, radiation therapy is given for 5 to 6 weeks.

• **After a mastectomy**. For those who need radiation therapy after a mastectomy, it is usually given 5 days a week for 5 to 6 weeks. Radiation therapy can be given before or after reconstructive surgery.

• **Proton therapy.** Standard radiation therapy for breast cancer uses x-rays, also called photon therapy, to kill cancer cells. Proton therapy is a type of external-beam radiation therapy that uses protons rather than x-rays. At high energy, protons can destroy cancer cells.

Therapies using medication

Systemic therapy is the use of medication to destroy cancer cells. Medications circulate through the body and therefore can reach cancer cells throughout the body. Systemic therapies are generally prescribed by a medical oncologist, a doctor who specializes in treating cancer with medication.

Common ways to give systemic therapies include an intravenous (IV) tube placed into a vein using a needle, an injection into a muscle or under the skin, or in a pill or capsule that is swallowed (orally).

The types of systemic therapies used for breast cancer include:

• Chemotherapy

• Hormonal therapy

•Targeted therapy

•Immunotherapy

Chemotherapy

Neoadjuvant Chemotherapy : Chemotherapy is the use of drugs to destroy cancer cells, usually by keeping the cancer cells from growing, dividing, and making more cells. It may be given before surgery to shrink a large tumor, make surgery easier, and/or reduce the risk of recurrence, called neoadjuvant chemotherapy.

Adjuvant Chemotherapy : It may also be given after surgery to reduce the risk of recurrence, called adjuvant chemotherapy.

A chemotherapy regimen, or schedule, usually consists of a combination of drugs given in a specific number of cycles over a set period of time. Chemotherapy may be given on many different schedules depending on what worked best in clinical trials for that specific type of regimen. It may be given once a week, once every 2 weeks, once every 3 weeks, or even once every 4 weeks. There are many types of chemotherapy used to treat breast cancer. Common drugs include:

• Docetaxel (Taxotere), Paclitaxel (Taxol), Doxorubicin (available as a generic drug),Epirubicin (Ellence), Pegylated liposomal doxorubicin (Doxil), Capecitabine (Xeloda), Carboplatin (available as a generic drug), Cisplatin (available as a generic drug),Cyclophosphamide (available as a generic drug), Eribulin (Halaven), Fluorouracil (5-FU), Gemcitabine (Gemzar), Ixabepilone (Ixempra), Methotrexate (Rheumatrex, Trexall), Protein-bound paclitaxel (Abraxane),

A patient may receive 1 drug at a time or a combination of different drugs given at the same time. Research has shown that combinations of certain drugs are sometimes more effective than single drugs for adjuvant treatment.

Hormonal therapy

Hormonal therapy, also called endocrine therapy, is an effective treatment for most tumors that test positive for either estrogen or progesterone receptors (called ER positive or PR positive;) This type of tumor uses hormones to fuel its growth. Blocking the hormones can help prevent a cancer recurrence and death from breast cancer when hormonal therapy is used either by itself or after chemotherapy.

Hormonal therapy for breast cancer treatment is different than menopausal hormone therapy (MHT). MHT may also be called postmenopausal hormone therapy or hormone replacement therapy (HRT). Hormonal therapies used in breast cancer treatment act as “anti-hormone” or “anti-estrogen” therapies. They block hormone actions or lower hormone levels in the body. Hormonal therapy may also be called endocrine therapy. The endocrine system in the body makes hormones.

TYPES OF HORMONAL THERAPY

• **Tamoxifen:** Tamoxifen is a drug that blocks estrogen from binding to breast cancer cells. It is effective for lowering the risk of recurrence in the breast that had cancer, the risk of developing cancer in the other breast, and the risk of distant recurrence. Tamoxifen works in women who have been through menopause as well as those who have not.

• **Aromatase inhibitors (AIs):** AIs decrease the amount of estrogen made in tissues other than the ovaries in post-menopausal women by blocking the aromatase enzyme. This enzyme changes weak male hormones called androgens into estrogen when the ovaries have stopped making estrogen during menopause. These drugs include anastrozole (Arimidex), exemestane (Aromasin), and letrozole (Femara). All of the AIs are pills taken daily by mouth. Only women who have gone through menopause or who take medicines to stop the ovaries from making estrogen can take AIs.

• Begin hormone therapy with an AI. When an AI is the only hormone therapy given, it’s taken for 5 to 10 years.

• Begin hormone therapy with tamoxifen and then after a few years, switch to an AI. When an AI is taken after tamoxifen, the drugs are taken for a combined total of 5 to 10 years.

• **Ovarian suppression or ablation.** Ovarian suppression is the use of drugs to stop the ovaries from producing estrogen. Ovarian ablation is the use of surgery to remove the ovaries.

• For ovarian suppression, gonadotropin or luteinizing releasing hormone (GnRH or LHRH) agonist drugs are used to stop the ovaries from making estrogen, causing temporary menopause. Goserelin (Zoladex) and leuprolide (Eligard, Lupron) are types of these drugs. They are given by injection every 4 weeks and stop the ovaries from making estrogen. The effects of GnRH drugs go away if treatment is stopped.

• For ovarian ablation, surgery to remove the ovaries is used to stop estrogen production. While this is permanent, it can be a good option for women who no longer want to become pregnant, especially since the cost is typically lower over the long term.

Hormonal therapy for women after menopause

Women who have gone through menopause and are prescribed hormonal therapy have several options:

• Tamoxifen for 5 to 10 years

• An AI for 5 to 10 years

• Tamoxifen for 5 years, followed by an AI for up to 5 years. This would be a total of 10 years of hormonal therapy.

• Tamoxifen for 2 to 3 years, followed by 2 to 8 years of an AI for a total of 5 to 10 years of hormonal therapy.

Targeted therapy

Targeted therapy is a treatment that targets the cancer's specific genes, proteins, or the tissue environment that contributes to cancer growth and survival. These treatments are very focused and work differently than chemotherapy. This type of treatment blocks the growth and spread of cancer cells and limits damage to healthy cells.

HER2-targeted therapy

• **Trastuzumab** (FDA-approved biosimilar forms are available). This drug is approved as a therapy for non-metastatic HER2-positive breast cancer. It is given either as an infusion into a vein every 1 to 3 weeks or as an injection into the skin every 3 weeks. Pertuzumab (Perjeta). This drug is approved for stage II and stage III breast cancer in combination with trastuzumab and chemotherapy. It is given as an infusion into a vein every 3 weeks.

• **Pertuzumab**, trastuzumab, and hyaluronidase–zzxf (Phesgo). This combination drug, which contains pertuzumab, trastuzumab, and hyaluronidase-zzxf in a single dose, is approved for people with early-stage HER2-positive breast cancer. It may be given in combination with chemotherapy. It is given by injection under the skin and can be administered either at a treatment center or at home by a health care professional.

• **Neratinib** (Nerlynx). This oral drug is approved as a treatment for higher-risk HER2-positive, early-stage breast cancer. It is taken for a year, starting after patients have finished 1 year of trastuzumab

Bone modifying drugs

Bone modifying drugs block bone destruction and help strengthen the bone. They may be used to prevent cancer from recurring in the bone or to treat cancer that has spread to the bone. Certain types are also used in low doses to prevent and treat osteoporosis. Osteoporosis is the thinning of the bones.

There are 2 types of drugs that block bone destruction:

• **Bisphosphonates.** These block the cells that destroy bone, called osteoclasts.

• **Denosumab** (Prolia, Xgeva). An osteoclast-targeted therapy called a RANK ligand inhibitor. The use of denosumab to lower the risk of breast cancer recurrence is under study.

Immunotherapy

Immunotherapy, also called biologic therapy, is designed to boost the body's natural defenses to fight the cancer. It uses materials made either by the body or in a laboratory

to improve, target, or restore immune system function. The following drugs, which are a type of immunotherapy called immune checkpoint inhibitors, are used for recurrent and advanced or metastatic breast cancer. Pembrolizumab is also used for high-risk, early-stage disease.

Recurrent breast cancer

If the cancer returns after treatment for early-stage disease, it is called recurrent cancer. When breast cancer recurs, it may come back in the following parts of the body:

•The same place as the original cancer. This is called a local recurrence.

•The chest wall or lymph nodes under the arm or in the chest on the same side as the original cancer. This is called a regional recurrence.

•Another place, including distant organs such as the bones, lungs, liver, and brain. This is called a distant recurrence or a metastatic recurrence. People with recurrent breast cancer often experience emotions such as disbelief or fear.

Physical, emotional, and social effects of cancer

In general, cancer and its treatment cause physical symptoms and side effects, as well as emotional, social, and financial effects. Managing all of these effects is called palliative care or supportive care.

Palliative care focuses on improving how you feel during treatment by managing symptoms and supporting patients and their families with other, non-medical needs. Any person, regardless of age or type and stage of cancer, may receive this type of care. And it often works best when it is started right after a cancer diagnosis. People who receive palliative care along with treatment for the cancer often have less severe symptoms, better quality of life, and report that they are more satisfied with treatment. Palliative treatments vary widely and often include medication, nutritional changes, relaxation techniques, emotional and spiritual support, and other therapies. Patients receive palliative treatments similar to those meant to get rid of the cancer, such as chemotherapy, surgery, or radiation therapy.

GENERAL ASPECTS OF NURSING CARE

1.Monitor for adverse effects of radiation therapy such as fatigue, sore throat, dry cough, nausea, anorexia.

2.Monitor for adverse effects of chemotherapy; bone marrow suppression, nausea and vomiting, alopecia, weight gain or loss, fatigue, stomatitis, anxiety, and depression.

3.Realize that a diagnosis of breast cancer is a devastating emotional shock to the woman. Provide psychological support to the patient throughout the diagnostic and treatment process.

4.Involve the patient in planning and treatment.

5.Describe surgical procedures to alleviate fear.

6.Prepare the patient for the effects of chemotherapy, and plan ahead for alopecia, fatigue.

7.Administer antiemetics prophylactically, as directed, for patients receiving chemotherapy.

8.Administer I.V. fluids and hyperalimentation as indicated.

9.Help patient identify and use support persons or family or community.

10.Suggest to the patient the psychological interventions may be necessary for anxiety, depression, or sexual problems.

11.Teach all women the recommended cancer-screening procedures.

NURSING CARE PLANS

Providing perioperative nursing care for patients who are to undergo Mastectomy is an integral part of the therapeutic regimen. The nursing goal is to provide support, alleviating anxiety, managing pain, and providing information.

Nursing diagnosis for a patient undergoing Mastectomy:

1.Fear/Anxiety

2.Impaired Skin Integrity

3.Acute Pain

4.Situational Low Self-Esteem

5.Impaired Physical Mobility

6.Deficient Knowledge

7.Risk for Injury

8.Impaired Skin Integrity

9.Activity Intolerance

10.Risk for Ineffective Breathing Pattern

11.Risk for Infection

12.Ineffective Therapeutic Management

13.Risk for Dysfunctional Grieving

14.Ineffective Peripheral Tissue Perfusion

1 Fear/Anxiety

Nursing Diagnosis

•Fear

•Anxiety

May be related to

•Threat of death, e.g., extent of disease

•Threat to self-concept: change of body image; scarring, loss of body part, sexual attractiveness

•Change in health status

Possibly evidenced by

•Increased tension; apprehension; feelings of helplessness/inadequacy

•Decreased self-assurance

•Self-focus; restlessness; sympathetic stimulation

•Expressed concerns regarding actual/anticipated changes in life

Desired Outcomes

•Client will acknowledge and discuss concerns.

•Client will demonstrate appropriate range of feelings.

•Client will report fear and anxiety are reduced to a manageable level.

Nursing Interventions	Rationale
Check out and explore what information the patient has about diagnosis, expected surgical intervention, and future therapies. Note presence of denial or extreme anxiety.	Provides knowledge base for the nurse to enable the reinforcement of needed information, and helps identify patient with high anxiety, low capacity for information processing, and need for special attention. Note: Denial may be useful as a coping method for a time, but extreme anxiety needs to be dealt with immediately.
Ascertain purpose and preparation for diagnostic tests.	More understanding of procedures and what is happening increases feelings of control and lessens anxiety.
Implement an ambiance of concern, openness, and availability, as well as privacy for patient and so. Suggest that so be present as much as possible.	Time and privacy are needed to provide support, discuss feelings of anticipated loss and other concerns. Therapeutic communication skills, open questions, listening, and so forth facilitate this process.
Encourage questions and provide time for expression of fears. Tell patient that stress related to breast cancer can persist for many months and to seek help and support.	Provides an opportunity to identify and clarify misconceptions and offer emotional support.
Determine the degree of support available to the patient. Give information about community resources, such as Reach to Recovery, YWCA Encore program. Encourage and provide for a visit with a woman who has recovered from a mastectomy.	Can be a helpful resource when patient is ready. A peer who has experienced the same process serves as a role model and can provide validity to the comments, hope for recovery and normal future.
Consider role of rehabilitation after surgery.	Rehabilitation is an essential component of therapy intended to meet physical, social, emotional, and vocational needs so that the patient can achieve the best possible level of physical and emotional functioning.

2 IMPAIRED SKIN INTEGRITY

Nursing Diagnosis

Impaired Skin Integrity

May be related to

- Surgical removal of skin/tissue; altered circulation, presence of edema, drainage; changes in skin elasticity, sensation; tissue destruction (radiation)
- Disruption of skin surface, destruction of skin layers/subcutaneous tissues

Desired Outcomes

- Client will achieve timely wound healing, free of purulent drainage or erythema.
- Client will demonstrate behaviors/techniques to promote healing/prevent complications.

Nursing Interventions	Rationale
Inspect dressings anteriorly and posteriorly for characteristics of drainage. Monitor amount of edema, redness, and pain in the incision.	Use of dressings depends on the extent of surgery and the type of wound closure. (Pressure dressings are usually applied initially and are reinforced, not changed.) Drainage occurs because of the trauma of the procedure and manipulation of the numerous blood vessels and lymphatics in the area.
Perform routine assessment of involved arm. Elevate hand or arm with shoulder positioned at appropriate angles (no more than 65 degrees of flexion, 45–65 degrees of abduction, 45–60 degrees of internal rotation) and forearm resting on wedge or pillow, as indicated.	Preventing or minimizing edema reduces the discomfort and complications associated with it. Elevation of affected arm facilitates drainage and resolution of edema. Note: Lymphedema is present in about 25% of patients and may develop immediately after surgery or years later.
Monitor temperature.	Early recognition of developing infection can enable the rapid institution of treatment.
Maintain in semi-Fowler's position on the back or unaffected side; avoid letting the affected arm dangle.	Assists with drainage of fluid through use of gravity.
Refrain from measuring blood pressure (BP), injecting medications, or inserting IVs in the affected arm.	Increases potential of constriction, infection, and lymphedema on the affected side.
Observe graft site (if done) for color, blister formation; note drainage from donor site.	Color will be affected by the availability of circulatory supply. Blister formation provides a site for bacterial growth or infection.
Assess wound drains, periodically noting amount and characteristics of drainage.	Drainage of accumulated fluids (lymph, blood) enhances healing and reduces the susceptibility to infection. Suction devices (Hemovac, Jackson-Pratt) are often inserted during surgery to maintain negative pressure in the wound. Tubes are usually removed around the third day or when drainage ceases.
Encourage wearing of loose-fitting or non-constrictive clothing. Tell patient not to wear a wristwatch or other jewelry on affected arm.	Reduces pressure on compromised tissues, which may improve circulation and healing and minimize lymphedema.
Carry out antibiotics as indicated.	May be given prophylactically or to treat specific infection and enhance healing.

3 DEFICIENT KNOWLEDGE

Nursing Diagnosis

- **Deficient Knowledge**

May be related to

- Lack of exposure/recall
- Information misinterpretation

Desired Outcomes

- Client will verbalize understanding of disease process and potential complications.
- Client will perform necessary procedures correctly and explain reasons for actions.
- Client will initiate necessary lifestyle changes and participate in the treatment regimen.

Nursing Interventions	Rationale
Review disease process, surgical procedure, and future expectations.	Provides knowledge base from which patient can make informed choices, including participation in radiation and chemotherapy programs.
Have patient demonstrate care of drains and wound sites.	Shorter hospital stays may result in discharge with drains in place, requiring more complex care by patient or caregivers. Drains may be removed 7–10 days after surgery.

Nursing Interventions	Rationale
Encourage continuation of exercises, increasing program as healing progresses, for at least a year.	Enhances development of collateral lymphatic channels, reduces the tightening of scar tissue, and maintains muscle strength and function. Note: Moderation is important because strenuous activity and exercise increases heart rate and body temperature, which can potentially increase edema.
Discuss necessity for well-balanced, nutritious meals and adequate fluid intake.	Provides optimal nutrition and maintains circulating volume to enhance tissue regeneration and healing process.
Suggest alternating schedule of frequent rest and activity periods, especially in situations when sitting or standing is prolonged.	Prevents or limits fatigue, promotes healing, and enhances feelings of general well-being. Positions in which arm is dangling and extended intensify stress on affected structures, creating muscle tension and stiffness, and may interfere with healing.
Instruct patient to protect hands and arms by wearing long sleeves and gloves when gardening; use thimble when sewing; use potholders when handling hot items; use plastic gloves when doing dishes; avoid lifting or moving heavy objects; and do not carry a purse or wear jewelry and wristwatch on the affected side.	Compromised lymphatic system causes tissues to be more susceptible to infection or injury, which may lead to lymphedema.
Demonstrate holding affected arm appropriately by not dangling the arm, swinging arms with elbows bent when walking, placing arm above heart level when sitting or lying down.	Helps prevent or minimize lymphedema and "frozen shoulder."
Warn against having blood withdrawn or receiving IV fluids, medications or BP measurements on the affected side.	May restrict the circulation and increase the risk of infection when the lymphatic system is compromised.
Recommend wearing of a medical identification device.	Prevents unnecessary trauma (BP measurements, injections) to affected arm in emergency situations.
Suggest gentle massage of the healed incision with emollients.	Stimulates circulation, promotes elasticity of the skin, and reduces discomfort associated with phantom breast sensations.
Recommend use of sexual positions that avoid pressure on the chest wall. Encourage alternative forms of sexual expression (cuddling, touching) during the initial healing process while operative area is still tender.	Promotes feelings of femininity and sense of ability to resume sexual activities.
Encourage regular self-examination of remaining breast. Determine the recommended schedule for mammography.	Identifies changes in breast tissue indicative of recurrent or new tumor development.
Identify signs and symptoms requiring medical evaluation (breast or arm red, warm, and swollen; edema, purulent wound drainage; fever or chills).	Lymphangitis can occur as a result of infection, causing lymphedema.

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Cervical Cancer – Diagnosis and Management

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INTRODUCTION

Cervical cancer starts in the cervix, which is the lower, narrow part of the uterus. The uterus holds the growing fetus during pregnancy. The cervix connects the lower part of the uterus to the vagina and, with the vagina, forms the birth canal.

Cervical cancer begins when healthy cells on the surface of the cervix change or get infected with human papillomavirus (HPV) and grow out of control, forming a mass called a tumor. Long-term infection of HPV on the cervix can result in cancer, leading to a mass or tumor on the cervix. A tumor can be cancerous or benign. A cancerous tumor is malignant, meaning it can spread to other parts of the body. A benign tumor means the tumor will not spread.

Cervical cancer is most often diagnosed between the ages of 35 and 44. The average age of diagnosis is 50. About 20% of cervical cancers are diagnosed after age 65. Usually these cases occur in people who did not receive regular cervical cancer screenings before age 65. It is rare for people younger than 20 to develop cervical cancer.

DEFINITION

Cancer that forms in tissues of the cervix (the organ connecting the uterus and vagina). It is usually a slow-growing cancer that may not have symptoms but can be found with regular Pap tests (a procedure in which cells are scraped from the cervix and looked at under a microscope). Cervical cancer is almost always caused by human papillomavirus (HPV) infection.

RISK FACTOR

- Human papillomavirus (HPV) infection
- Immune system deficiency
- Herpes
- Smoking
- Age
- Socioeconomic factors
- Oral contraceptives
- Exposure to diethylstilbestrol (DES)

SIGNS AND SYMPTOMS

- Any of the following could be signs or symptoms cervical cancer
- Blood spots or light bleeding between or following periods
- Menstrual bleeding that is longer and heavier than usual
- Bleeding after intercourse, douching, or a pelvic examination
- Increased vaginal discharge
- Pain during sexual intercourse
- Bleeding after menopause
- Unexplained, persistent pelvic and/or back pain

DIAGNOSIS

The following tests may be used to diagnose cervical cancer:

Bimanual pelvic examination and sterile speculum examination-

Any unusual changes in the patient's cervix, uterus, vagina, ovaries, and other nearby organs, changes in vulva outside the body is visualized using an instrument called a speculum to keep the vaginal walls open. A Pap test is often done at the same time. Some of the nearby organs are not visible during this exam, so insert 2 fingers of 1 hand inside the vagina while the other hand gently presses on the lower abdomen to feel the uterus and ovaries.

Pap test

During a Pap test, gently scrapes the outside and inside of the cervix, take samples of cells for testing.

Improved Pap test methods have made it easier to find cancerous cells. Traditional Pap tests can be hard to read because cells can be dried out, covered with mucus or blood, or may clump together on the slide.

The liquid-based cytology test, often referred to as ThinPrep or SurePath, transfers a thin layer of cells onto a slide after removing blood or mucus from the sample. The sample is preserved so other tests can be done at the same time, such as the HPV test.

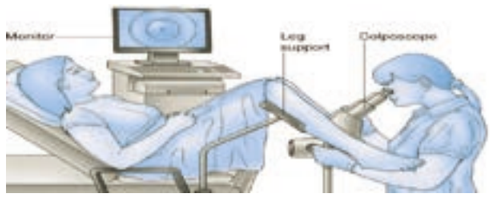
Computer screening, often called AutoPap or FocalPoint, uses a computer to scan the sample for abnormal cells.

HPV typing test

An HPV test is similar to a Pap test. The test is done on a sample of cells from the cervix. Test for HPV at the same time as a Pap test or after Pap test results show abnormal changes to the cervix. Certain types or strains of HPV, called high-risk HPV, such as HPV16 and HPV18, are seen more often in women with cervical cancer and may help confirm a diagnosis. If the HPV test is "positive," this means the test found the presence of high-risk HPV. Many women have HPV but do not have cervical cancer, so HPV testing alone is not enough for a diagnosis of cervical cancer.

Colposcopy

Colposcopy may done to check the cervix for abnormal areas. Colposcopy can also be used to help guide a biopsy of the cervix. During a colposcopy, a special instrument called a colposcope is used. The colposcope magnifies the cells of the cervix and vagina, similar to a microscope. It gives the lighted, magnified view of the tissues of the vagina and the cervix. The colposcope is not inserted into the body, and the examination is similar to a speculum examination. It can be done in the clinics and has no side effects. It can also be done on pregnant women.



Biopsy

A biopsy is the removal of a small amount of tissue for examination under a microscope. Other tests can suggest that cancer is present, but only a biopsy can make a definite diagnosis. If the lesion is small, it may remove all during the biopsy.

There are several types of biopsies. Most are usually done in the Clinics, sometimes using a local anesthetic to numb the area. There may be some bleeding and other discharge after a biopsy. There may also be discomfort similar to menstrual cramps.

One common biopsy method uses an instrument to pinch off small pieces of cervical tissue. Other types of biopsies include:

Endocervical curettage (ECC). To check an area inside the opening of the cervix that cannot be seen during a colposcopy, then use ECC. During this procedure, a small, spoon-shaped instrument called a curette is used to scrape a small amount of tissue from inside the cervical opening.

Loop electrosurgical excision procedure (LEEP). LEEP uses an electrical current passed through a thin wire hook. The hook removes tissue for examination in the laboratory. A LEEP may also be used to remove a precancer or an early-stage cancer.

Conization (a cone biopsy). This removes a cone-shaped piece of tissue from the cervix. Conization may be done as treatment to remove a precancer or an early-stage cancer. It is done under a general or local anesthetia.

Pelvic examination under anesthesia. In cases where it is necessary for treatment planning, re-examine the pelvic area while the patient is under anesthesia to see if the cancer has spread to any organs near the cervix, including the uterus, vagina, bladder, or rectum.

X-ray. An x-ray is a way to create a picture of the structures inside of the body using a small amount of radiation. An intravenous urography is a type of x-ray that is used to view the kidneys and bladder.

Computed tomography (CT or CAT) scan. A CT scan takes pictures of the inside of the body using x-rays taken from different angles. A computer combines these pictures into a detailed, 3-dimensional image that shows any abnormalities or tumors. A CT scan can be used to measure the tumor's size. Sometimes, a special dye called a contrast medium is given before the scan to provide better detail on the image. This dye can be injected into a patient's vein or given as a pill or liquid to swallow.

Magnetic resonance imaging (MRI). An MRI uses magnetic fields, not x-rays, to produce detailed images of the body. MRI can be used to measure the tumor's size. A special dye called a contrast medium is given before the scan to create a clearer picture. This dye can be injected into a patient's vein or given as a pill or liquid to swallow.

Positron emission tomography (PET) or PET-CT scan. A PET scan is usually combined with a CT scan, called a PET-CT scan. However, you may hear your doctor refer to this procedure just as a PET scan. A PET scan is a way to create pictures of organs and tissues inside the body. A small amount of a radioactive sugar substance is injected into the patient's body. This sugar substance is taken up by cells that use the most energy. Because cancer tends to use energy actively, it absorbs more of the radioactive substance. A scanner then detects this substance to produce images of the inside of the body.

Cystoscopy. A cystoscopy is a procedure that allows the doctor to view the inside of the bladder and urethra (the canal that carries urine from the bladder) with a thin, lighted tube called a cystoscope. The person may be sedated as the tube is inserted in the urethra. A cystoscopy is used to determine whether cancer has spread to the bladder.

Sigmoidoscopy (also called proctoscopy) A sigmoidoscopy is a procedure that allows the doctor to see the colon and rectum with a thin, lighted, flexible tube called a Sigmoidoscope. The person may be sedated as the tube is inserted in the rectum. A sigmoidoscopy is used to see if the cancer has spread to the rectum

VACCINE RECOMMENDATION

1.Gardasil- Quadrivalent Vaccine

Prevent from 4 HPV infection i.e. Human Papilloma Virus Type- 6,11,16,18

2.Cervarix- Bivalent Vaccine

Prevent from 2 HPV infection i.e. Human Papilloma Virus Type- 6,11

3.9vHPV- Nenavalent Vaccine also called Gardasil 9

Prevent from 9 HPV infection i.e. Human Papilloma Virus Type-6,11,16,18,31,33, 45,52,58

MANAGEMENT

Treatment

Treatment for cervical cancer depends on several factors, such as the stage of the cancer, other health problems you may have and your preferences. Surgery, radiation, chemotherapy or a combination of the three may be used.

Surgery

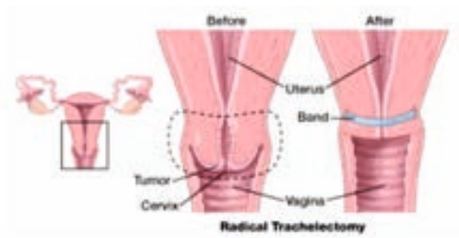
Early-stage cervical cancer is typically treated with surgery. Which operation is best for you will depend on the size of your cancer, its stage and whether you would like to consider becoming pregnant in the future.

Options might include:

Surgery to cut away the cancer only. For a very small cervical cancer, it might be possible to remove the cancer entirely with a cone biopsy. This procedure involves cutting away a cone-shaped piece of cervical tissue, but leaving the rest of the cervix intact. This option may make it possible for you to consider becoming pregnant in the future.

Surgery to remove the cervix (trachelectomy). Early-stage cervical cancer might be treated with a radical trachelectomy procedure, which removes the cervix and some surrounding tissue. The uterus remains after this procedure, so it may be possible to become pregnant, if you choose.

Surgery to remove the cervix and uterus (hysterectomy). Most early-stage cervical cancers are treated with a radical hysterectomy operation, which involves removing



Radical Trachelectomy

the cervix, uterus, part of the vagina and nearby lymph nodes. A hysterectomy can cure early-stage cervical cancer and prevent recurrence. But removing the uterus makes it impossible to become pregnant.

Minimally invasive hysterectomy, which involves making several small incisions in the abdomen rather than one large incision, may be an option for early-stage cervical cancer. People who undergo minimally invasive surgery tend to recover more quickly and spend less time in the hospital.

RADIATION

Radiation therapy uses high-powered energy beams, such as X-rays or protons, to kill cancer cells. Radiation therapy is often combined with chemotherapy as the primary treatment for locally advanced cervical cancers. It can also be used after surgery if there's an increased risk that the cancer will come back.

Radiation therapy can be given:

·Externally, by directing a radiation beam at the affected area of the body (external beam radiation therapy)

·Internally, by placing a device filled with radioactive material inside your vagina, usually for only a few minutes (brachytherapy)

·Both externally and internally

Chemotherapy

Chemotherapy is a drug treatment that uses chemicals to kill cancer cells. It can be given through a vein or taken in pill form. Sometimes both methods are used.

For locally advanced cervical cancer, low doses of chemotherapy are often combined with radiation therapy, since chemotherapy may enhance the effects of the radiation. Higher doses of chemotherapy might be recommended to help control symptoms of very advanced cancer.

Targeted therapy

Targeted drug treatments focus on specific weaknesses present within cancer cells. By blocking these weaknesses, targeted drug treatments can cause cancer cells to die. Targeted drug therapy is usually combined with chemotherapy. It might be an option for advanced cervical cancer.

Immunotherapy

Immunotherapy is a drug treatment that helps your immune system to fight cancer. Body's disease-fighting immune system might not attack cancer because the cancer cells produce proteins that make them undetectable by the immune system cells. Immunotherapy works by interfering with that process. For cervical cancer, immunotherapy might be considered when the cancer is advanced and other treatments aren't working.

Supportive (palliative) care

Palliative care is specialized medical care that focuses on providing relief from pain and other symptoms of a serious illness. When palliative care is used along with all

of the other appropriate treatments, people with cancer may feel better and live longer.

Palliative care is provided by a team of doctors, nurses and other specially trained professionals. Palliative care teams aim to improve the quality of life for people with cancer and their families. This form of care is offered alongside curative or other treatments you may be receiving.

NURSING MANAGEMENT

Oncology nurses are important in the patient's health care team, providing support, education, and connecting patients with resources. Nurses are involved in the care of the patient in many different settings:

- **Gynecological oncology**
- **Radiation oncology**
- **Medical oncology**
- **Infusion centers**
- **Inpatient and procedural visits**

In these various settings, nurses can educate cervical cancer patients on the importance of adhering to treatment schedules, anticipated side effects, and how to manage them. Nurses also have the opportunity to educate patients on HPV vaccinations and regular cancer screenings in efforts of primary and secondary prevention.

Nurses may need to follow lab results and report any abnormal findings, especially with white blood cell and red blood cell counts. Patients are at risk for neutropenia and anemia when receiving chemotherapy and if experiencing any bleeding. Patients undergoing radiation therapy may need skincare guidance. Potential side effects of treatment are nausea, vomiting, and diarrhea, so it is also important to monitor lab values and vital signs for signs of dehydration or electrolyte imbalance.

- Identify the cause of cervical cancer
- Explain the current cervical cancer screening and vaccination recommendations
- Discuss disparities in cervical cancer screening and diagnosis among various populations
- Identify potential nursing diagnoses for people with cervical cancer
- Analyze the role of the nurse in interdisciplinary cervical cancer care

Nursing Management in Radiation Therapy

- Assessment. The nurse assesses the patient's skin and oropharyngeal mucosa regularly when radiation therapy is directed to these areas, and also the nutritional status and general well-being should be assessed.
- Symptoms. If systemic symptoms, such as weakness and fatigue, occur, the nurse explains that these symptoms are a result of the treatment and do not represent deterioration or progression of the disease.
- **Safety precautions**. Safety precautions used in caring for a patient receiving brachytherapy include assigning the patient to a private room, posting appropriate notices about radiation safety precautions, having staff members wear dosimeter badges, making sure that pregnant staff members are not assigned to the patient's care, prohibiting visits by children and pregnant visitors, limiting visits from others to 30 minutes daily, and seeing that visitors maintain a 6 foot distance from the radiation source.

Chemotherapy

In chemotherapy, antineoplastic agents are used in an attempt to destroy tumor cells by interfering with cellular functions, including replication.

- Goal. The goal of treatment is the eradication of enough tumor so that the remaining tumor cells can be destroyed by the body's immune system.
- Proliferating cells. Actively proliferating cells within a tumor are the most sensitive to chemotherapeutic agents.
- Nondividing cells. Nondividing cells capable of future proliferation are the least sensitive to antineoplastic medications and consequently are potentially dangerous.
- Cell cycle-specific. Cell cycle-specific agents destroy cells that are actively reproducing by means of the cell-cycle; most affect cells in the S phase by interfering with DNA and RNA synthesis.
- Cell cycle-nonspecific. Chemotherapeutic agents that act independently of the cell cycle phases are cell cycle nonspecific, and they usually have a prolonged effect on cells, leading to cellular damage and death.

Antineoplastic Agents

Chemotherapeutic agents are also classified by chemical group, each with a different mechanism of action.

- Alkylating agents. Alters DNA structure by misreading DNA code, initiating breaks in the DNA molecule, cross-linking DNA strands
- Nitrosoureas. Similar to the alkylating agents, but they can cross the blood-brain barrier.
- Topoisomerase I inhibitors. Induce breaks in the DNA strand by binding to enzyme topoisomerase I, preventing cells from dividing.
- Antimetabolites. Antimetabolites interfere with the biosynthesis of metabolites or nucleic acids necessary for RNA and DNA synthesis.
- Antitumor antibiotics. Interfere with DNA synthesis by binding DNA and prevent RNA synthesis.
- Mitotic spindle poisons. Arrest metaphase by inhibiting mitotic tubular formation and inhibiting DNA and protein synthesis.
- Hormonal agents. Hormonal agents bind to hormone receptor sites that alter cellular growth; blocks binding of estrogens to receptor sites; inhibit RNA synthesis; suppress aromatase of P450 system, which decreases level.

Nursing Management in Chemotherapy

Nurses play an important role in assessing and managing many of the problems experienced by patients undergoing chemotherapy.

- Assessing fluid and electrolyte balance. Anorexia, nausea, vomiting, altered taste, mucositis, and diarrhea put patients at risk for nutritional and fluid electrolyte disturbances.
- Modifying risks for infection and bleeding. Suppression of the bone marrow and immune system is expected and frequently serves as a guide in determining appropriate chemotherapy dosage but increases the risk of anemia, infection, and bleeding disorders.
- Administering chemotherapy. The patient is observed closely during its administration because of the risk and consequences of extravasation, particularly of vesicant agent.
- Protecting caregivers. Nurses must be familiar with their institutional policies regarding personal protective equipment, handling and disposal of chemotherapeutic agents and supplies, and management of accidental spills or exposures.

Bone Marrow Transplantation

The role of bone marrow transplantation (BMT) for malignant and some nonmalignant diseases continues to grow.

Type of Bone Marrow Transplant

Types of BMT based on the source of donor cells include:

- Allogeneic. Allogeneic is from a related donor other than the patient; donor may be a related donor or a matched unrelated donor.
- Autologous. Autologous BMT is from the patient himself.
- Syngeneic. Syngeneic BMT is from an identical twin.

Nursing Management in Bone Marrow Transplantation

Nursing care of patients undergoing BMT is complex and demands a high level of skill.

- Implementing pretransplantation care. Nutritional assessments, extensive physical examinations, organ function tests, and psychological evaluations are conducted, with blood work that includes assessing past antigen exposure, and the patient's support system, financial, and insurance resources are also evaluated.
- Providing care during treatment. Nursing management during bone marrow infusion or stem cell infusions consists of monitoring the patient's vital signs and blood oxygen saturation; assessing for adverse effects such as fever, chills, shortness of breath, chest pain, cutaneous reactions, nausea, vomiting, hypotension, or hypertension, tachycardia, anxiety, and taste changes; and providing ongoing support and patient teaching.
- Providing post-transplantation care. Ongoing nursing assessments such as psychosocial assessments in follow-up visits are essential to detect late effects of therapy after BMT, which occur 100 days or more after the procedure, and donors also require nursing care through being assisted in maintaining realistic expectations of themselves as well as of the patient.

Maintaining Tissue Integrity

- Stomatitis. Assessment of the patient's subjective experience and an objective assessment of the oropharyngeal tissues and teeth are important and for the treatment of oral mucositis, Palifermin (Kepivance), a synthetic form of human keratinocyte growth factor, could be administered.
- Radiation-associated skin impairment. Nursing care for patients with impaired skin reactions includes maintaining skin integrity, cleansing the skin, promoting comfort, reducing pain, preventing additional trauma, and preventing and managing infection.
- Alopecia. Nurses provide information about hair loss and support the patient and family in coping with changes in body image.
- Malignant skin lesions. Nursing care includes cleansing the skin, reducing superficial bacteria, controlling bleeding, reducing odor, protecting the skin from further trauma, and relieving pain.

Promoting Nutrition

- Anorexia. Anorexia may occur because people feel full after eating only a small amount of food.
- Malabsorption. Surgical intervention may change peristaltic patterns, later gastrointestinal secretions, and reduce the absorptive surfaces of the gastrointestinal mucosa, all leading to malabsorption.
- Cachexia. Nurses assess patients who are at risk of altered nutritional intake so that appropriate measures may be instituted prior to nutritional decline.

Relieving Pain

- Assessment. The nurse assesses the patient for the source and site of pain as well as those factors that increase the patient's perception of pain.
- Cancer pain algorithm. Various opioid and nonopioid medications may be combined with other medications to control pain as adapted from the World Health Organization three-step ladder approach.
- Education. The nurse provides education and support to correct fears and misconceptions about opioid use.

Decreasing Fatigue

- Assessment. The nurse assesses physiologic and psychological stressors that can contribute to fatigue and uses several assessment tools such as a simple visual analog scale to assess levels of fatigue.
- Exercise. The role of exercise as a helpful intervention has been supported by several controlled trials.
- Pharmacologic interventions. Occasionally pharmacologic interventions are utilized, including antidepressants for patients with depression, anxiolytics for those with anxiety, hypnotics for patients with sleep disturbances, and psychostimulants for some patients with advanced cancer or fatigue that does not respond to any medication.

Improving Body Image and Self-esteem

- Assessment. The nurse identifies potential threats to the patient's body image experience, and the nurse assesses the patient's ability to cope with the many assaults to the body image experienced throughout the course of the disease and treatment.
- Sexuality. Nurses who identify physiologic, psychologic or communication difficulties related to sexuality or sexual function are in a key position to help patients seek further specialized evaluation and intervention if necessary.

Assisting in the Grieving Process

• Assessment. The nurse assesses the patient's psychological and mental status, as well as the mood and emotional reaction to the results of diagnostic testing and prognosis.

Grieving

• Grieving is a normal response to these fears and to actual or potential losses.

Monitoring and Managing Potential Complications

• Infection. The nurse monitors laboratory studies to detect any early changes in WBC counts.

Septic shock

• Neurologic assessments are carried out, fluid and electrolyte status is monitored, arterial blood gas values and pulse oximetry are monitored, and IV fluids, blood, and vasopressors are administered by the nurse.

• **Bleeding and hemorrhage**. The nurse may administer IL-11, which has been approved by the FDA to prevent severe thrombocytopenia, and additional medications may be prescribed to address bleeding due to disorders of coagulation.

Promoting Home and Community-Based Care

Nurses in the outpatient settings often have the responsibilities for patient teaching and for coordinating care in the home.

• **Teaching patientself-care**. Follow-up visits and telephone calls from the nurse assist in identifying problems and are often reassuring, increasing the patient's and the family's comfort in dealing with complex and new aspects of care.

• **Continuing care**. The responsibilities of the home care include assessing the home environment, suggesting modifications at home or in care to help the patient and the family address the patient's physical needs.

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Intrahepatic Bile Duct Adenoma Masquerading as Hepatic Metastasis in a case of Carcinoma Rectum

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ABSTRACT

Intrahepatic bile duct adenoma (BDA) is a rare benign tumor arising from the epithelium of the intrahepatic bile duct. In oncology, when a new onset hepatic nodule develops, it is often looked with suspicion for metastasis. However, many of these small liver nodules can be benign. Hence, it is important to obtain tissue for cytological/histopathological diagnosis before labeling it as disease progression. We report imaging findings of bile duct adenoma, which was discovered during surveillance CT scan and was a new finding in a treated case of carcinoma anorectum. Since the new-onset, it was suspicious for metastasis on imaging. Ultrasound-guided FNAC was performed to confirm its etiology and the cytology report showed findings of bile duct adenoma.

Keywords: Liver, Bile duct adenoma, metastasis, carcinoma rectum.

CASE HISTORY

A 46-years-old female, a known case of adenocarcinoma of the rectum, received neoadjuvant chemo-radiotherapy and underwent posterior exenteration surgery. Histopathology report of the primary revealed a small residual focus of viable adenocarcinoma without nodal involvement. She received adjuvant chemotherapy and was on surveillance at a tertiary referral oncology center. Surveillance contrast-enhanced CT scan of abdomen and pelvis was obtained 9 months after the surgery on a 16-slice GE Discovery CT scan machine. Pre contrast plain images and post-contrast images in port venous phase (60 seconds after intravenous injection of iodinated contrast) and delayed / equilibrium phase (180 seconds after intravenous injection of iodinated contrast) were obtained. Arterial phase images were not obtained, as it was a routine surveillance CT scan. CT scan revealed a 14 mm-sized hypodense lesion in the right lobe of the liver, which was not evident on the previous pre-op CT. The liver lesion was hypoattenuating on pre-contrast plain images and post-contrast images in the port venous phase while showing hyperattenuating on delayed / equilibrium phase images. It was located at the periphery. (Fig. 1). Since it was a new onset lesion in a known case of carcinoma, it was suspicious for metastasis. The liver lesion seen on the CT scan did not show FDG uptake on the FDG PET-CT scan. (Fig. 2). Still, it was suspicious for metastasis since was new-onset. There is no evidence of metabolically active disease elsewhere in PET-CT. The case was discussed in the multidisciplinary tumor board and to know the exact pathology, whether benign or malignant, it was referred to us for ultrasound (USG) guided FNAC. When the patient was taken for ultrasound-guided FNAC, pre-procedural USG reveals an isoechoic lesion with a thin peripheral rim of hypoechogenicity (Fig. 3). Under all aseptic precautions & local anesthesia, USG guided FNAC was done with a 25 G spinal needle. Smears were prepared from the aspirate and sent for cytological examinations. On cytology, smears were cellular and showed groups of cuboidal epithelial cells with uniform nuclei, fine chromatin, and scanty cytoplasm. There was no atypia or mitoses. (Fig. 4) Hence cytological diagnosis was benign bile duct lesion, bile duct adenoma. The absence of atypia and mitoses ruled out metastasis and other neoplastic lesions like cholangiocarcinoma. In addition, the absence of dilated lumina and intraluminal bile ruled out Von Meyenberg Complexes. The patient was then put on routine surveillance

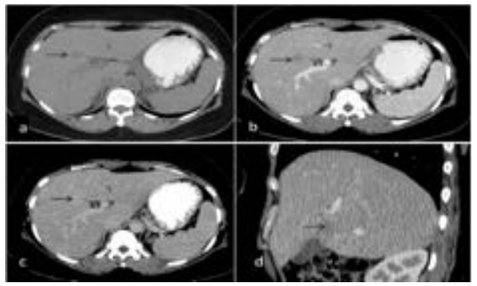

Figure 1: Axial CT scan non contrast (a) images and post contrast images in portovenous (b) and delayed phase (c) images show a hypodense nodule (arrows) which is hypoattenating to liver parenchyma on non contrast and post contrast portovenous phases, while is hyperattenuating on delayed phase images. (d) Sagittal reformatted image shows peripheral location of the lesion..

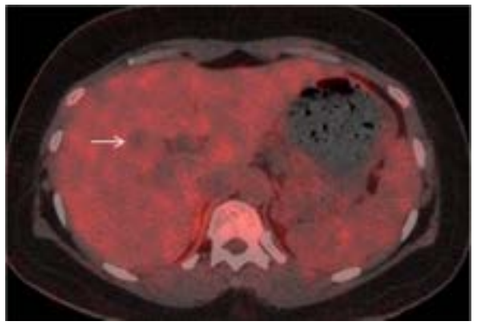

Figure 2: Axial fused images of PET CT scan shows no uptake in liver lesion (arrow)

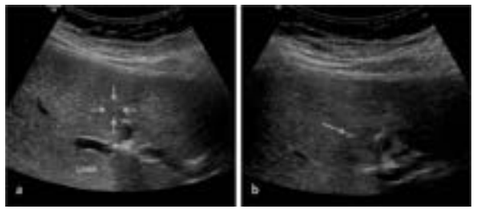

Figure 3: (a) Ultrasound images shows an isoechoic lesion with thin peripheral halo (marked with arrows). (b) USG guided FNAC was done. Arrow shows an echogenic tip of the needle in the liver lesion.

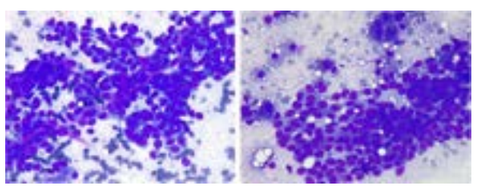

Figure 4: MGG stain 40x. It shows uniform cuboidal bile duct epithelial cells, with monomorphic nuclei, scanty cytoplasm. No atypia and no mitoses seen.

DISCUSSION

Bile duct adenoma is a rare benign tumor arising from the epithelial cells of the intrahepatic bile duct.

[1,2,3] The largest studies to date by Allaire et al [1], a study of 152 cases, found that most bile duct adenoma is asymptomatic and found incidentally during the intrabdominal surgery (103 case) or at autopsy (49). Bile duct adenoma constitutes around 1.3% of liver tumors. They are usually subcapsular in location, range from 1 to 20 mm in size and were well-circumscribed but non encapsulated. The majority occurred in patients between 20 to 70 years, with a mean age of 55 years.[1]

Microscopically, BDA is seen as the proliferation of disorganized and mature peribiliary gland acini and ductules within a variable amount of connective tissue stroma with signs of chronic inflammation and collagenization. There is no atypia or mitosis, which helps in distinguishing them from cholangiocarcinoma. BDA can also be confused with bile duct hamartoma (Von Meyenberg Complex), but lack of dilated lumina and intraluminal bile helps differentiate BDA from hamartoma.[4]

On ultrasound, BDA appears as a hyperechoic nodule with or without a surrounding halo. They can be isoechoic to the liver and could not be identified or can be hypoechoic.[5,6] In our case, BDA was isoechoic to the liver parenchyma and shows a thin peripheral hypoechoic rim (peripheral halo).

On an unenhanced CT scan, BDA is hypodense. It can appear hyperdense which is due to calcifications within.[7] In arterial phase images, hyperenhancement is a common feature but may appear hypodense.[6] They are hyperattenuating relative to liver parenchyma on port venous and equilibrium phase images.[5,6,8] This delayed enhancement is likely due to fibrous stroma which is seen in BDA.[6,9] This enhancement may vary depending upon the amount of fibrous stroma and may appear hypodense on delayed phase images.[6] In our case, BDA was hypoattenuating to the hepatic parenchyma on the port venous phase and hyperattenuating on delayed phase images.

On MRI, BDA appears as hypointense relative to liver on T1-weighted images, hyperintense on T2-weighted images, and hyperintense on DWI. BDA also demonstrated characteristic features on dynamic enhanced MRI, i.e., hyperenhancement in portal venous and delayed phase images.[6,10,11] However, there are case reports which showed hypointense signal[7] and isointense signal [8] on T2 weighted images. MRI was not done in our case.

To our knowledge, there is no data in the literature about the role of FDG PET in intrahepatic BDA. Our case showed no uptake on FDG PET which was in favor of benign findings. However, some low-grade tumors, mucinous tumors and small lesions may not show FDG uptake [12] and given known primary malignancy with the new-onset liver lesion, it was reported as suspicious for metastasis.

In patients with known malignancy, definite characterization of small liver lesions into benign vs. malignant is crucial in determining the prognosis and treatment. Jones et al[13] reported in their study that liver lesions less than or equal to 15 mm were found in 17% of the cases and were benign in 51% of the 82% of patients with known malignancy. Schwartz et al[14] in their study reported that hepatic lesions less than or equal to 1 cm, deemed too small to characterize, are most often benign, but approximately 11.6 % of these lesions were malignant. Schwartz et al also reported in their study that when these too small to characterize liver lesions were followed, the average reported time for an increase in the size of these TSTC liver lesions was 13 months if malignant in etiology. Therefore, it is helpful to obtain tissue for cytological/histopathological examination to obtain an accurate diagnosis and for better patient care.

"In conclusion, BDA, a rare primary liver tumor, have variable imaging characteristics ultrasound, but on dynamic contrast enhanced CT and MRI scans show arterial phase enhancement with progressive enhancement on delayed phase images, which are characteristics of BDA". However, some unusual imaging findings such as hypoattenuation on the equilibrium phase of CT scan are also reported in the literature. Being the rare tumor and possibility of unusual imaging findings, in a patient with known primary cancer, it is preferable to obtain tissue for cytology/histopathology to differentiate it from metastasis, which is more common than BDA.

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Shared Pathogenesis in Depression and Cancer Depicting the Anti-cancer Properties of Anti-depressants

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ABSTRACT

Pathogenesis of depression is similar to that of cancer in many aspects. Important mechanisms include effects on hypothalamo-pituitary-adrenal axis (HPA axis), functions of prostaglandins, inflammatory markers and cellular immunity. Anti-depressants must have the actions through above mentioned mechanisms when used to treat depression. Literature has mentioned the effects of various anti-depressant agents in reversing or modifying the pathogenic changes that occur in cancer too. Itâ€™s worth exploring the anti-cancer properties of anti-depressants and utilize those for the treatment of cancer whenever used for treating associated depression or other psychiatric conditions. Long term studies are needed to prove this less researched aspect of antidepressants.

Keywords: Depression- cancer- anti-depressants- anti-cancer properties

INTRODUCTION

Depression is common occurrence in cancer patients and antidepressants are widely used to treat depression, pain symptoms, chronic fatigue and anxiety among many other indications in cancer patients. Depression is associated with stress related chronic inflammatory changes and effects on hypothalamo-pituitary adrenal axis (HPA axis) in the body besides alteration in the levels and functioning of neurotransmitters like serotonin, nor-epinephrine & dopamine. Anti-depressants are known to act through all these mechanisms. There are many such molecular, pathological or immunological reactions that occur both in cancer too.

HPA AXIS & STRESS

Depression and stress are positively correlated. Depression is either caused or precipitated by the stress of any kind. The chronic activation of the HPA axis in depression impairs the immune response and may contribute to the development and progression of certain cancers (e.g breast & prostate cancer). Studies have described the instances where the onset of cancer has been first recognized immediately following some stressor, a financial crisis, a disaster, bereavement or an accident.

PROSTAGLANDINS

Prostaglandins are the ephemeral signallers self-regulating every cell in the body, including those serving for mood and immunity. Depression predisposes an individual to infection, osteoporosis, cancer, cardio-vascular diseases, neurodegenerative and auto-immune disorders and prostaglandins are incriminated in this causation. Excessive prostaglandin synthesis may depress immune function and induce cancer [1]. Similarly, prostaglandins are involved in various processes of carcinogenesis like signal disruption, cyclo-oxygenase up regulation, synthesis & expression of oncogene, increased cell replication, viral activation, changes in apoptosis, tumour initiation & promotion, metastasis, angiogenesis, immune-suppression and activation of mitochondria. Research mentions that chronic use of prostaglandin inhibitors like aspirin or ibuprofen reduced the risk of colon cancer by around 40%. Prostaglandins and thromboxanes are also involved in metastasis by neovascularisation and proteolytic enzyme production.

INFLAMMATORY MARKERS

Recently, the role of neuro-inflammation has been found in the pathogenesis of depression especially that of NLRP3-inflammasome complex [2]. Studies have mentioned the role of inflammasomes or their products, mainly IL 1β and IL-18 on carcinogenesis and progression of tumor also. These inflammasomes can be the therapeutic targets in cancer.

CELLULAR IMMUNITY

Depression is associated with the decreased activity of cytotoxic T cell and natural killer cells which affects the immune surveillance of tumours, occurrence & accumulation of somatic mutations and genomic instability [3]. Thus immune-suppression can be the aetiology or the consequence of the cancer and same is true for depression.

ANTIDEPRESSANTS

Studies showed that antidepressants have potent anti-neoplastic properties, both in vitro and in vivo. They are found to destroy the cells or arrest their proliferation [4]. Antidepressants keep a check on prostaglandin-synthesizing enzymes, they are cytotoxic and cytostatic (convert multidrug resistant cells to sensitive, and protect non-malignant cells from radiation and chemotherapy).

Antidepressant like fluoxetine, paroxetine, amitriptyline, mirtazapine, desvenlafaxine, venlafaxine, mianserin, imipramine and agomelatine are found to inhibit inflammasome by decreasing the serum levels of IL-1β & IL-18 and by reducing the NLRP3 & IL-1β (p17) protein expression [2]. They also have anti-inflammatory action on IL-6 and TNF-α. Research evidence shows that sertraline has an anti-tumor activity noticed by its effect on the cell viability and cell proliferation. Similarly, by inducing the apoptosis in myeloid leukemia HL-60 cells clomipramine, imipramine and citalopram were found to have anti-cancer properties. Paroxetine was also found to induce the apoptosis in human osteosarcoma cells. The effect was associated with p38 MAPK and caspase-3 pathways activation [5].

Thus, there is a sharing of pathogenesis' mechanisms by depression & cancer and anti-cancer properties of antidepressants can be utilized for the treatment of cancer whenever used for treating associated depression or other psychiatric conditions. Long term studies are needed to prove this less researched aspect of antidepressants.

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Psychological Impact of Corona on Mental Health of Cancer Patients

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SOUTH ASIAN J CANCER

The novel coronavirus disease 2019 (COVID 19), caused by corona virus, has affected the whole world. Infected cases are in lakhs but the fear of getting corona infection has affected almost everyone in the world. Cancer, on the other hand, is an already existing major health burden with high morbidity and mortality.[1] Cancer patients usually have lower immunity, and those on chemotherapy or radiation therapy (RT) are even more vulnerable to any kind of infection due to reduced immunity to combat any pathogen. First, research till date mentions that corona patients with comorbidities, like diabetes mellitus, hypertension, or cancer, have more mortality rate.[2] Second, many cancer patients have already existing psychological problems secondary to illness or its treatment. The fear of getting infected with corona may fur-ther jeopardize their mental health and coping ability to fight with cancer.

With daily increase in spread of corona virus, worries about infection, uncertainty about the end of its spread, psy-chological effects of lockdown (feeling of restriction in free-dom, irritability, and frustration), fear, panic, etc., are found in majority of cancer patients. This is over and above their worries and preoccupation about the cancer, chemotherapy schedules, adverse effects of chemotherapy or radiotherapy, financial burden, stigma and myths related to cancer, issues regarding the personal cancer care, etc. This has resulted in many cancer patients to present with increased severity of their psychological problems, aggravation of preexisting mental health issues, corona-related anxiety as a separate problem in addition to already diagnosed psychiatric illness and newly experiencing anxiety in patients who are other-wise coping well with cancer.[3,4] Few patients are found to have new appearance of symptoms of obsessive compulsive disorder and depression during the corona pandemic.

Psychological problems are known to affect the overall treatment outcome, prognosis and compliance to the can-cer treatment,[5] and additional anxiety of suffering corona infection may further complicate the course of cancer. It is therefore necessary to monitor all the cancer patients for this additional anxiety during the corona pandemic.

Many patients are found to request their oncologists to reschedule their chemotherapy or RT appointments which is happening from health care provider's side also. Elective surgeries are getting postponed either by surgeon or on the request of patient. Overall, the decisions about cancer treatments are being changed or delayed due to this "fear of corona infection" which can lead to the harmful conse-quences in cancer patients.

To reduce this fear, it is advisable for the cancer patients and their family members to take all the precautions neces-sary to avoid contracting the corona infection including fre-quent hand sanitization, wearing of mask while going out, avoid visiting others/going out of home as far as possible, and not to listen the news related to COVID 19 every now and then. Patients should seek help of mental health care pro-vider whenever needed. Cancer care providers also need to be sensitized about the psychological aspects of corona infec-tion in cancer patients, so that they can refer the patients needing specific psychosocial care to mental health workers. Psychosocial interventions like reassurance, supportive ther-apy, and cognitive behavioral therapy can be useful in this context along with psychotropic medications if required.

There has to be certain guidelines in all the cancer institu-tions regarding the screening and management of the mental health problems in cancer patients during the corona pan-demic, as, if left untreated, it may have long-lasting conse-quences besides a negative impact on cancer outcome and compliance.

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Ileal Conduit - Dissertation

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ABSTRACT

BACK GROUND OF THE STUDY:Cancer diagnosis is often perceived as a traumatic event that changes an individual's basic assumptions about the self as effective and powerful, and the world as benevolent, controllable, and predictable. Carcinoma of bladder is a heterogeneous disease which presents as superficial non-invasive, muscle invasive and metastatic disease. Bladder cancer is the ninth most common cancer in the world, with 430,000 new cases diagnosed in 2012. Bladder cancer is the second most common urologic malignancy in India and 80% of cases occur in patients over 50 years of age. In TMH in the year 2013, 62 cases were operated for radical cystectomy with ileal conduit. In cancer of bladder, patients undergo various surgeries such as radical cystectomy, neobladder, kock's pouch. Radical cystectomy remains one of the most effective methods of control of invasive bladder cancer. In men, the removal of the bladder may also include a prostatectomy and removal of the prostatic urethra and seminal vesicles. Often, loss of sexual function is a consequence. In women, a radical cystectomy includes removal of the bladder with perivesical fat, peritoneal attachments, proximal urethra, ovaries, fallopian tubes, uterus, cervix, anterior vaginal vault, and lymph nodes.The ileal conduit introduced by Seiffert and popularized by Bricker has been used for half a century, and it is still considered a standard form of urinary diversion following cystectomy for bladder cancer. During immediate postoperative phase the nurses role is to monitor the functioning of stoma, urine output, foleys catheter and stents are in situ, drainage and peristaltic movement.

STATEMENT OF THE STUDY

A study to identify the problems faced by the patients with ileal conduit and coping strategies adopted by them in a selected cancer hospital

OBJECTIVES OF THE STUDY

• To assess the problems faced by the patient's with ileal conduit.

• To assess the coping strategies adopted by the patient's with ileal conduit.

• To find association between problems faced and coping strategies adopted by the patient's with ileal conduit.

• To find association between problems faced and coping strategies adopted by the patient's with ileal conduit with their demographic variables.

RESEARCH METHODOLOGY
RESEARCH APPROACH

Exploratory descriptive survey research design approach is used in this study. Setting of the study was at Uro-oncology surgery outpatient department, Tata Memorial Hospital, Parel. The population selected for this study, are the target population which consist of patients with ileal conduit in Tata Memorial Hospital.

The sample selected for the study was 30 subjects with ileal conduit in a selected cancer hospital. Sampling technique used is non-probability convenience sampling.

The tool used was semistructured survey to identify the problems faced by the patients with ileal conduit and coping strategies adopted by them. Main study was conducted for duration of 6 weeks. Pilot study was conducted at Tata Memorial Hospital (TMH) from 30.12.13 to 4.1.14 after taking prior administrative permission from the Institutional Review Board (IRB) of TMH. The Pilot study was conducted to assess the feasibility and reliability of the tool and to decide the practicability of the research. The pilot study was conducted on 3 subjects operated for ileal conduit. Subjects were selected by non-probability convenience sampling.

SECTION I

Part I: Demographic variables are analyzed by frequency and percentage.

SECTION II

PART II Analysis of data to assess the problems faced by frequency and percentage.

PART III- Analysis of data to assess the coping strategies adopted by frequency and percentage.

PART IV-Association between problems faced and the coping strategies adopted is analyzed by Chi- Square test.

PART V-Association between problems faced with their selected demographic variables analyzed by Chi- Square test.

PART VI- Association between coping strategies adopted with their selected demographic variables analyzed by Chi-Square test.

SUMMARY OF FINDINGS

Part I: FINDINGS RELATED TO THE DEMOGRAPHIC CHARACTERISTICS OF SUBJECTS:-

• Demographic variables were categorized as age in years, gender, educational background, religion, duration after surgery, geographical area, marital status, and source of information.

• Majority 53.3% of the subjects were in the age group 51-60 years, 16.7% of them were from the age group 41-50 years and 71-80 years, and 13.3% in the age group of 61-70 years.

• Majority 90% were males and 10% only were females.

• 36.7% were graduate and above, 33.3% had secondary education, 10% were illiterate, 10% had primary education, and 10% had higher secondary education.

• Majority were Hindus 76.7%, 10% were from Muslim religion, 10% from Christian religion, and 3.3% from Sikh religion.

• 36.7% of the subjects were from 7-12 months of duration after surgery, 33.3% from 1-6 months, 16.7 % were from 19-24 months duration after surgery, and 13.3% were from 13-18 months duration after surgery.

• Majority 53.3% of subjects were from South, 23.3% were from North, 20% were from West and 3.4% from East India.

• Majority 93.3% were married and 6.7% were widows.

• 100% subjects were the source of information.

PART II: ANALYSIS OF DATA TO ASSESS THE PROBLEMS FACED BY FREQUENCY AND PERCENTAGE. PROBLEMS IDENTIFIED-PHYSICAL PROBLEMS

• 70% subjects were unable to fix the pouch at the stoma site

• 83.3% subjects observed leakage from the stoma pouch.

• 66.7% subjects got tape allergy around the stoma pouch.

• 93.3% subjects had complaints of mucus settling down around the stoma.

• 76.7% (23) subjects experience crystal formation around the stoma

PHYSIOLOGICAL PROBLEMS

• 60% subjects felt thirsty and experienced dryness of mouth

• 86.7% subjects were worried about change in body image.

• 86.7% subjects had anxiety and fear about stoma.

• 93.3% subjects were worried about functioning of stoma

• All subjects bothered about bad odor from stoma

• 56.7% experiencing difficulty during sexual activity

• 60% subjects had feeling to pass urine through urinary path

• 90% subjects had fear of uncertainty of living with stoma

• 60% subjects had experienced threat about change in role within family due to presence of stoma

SOCIAL PROBLEMS

• 50% subjects often felt lonely or isolated

VOCATIONAL PROBLEM

• Subjects had faced in getting back to their job.

PREVENTION OF COMPLICATIONS

• Prevented bulging stoma coming out from the abdomen, and stoma going inside in the abdomen

PART III: ANALYSIS OF DATA TO ASSESS THE COPING STRATEGIES ADOPTED BY FREQUENCY AND PERCENTAGE.

COPING STRATEGIES ADOPTED PHYSICAL PROBLEMS

• Chosen the appropriate pouch

• Measured the size of stoma

• Took appropriate steps to fix the pouch

• Asked others to help while fixing the stoma pouch.

• All subjects always cut the stoma size properly before application

• Always kept the skin around the stoma dry

• Always used skin barrier and paste

• Always changed the pouch early in the morning

• Always fixing the pouch around the stoma with double tape

• Other coping strategy elicited by the 24 subjects was themptying the ¾ th full pouch.

• 45% subjects always seeked stoma nurse advice for tape allergy around the stoma,

• Some subjects always made use of micropore paper tape

• Other coping strategy elicited by the 5 subjects used spirit to clean the skin around the stoma before applying the stoma pouch, used nycil powder over skin around the stoma and used dettol soap for cleaning the skin around the stoma.

• 43% subjects always use to seek stoma nurse advice

• 50% subjects always drank lemon juice in the morning

• 71.4% subjects always cleaned the stoma mouth whenever mucus settles around the stoma,

• Other coping strategy elicited by the 1 subject cleaned the stoma mouth with sodium bicarbonate powder diluted in water before attaching the stoma pouch.

• 56.5% subjects sometimes used to seek stoma nurse advice for crystal formation around the stoma,

• 91.3% subjects always used pouch with skin barrier

PHYSIOLOGICAL PROBLEMS

• 42.8% subjects always drank lemon juice

• Use to drink 8-10 glass of water

• 71.4% subjects always took high protein diet

PSYCHOLOGICAL PROBLEMS

• All subjects secured the pouch beneath the clothes.

• All subjects have developed their confidence about the stoma

• Other coping strategy elicited by the 3 subjects meditating to God and avoid thinking about stoma.

• 76.9% subjects never blamed God for their problems

• 61.5% subjects never isolated themselves from others.

• 73% subjects always used fantasy about being normal

• 50% (14) subjects always discussed with stoma nurse about functioning of stoma

• Other coping strategy elicited by the 6 subjects praying God to give strength to face the problem.

• Always drank daily 8-10 glasses of water to prevent bad odor

• Cuddles private parts of the spouse

• Other coping strategy elicited by the 15 subjects was day dreaming, kissing, hugging, and sleeping together with the spouse

• Always had phantom feeling and also had feeling to go to toilet to empty the bladder

• Majority of the subjects had feeling of hopelessness and loneliness due to fear of uncertainty of living with stoma

• 81.5% never isolated self

• Other coping strategy elicited by the 1 subject was praying to God and tried to avoid thinking about the presence of stoma.

• Always discussed the feelings with family members

• Always prayed to God for giving them grace

SOCIAL PROBLEMS

• Subjects always met friends

• Always tried to ignore the situation

• Always avoided phone calls/ emails

VOCATIONAL PROBLEM

• Always took financial help from family members

PREVENTION OF COMPLICATIONS

• Subjects always avoided using very tight fitting stoma pouch,

• Always supported the abdomen with hands while coughing

• Always avoided using sharp face plate while doing work

• Always avoided bending forward while doing work

• Always avoided strenuous activities

PART IV: ASSOCIATION BETWEEN PROBLEMS FACED AND THE COPING STRATEGIES ADOPTED IS ANALYZED BY CHI- SQUARE TEST.

Problems faced and coping strategies have a calculated Chi- Square value (x) is greater than the tabulated value at the level of significance p>0.05. Hence it is proved that there is no statistical association between problems faced and coping strategies adopted by the subjects with ileal conduit. From this it is evident that subjects adopt different coping strategies depending on each problem.

PART V: ASSOCIATION BETWEEN PROBLEMS FACED WITH THEIR SELECTED DEMOGRAPHIC VARIABLES IS ANALYZED BY CHI- SQUARE TEST.

Problems faced were divided in to two categories for the benefit of simplification of the data. From the above table it can be interpreted that demographic variables (age in years and duration after surgery) have a calculated Chi Square value (x^2)tabulated value at the level of significance P>0.05 Hence both the demographic variables have no statistical significant association between problems faced by the patients with ileal conduit with their demographic variables.

PART VI: ASSOCIATION BETWEEN COPING STRATEGIES ADOPTED WITH THEIR SELECTED DEMOGRAPHIC VARIABLES IS ANALYZED BY CHI- SQUARE TEST.

Demographic variables (age in years and duration after surgery) have a calculated Chi Square value (x) and the tabulated Chi Square value at the level of significance P>0.05. Hence both the demographic variables have no statistical significant association between coping strategies adopted by the patients with ileal conduit.

CONCLUSION

The present Study was conducted to identify the problems faced by the patients with ileal conduit and coping strategies adopted in a selected cancer hospital. This chapter dealt with the analysis and interpretation of data. 30 subjects were included in the study. From this study it is , evident that subjects adopt different coping strategies depending on each problem. Secondly there are different problems are idenitified mainly in the domains of physical and psychological. Along with different coping mechanisms have come to surface in the domains of physical, physiological, psychological, social, vocational, and in prevention of complications.

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Measurable Residual Disease in Acute Lymphoblastic Leukemia Treated with Non-MRD Based Protocol

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BACKGROUND

Age, presenting total leukocyte counts. steroid response and cytogenetic are known prognostic markers for acute lymphoblastic leukemia (ALL). Measurable Residual Disease (MRD) (or minimal residual disease) after induction chemotherapy is well accepted prognostic marker in childhood leukemia.

Objectives

To study correlation of known risk factors with MRD at the end of induction therapy. Can MRD be avoided in various morphology based risk groups?

DESIGN/METHOD

This is a retrospective analysis of newly diagnosed pediatric patients withALL. who received their induction chemotherapy from September 2017 to August 2020. Patients were treated with IC-BFM 2002 protocol (non-MRD based), and were risk stratified into three risk groups as per protocol. At the end of induction chemotherapy. MRD was done by flow- cytometry on bone marrow sample. Statistical analysis was done to see correlation of various known risk factors and risk groups with MRD.

RESULTS

Total 68 children were included over a 3-year period. Median age was 6 years (1-16 years) with male preponderance (male: female = 1.83). Median total leukocyte count was 14560/cu.mm (72390-330). Eighty-three percent (57/68) were B cell ALL and 16% (11/68) were T cell ALL. In B cell ALL. cytogenetic analyses done in 54/57 patients. t(12:21) was present in 8(15%) patients and was the commonest abnormality. Three (3.7%) were positive for t(9:22). Thirty-seven children (68%) had normal cytogenetic. Day-8(D8) steroid response was available for all 68 patients. Based on age, presenting counts. D8 response and cytogenetics. 21(29.4%) were in standard risk. 42(58.8%) were in intermediate risk and 5(11.7%) were in high risk group. Day-15(D15) marrow was done for 53 children. 51had M1,1had M2 and1had M3 marrow status. Seven out of Sixty-Eight children (10%), had positive MRD after 1 month of induction. All were pre B ALL. All standard risk except 1had negative MRD post induction chemotherapy. Seven perecent (3/42) of intermediated risk and 60% (3/5) of high risk had positive MRD post induction chemotherapy. Age, presenting counts, cytogenetic and D8 steroid response is not associated with MRD. D15 marrow morphology (P=0.015) and risk groups (P=0.001) had statistically significant association with MRD.

CONCLUSION

In resource constrained settings. MRD can be avoided in patients with standard risk ALL. Though morphology-based risk-group stratification allows identification of high-risk patients to some extent, still significant number of intermediate and high risk patients had positive MRD which was not identified by conventional risk stratification. MRD cannot be avoided in these risk groups, who require optimisation of therapy to prevent relapse based on their MRD status.

Safety, Feasibility and Acceptability of Peripherally Inserted Central Catheter (PICC) Line in Paediatric Oncology Patients: Experience from Tertiary Oncology Centre in Central India

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BACKGROUND AND AIMS

A long term venous access is essential inchildren when treating malignant disease. The peripherally inserted central catheter (PICC) is commonly used central venous access in children and adolescents. It's use has been increased over years, mainly in cancer patients, for the administration of intravenous chemotherapy and frequent transfusions. The purpose of study to determine safety. feasibility and acceptability of PICC use and to determine PICC related complication and reason of removal in Tertiary Care Pediatric Oncology Unit of Central India.

METHODS

All Pediatric patients (age below 16 years) with hematolym-phoid malignancy or solid tumor who underwent PICC line insertion at National Cancer Institute, Nagpur from February 2018 to December 2020 were enrolled in the study. Demographic features, primary diag- nosis, catheter days, complications, and reasons for removal of device were recorded during this period.

RESULTS

A total of 61 PICCs were inserted during February 2018 to December 2020. Insertion success rate was 100%. Catheter main- tenance success rate was 57.3% and median catheter life span was 107 days per device. PICC line infection seen in 27.86%, catheter block- age in 9.83%, accidental removal in 4.91%. Infections and catheter occlusion were the common complications.

CONCLUSIONS

PICC line use is safe, reliable and well acceptable in pedi-atric patient for long term use. Though infection control is main chal- lenge which require repeated training and counselling of nursing staff.

"Metronomic Chemotherapy for Burkitt Lymphoma in a Patient With HIV," Case Report

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SUMMARY

Burkitt lymphoma (BL) is an aggressive type of non-Hodgkin lymphoma (NHL). With high-dose combination chemo-therapy, cure rates are excellent. Treatment for HIV-positive BL is similar to that for HIV-negative BL. Offering long-term intensive chemotherapy is difficult in resource-limited settings. Oral metro-nomic chemotherapy, though in vogue as a treatment modality, has limited evidence of its efficacy in HIV-positive BL. Here, we present the case of a child who was diagnosed with BL and HIV and administered metronomic chemotherapy, and also review the liter-ature on the role of metronomic chemotherapy in non-Hodgkin lymphoma with and without HIV.

Key Words: Burkitt lymphoma, metronomic chemotherapy, non-Hodgkin lymphoma

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Burkitt lymphoma (BL) is an aggressive variant of non-Hodgkin lymphoma (NHL). With current short-term high-dose combination chemotherapy, cure rates are excel-lent. There is a 10% to 20% lifetime risk of developing BL in patients diagnosed with HIV.1 Morphologic, clinical, and cytogenetic characteristics of patients with BL and HIV are similar to those of patients with sporadic BL. Treatment for HIV-positive BL is derived from the HIV-negative BL treatment protocol along with highly active antiretroviral therapy (HAART2).

PATIENT AND METHODS

The patient is a 4-year-old boy, who presented to our clinic with a 20-day history of progressive swelling over his right cheek and left eyelid. Before this presentation, at the age of 8 months, he had global developmental delay and an epileptic disorder and was treated with sodium valproate.

At 3.5 years, he was admitted to the hospital in status epilepticus. Investigations revealed that he was suffering from HIV with encephalopathy. His absolute CD4+ count was 271 cells/cumm (430 to 1740 cells/cumm). He was treated with antiepileptic drugs (levetiracetam and cloba-zam) and HAART (efavirenz, lamivudine, and abacavir). Regular follow-up was recommended on discharge.

On presentation to our clinic, he was severely mal-nourished. Neurological examination showed normal superior mental functions, normal examination of the cra-nial nerve, increased muscle tone in the lower extremities, brisk deep tendon reflexes, a positive Babinski sign, and contractures in both ankle joints, possibly due to hypoxic injury to the brain secondary to the previous episode of status epilepticus. The rest of the clinical examination was unremarkable.

A biopsy of the submandibular mass was performed at another center and reviewed at our institute. This biopsy revealed a lymph node with complete effacement of lym-phoid architecture by atypical lymphoid cells that were intermediate in size, with moderate eosinophilia at places with vacuolated cytoplasm and large nuclei with prominent basophilic nucleoli were seen. Mitosis was brisk and apop-totic bodies were numerous. Plenty of tingible body mac-rophages were seen, giving it a starry sky appearance. The histopathology report was signed out as high-grade NHL suspected to be BL. On immunohistochemistry, tumor cells demonstrated diffuse and strong immunoreactivity for CD-20, CD-10, EBV-LMP, and c-Myc (Figs. 1A-D). The tin-gible body macrophages showed immunoreactivity for CD-68. Tumor cells were immune-negative for TdT and CD-99 (Figs. 1E, F). Occasional reactive T cells showed CD-3 immunoreactivity. The MIB-1 labeling index was 100%(Fig. 1G).

Cerebrospinal fluid analyses revealed the presence of atypical lymphoid cells. Atypical cells were not analyzed by flowcytometry. Bone marrow aspiration and biopsy were normal, same as his complete blood count and peripheral smear. His serum LDH was 546 U/L (85 to 227 U/L) and his CD4 count was 340/microliter (430 to 1740 cells/microliter).

STAGING

18F-fluorodeoxyglucose positron emission tomog-raphy/computed tomography (18F-FDG PET/CT3,4)(Figs. 2A, C–E) revealed an FDG avid lytic destructive mass lesion involving the right mandible with a large soft tissue component consistent with the clinical findings of a right cheek swelling. Another FDG avid soft tissue density was noted along the left periorbital region in the lateral aspect with the erosion of the adjacent orbital bones, which was causing left eyelid swelling.18F-PET/CT suggestive of widespread FDG avid lesions in the whole body scan seen in the maximum intensity projection image (Fig. 2) with cor-responding transaxial (Fig. 2E) and sagittal images (Figs. 2C, D).

Based on the histopathology report, IHC, and PET/CT, he was diagnosed with stage IV BL and stratified as R4.5 The child was started on prophase chemotherapy (Table 1) after 3 days of admission, as per the BFM95 lymphoma protocol along with intrathecal methotrexate.5 During prophase chemotherapy, he developed SIADH (syndrome of inappropriate antidiuretic hormone secretion),

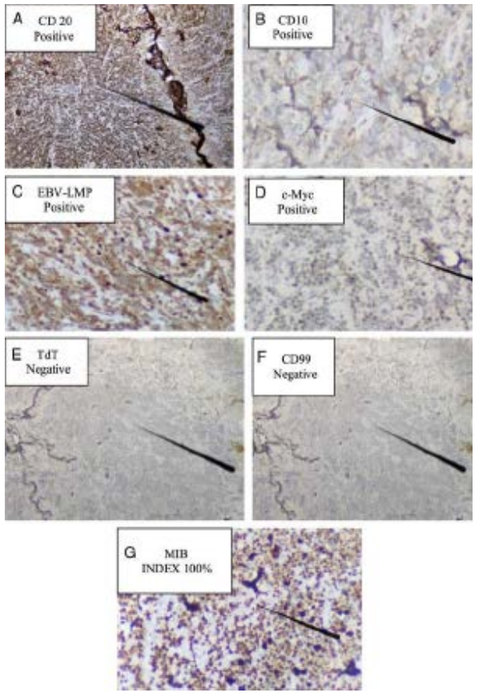


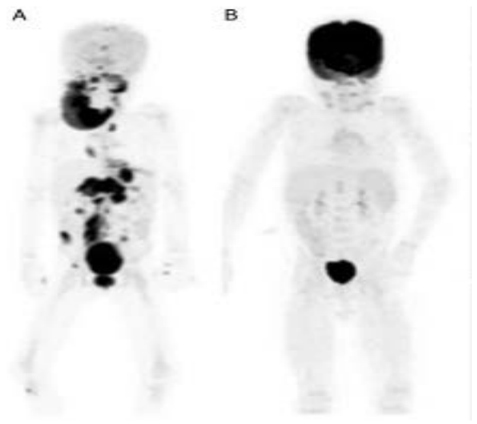
FIGURE 1. IHC of tissue biopsy from submandibular region. Tumor cells showed diffuse and strong immunoreactivity for CD-20 (A), CD-10 (B), EBV-LMP (C), and c-Myc (D). Tumor cells were negative for TdT (E) and CD99 (F). MIB index was 100% (G).

which was treated with 3% hypertonic saline and fluid restriction. SIADH might have been a side effect of the cyclophosphamide or due to the presence of a disease involving the CNS. Within a few days, his clinical condition improved. Postprophase, no imaging was done for response evaluation, though the mandible swelling and orbital swel-ling decreased in size. Parents were counseled regarding the standard chemotherapy plan but they were not willing to undergo intensive chemotherapy. Then, they received explanations on Oral metronomic chemotherapy (OMCT) along with intrathecal methotrexate, to which they con-sented. OMCT was started along with intrathecal metho-trexate from day 8 of prophase. OMCT consists of 40 mg/m2 of prednisolone divided into two doses for two weeks per month, 50 mg/m2 of cyclophosphamide and 50 mg/m2 of etoposide once a day for 21 days every month. Intrathecal methotrexate was given initially weekly till cerebrospinal fluid became clear of blasts (total 4) and then monthly. His HAART was continued during oral chemotherapy.

He underwent 12 months of OMCT along with intrathecal methotrexate. He was transfused with packed red blood cells once during OMCT. His absolute CD4 counts were in the range of 271 to 243 cell/cumm during OMCT. Clinical examination, hematological monitoring, and biochemical monitoring were performed once a month during OMCT. He had normal absolute neutrophil and platelet counts. His biochemical parameters were in the normal range during the course of OMCT.

RESULTS

At the end of 12 cycles, PET/CT (Fig. 2) was suggestive of complete remission of the disease. During the 21-month follow-up, the child was asymptomatic and his nutritional status improved. Although receiving HAART, he is being followed up by a pediatric neurologist for his global developmental delay.



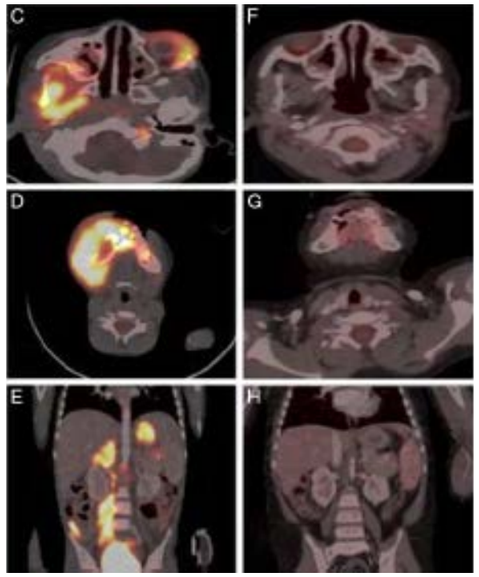


FIGURE 2. 18 F Fluorodeoxyglucose positron emission tomography/computed tomography (18F PET/CT) with pretreatment maximum intensity projection (MIP) image (A) and posttreatment (MIP) image (B). Corresponding transaxial images shows a lesion in the left orbit shown with (C), right mandible (D) and extensive abdomino-pelvic nodes (E). Posttreatment transaxial images (F–H) show complete metabolic treatment response.

DISCUSSION

BL is an aggressive type of lymphoma and requires intensive chemotherapy, with the current protocolsâ€™ cure rates ranging from 50% in low-income and middle-income countries to more than 85% in high-income countries.6 In recent years, the addition of rituximab to standard chemo-therapy has improved event-free survival (EFS) and overall survival (OS) as compared to standard chemotherapy.7

The standard treatment for HIV-positive patients with BL is no different from that for those who are HIV-negative. Most of the protocols used for adult and pediatric NHL are intensive ones with a range of associated morbidity and mortality rates. There are studies on elderly patients diagnosed with NHL (low-grade and high-grade) who were treated with metronomic chemotherapy with various success rates.8 The term metronomic therapy was first used by Hanahan et al9 in his commentary where low-dose therapy was used in an animal model. Metronomic chemotherapy consists of low doses of chemotherapeutic agents given at regular intervals without much treatment-free break.10 Metronomic chemotherapy works on different targets such as cancer stem cells, endothelial cells, tumor vasculature, and the immune system.10 Because of the low dose, there is decreased risk of adverse reactions and a lower risk of acquired drug resistance compared with conventional chemotherapy.

TABLE 1. Drugs Used in Prophase Chemotherapy	
Inj Dexamethasone	5 mg/m2 day1 and day 2
Inj Cyclophosphamide	10 mg/m2 (day 3â€“5)
Intrathecal Methotrexate	200 mg/m2 day 1 and day 2 12 mg

Safety data and the effectiveness of OMCT: A prospective study by Zeng et al11 described the outcomes of relapsed NHL patients treated with metronomic chemo-therapy. The study included a test arm (patients treated with metronomic chemotherapy) and a control arm where patients received conventional chemotherapy. After 12 months of treatment, the overall response rate and disease control rate of the test group (47.8% and 69.6%, respectively) were significantly higher than those of the control group (19.0% and 33.3%, respectively). This study had a few remarkable findings: (1) metronomic chemotherapy is effective in relapsed refractory NHL patients and improves response rates and progression-free survival in this group of patients. (2) Combination of prednisone, etoposide, and cyclophosphamide is a well-tolerated metronomic chemo-therapy regimen. (3) Lowering the vascular endothelial growth factor level and the number of circulating endothelial cells in the test group could be the reason for the therapeutic response. Although we used the same drugs used in the above study, there were differences in dose and schedule, we used for our patient as Zeng et al.[11]

In the aforementioned study, prednisone 15 mg per day, etoposide capsule 25 mg per day, and cyclo-phosphamide 50 mg per day were administered continuously. Our patient received 40 mg/m^2 of prednisolone divided into 2 doses of 2 weeks per month, 50 mg/m^2 of cyclophosphamide, and 50 mg/m^2 of etoposide once daily for 21 days each month. Data on the safety and effectiveness of metronomic chemotherapy in children were published by Andre et al.[12] They described the safety profiles of 4 drugs used for metronomic therapy in various relapsed refractory pediatric malignancies and concluded that these 4 drugs (cyclophosphamide, vinblastine, methotrexate, and cele-coxib) were well tolerated and associated with disease stabilization.

Literature mentioning the use of low-dose chemo-therapy in the treatment of BL with HIV infection is limited. Ngoma et al13 presented the outcomes of African children treated according to the International Network for Cancer Treatment and Research's strategy using low-intensity chemotherapy in BL. Post-treatment analyses revealed an event-free survival of ~54% over 1 year and 52% over 2 years. The overall survival was 67% over 1 year and 62% over 2 years. No separate analysis of HIV patients was available.

Treatment course and toxicities of oral metronomic chemotherapy: Orem et al14 described the role of dose-modified oral chemotherapy in the treatment of NHL in adult HIV-positive patients (n = 49). The overall objective response rate was 78% (95% CI, 62%-88%). They described compliance rates and various toxicities in HIV-positive patients on OMCT. The authors concluded that there were no challenges with oral chemotherapy and adherence to the protocol. Nausea and vomiting were negligible and car-diotoxicity was absent. Dose modifications were needed for hematological toxicity but not for other kinds of toxicity. No patient stopped treatment due to unresolved intervening myelotoxicity. Four episodes of grade 3 or 4 febrile neu-tropenia (5% of cycles) and 4 grade 3 infections were reported. Eight deaths occurred during chemotherapy, and three were considered directly related to chemotherapy (the treatment-related mortality rate was 6%). There was no significant drop in CD4+ counts, as the median CD4+ count was 198 cells/μL during the therapy. Our patient required a unit of packed red blood cells during therapy; otherwise, he tolerated OMCT well. His CD4+ counts did not reduce significantly during OMCT.

Duration of oral metronomic chemotherapy: Although there are no guidelines for the duration of OMCT, various studies mentioned a range of durations of OMCT in different diseases. A retrospective analysis by Mailankody et al15 reported that the median duration of OMCT was 6 months (1 to 49 mo) in adult patients diagnosed with NHL. They analyzed the data of 149 patients who received OMCT from 2007 to 2017. OMCT was used at the time of diagnosis in 41 patients (27.5%) and after relapse in 108 patients (72.5%). The overall response rates were 43.9% and 41.7% with clinical CR in 14 (34.1%) and 21 (19.4%) cases among patients given first-line and later lines of OMCT, respec-tively. We gave OMCT for 12 months, as most cases of BL recur within 6 months of completion of therapy.

Despite the literature records of OMCT, BL, and HIV, there is a lack of publications in the pediatric population. In the present case, the child's parents were counseled regarding the standard of care; however, they were not willing to have their child undergo high-intensity chemotherapy. On the basis of the available literature, the option of oral metro-nomic chemotherapy with monthly intrathecal methotrexate was discussed and after obtaining parental consent, the child was started on OMCT and intrathecal methotrexate.

Over 1 year of treatment, he did not require admission and tolerated oral chemotherapy and HAART.

CONCLUSION

This could be one of the rare case descriptions where an HIV-positive child with BL was cured with OMCT. In resource-limited settings, treatment with high-dose chemo-therapy is challenging and the treatment-related mortality rate is high. There is an urgent need for alternative treatment when resources are limited and comorbidities exist. Though metronomic chemotherapy is not a standard of care for BL, it can be a potential subject for randomized controlled trials to qualify as an effective and affordable therapy for BL.

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Carcinoma Cervix in a Rare Case of Uterine Didelphys: A Case Report and Review of Imaging Findings

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ABSTRACT

Uterine didelphys is an uncommon finding seen in 1 in 3000 females. Didelphys uterus with cervical cancer is an infrequent condition in clinical practice. There are few cases reported to date of these conditions co-existing. Association between Mullerian malformation and cervical cancer limited to medical references. Risk factors for cervical carcinoma include human papilloma virus (HPV) infection, becoming sexually active at a young age (especially younger than 18 years old) or having multiple sexual partners, smoking, HIV /AIDS, Chlamydia infection and long term use of oral contraceptives. The most common presentation is abnormal vaginal bleeding, as is the case with our patient. Here we present a rare case of carcinoma cervix in didelphys uterus..

CLINICAL PRESENTATION

This patient is a 50 year old female patient, G2P2L2A0 with both normal vaginal deliveries. She had no significant past medical history and was not diagnosed to have didelphys uterus. She presented with postmenopausal per vaginal bleeding since 3 months. Per-vaginal and per speculum examination revealed a 3x4 cm sized cervical mass with involvement of left posterior parametrium and supple right parametrium. Per-rectal examination revealed uterosacral involvement on left side and rectal mucosa was free. Clinically, the patient was diagnosed as carcinoma cervix stage IIB.

Cervical biopsy was performed which revealed squamous cell carcinoma involving cervix. Hence, referred to radiology department for staging CT scan and MRI.

Differential Diagnosis:

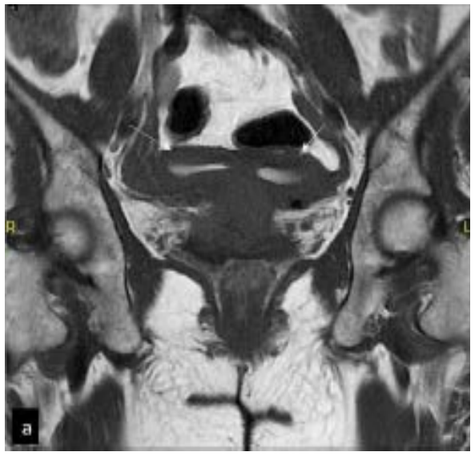
The differential diagnosis for postmenopausal bleeding includes both gynecologic and non-gynecologic etiologies, both benign and potentially malignant, such as endometrial atrophy, endometrial carcinoma, cervical carcinoma, polyp, endometrial hyperplasia, adenomyosis and infection.(3)

Imaging Findings:

Contrast enhanced (CE) MRI pelvis was performed on 1.5T GE Signa voyager, for local staging of carcinoma cervix. Sequences obtained are FSE T1W, FSE T2W, and small FOV frFSE T2W images dedicated to cervix. DWI and dynamic contrast enhanced images were also obtained since they provide a useful adjunct to the diagnostic information provided by the regionally recommended sequences. Contrast enhanced CT scan of thorax and abdomen was performed on 16 slice GE Discovery scanner from thoracic inlet to iliac crest before and after intravenous iodinated contrast administration to look for distant nodal/ visceral metastases. CE-MRI pelvis revealed a typical imaging finding of uterine didelphys, i.e., complete duplication of uterine horns, wide separation of the uterine fundi as well as duplication of cervix. Two vaginas were also seen with septum in upper vagina. There was an altered signal intensity mass involving both the cervixes with fistulous communication between them. There was also obliteration of their lumen and internal os with resultant hematometra in both uterine horns. (Fig 1) The mass extended to the lower uterine bodies of both uterine horns superiorly and upper third of the vagina inferiorly. Bilateral medial parametrium were involved. (Fig 2) It showed restricted diffusion on diffusion weighted images and moderate early and persistent enhancement on dynamic contrast enhanced images.

(Fig 3) There was no involvement of lower two third of vagina, upper uterine bodies, ureters, lateral pelvic wall, urinary bladder or rectum. There was no significant pelvic lymphadenopathy. CT scan revealed no retroperitoneal lymphadenopathy or distant visceral metastases. Hence, according to FIGO staging system for uterine cervical cancer 2018, radiologically it was stage IIB.

Following staging and regional multidisciplinary discussion, the patient underwent definitive concurrent chemo-radiotherapy.



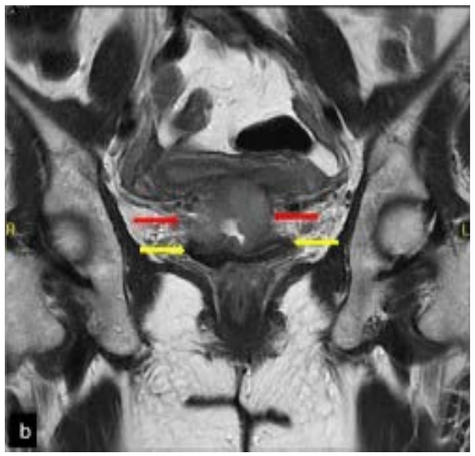


Figure 01: MRI T1W (a) and T2W(b) coronal images demonstrating two uterine cavities with hematometra (white arrows in a), mass involving both cervices (red arrows in b), two separate vagina (yellow arrows in b).

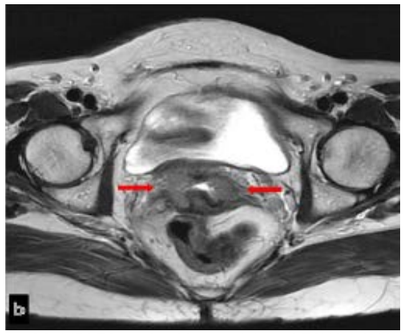


Figure 02: MRI T2 sagittal image(a) and T2W axial image (b) illustrating intermediate signal intensity mass involving the cervix, lower uterine body and upper vagina (white arrow in a) and bilateral medial parametrial infiltration (red arrows in b). Fistulous communication between two cervices is also seen in b

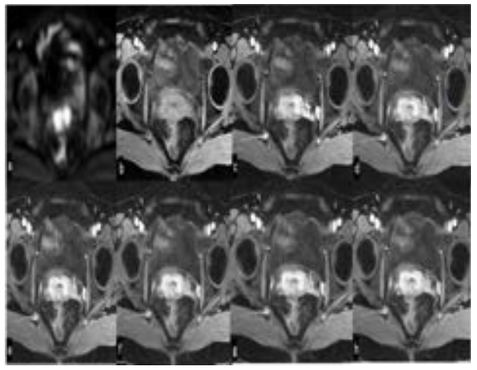
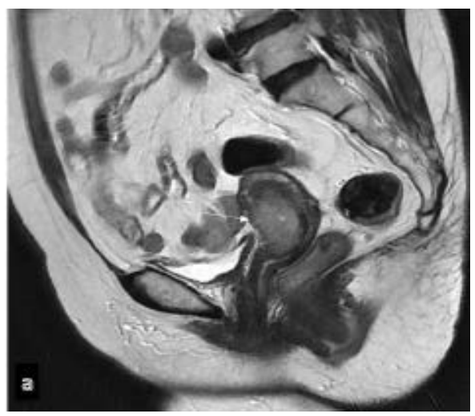


Figure 3. Axial MRI DWI (a) and Dynamic contrast enhanced fat saturated T1W axial image(b - h) illustrating , diffusion restriction in cervical mass (a), early and persistent contrast enhancement on dynamic contrast images (b-h).



DISCUSSION:

A didelphys uterus is a very rare Mullerian duct anomaly (4) and carcinoma cervix in anomalous uterus is even rarer with only case reports in the literature.(5)(6)(7) Most women with a didelphys uterus are asymptomatic, however in the presence of a thick, sometimes obstructing vaginal septum, they can present with dysmenorrhea or dyspareunia. This obstructing vaginal septum can lead to hematocolpos/hematometrocolpos and thus patient can present as chronic abdominal pain as well (5). Rarely, genital neoplasm's and renal anomalies are reported in association with didelphys uterus.(4) In our case report, the patient was unaware of presence of didelphys uterus because she had no problems at reproductive age and develops two pregnancies with successful evolution. Uterine anomalies such as our case of uterine didelphys can be diagnosed using Journal of MAR Oncology (Volume 3 Issue 4) multiple imaging modalities such as ultrasound, hysterosalphingography (HSG) and MRI.(8) Ultrasonography is widely available and is usually first investigation in evaluation of any pelvic

pathology. Ultrasound shows separate divergent uterine horns with a large fundal cleft. Endometrial cavities are uniformly separate, with no evidence of communication. Two separate cervices are seen.

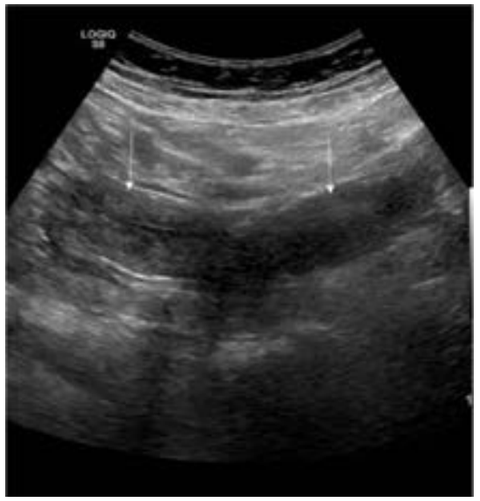


Figure 4. Ultrasonography image demonstrating two uterine cavities (white arrows).

(Fig 4) HSG demonstrates two separate endocervical canals that open into separate fusiform endometrial cavities, with no communication between the two horns. Each endometrial cavity ends in a solitary fallopian tube.(9)

Magnetic resonance imaging (MRI) has excellent soft tissue resolution. It helps in detail anatomical evaluation and to rule out associated pathology. MRI shows two separate uteri with widely divergent fundi, two separate cervices, and usually an upper vaginal longitudinal septum. Normal uterine zonal anatomy is preserved in each uterus (Fig 1).

Local staging of cervical malignancy is most accurately performed with dedicated MRI protocol. MRI provides excellent anatomical detail and characterization of both normal anatomy and co existing pathology. MRI is superior in its ability to not only stage cervical stromal involvement in cervical carcinoma but also assess invasion into adjacent structures such as parametrium, uterus, vagina, urinary bladder and rectum.(10) Demonstration of nodal involvement is of utmost importance in the treatment planning. MRI is a safe (with accurate check listing), noninvasive and usually well tolerated imaging method with good pathological correlation in staging gynecological malignancies. However, patient compliance, poor renal function and movement artifact more often due to bowel peristalsis may limit MRI staging. Limited spatial resolution also affects image interpretation.

In our case, both uterine anomaly and malignant pathology are clearly demonstrated and accurately staged with dedicated MRI pelvis. It is also essential for the surgeon / radiation oncologist to be aware of relevant anatomy before embarking on definitive surgery / radiotherapy. MRI is particularly useful in distinguishing between different uterine malformations and is in most case superior in this regard in comparison to ultrasonography and hysterosalpingography.

In this case, we have reported a rare occurrence of carcinoma cervix in a didelphys uterus and its imaging findings. The detail knowledge of anatomy, anomalies and staging are important in carcinoma cervix before planning surgery or radiotherapy.

KEY POINTS

1. MRI is the most useful imaging modality for defining Mullerian tract anomalies and staging gynaecological malignancies. 2. It is essential for the treating surgeon / radiation oncologist to be aware of the relevant anatomy prior to definitive surgery / planning of radiotherapy. 3. In this case MRI images clearly depicts anatomy as well as detail extent of the pathology.

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Unusual case of isolated post-styloid parapharyngeal space metastasis in a treated case of carcinoma supraglottis: A case report and review of literature

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ABSTRACT

Squamous cell carcinoma of supraglottis is a common head and neck malignancy, comprising 30% of laryngeal carcinoma. Supraglottic carcinoma commonly metastasizes to the Levels II, III, and IV cervical nodes, and distant metastases are uncommon. Delayed local and regional recurrences are known, local recurrence being more common. We report a case of carcinoma supraglottis with the advanced locoregional disease at initial presentation and treated with neoadjuvant chemotherapy followed by chemoradiotherapy with a complete response on post-treatment positron emission tomography-computed tomography (PET-CT) scan. Surveillance PET-CT showed an isolated lesion in the left post-styloid parapharyngeal space, where neurogenic tumors are more common and isolated nodal metastasis is unusual. We did ultrasound-guided FNAC and cytology confirmed the presence of metastatic poorly differentiated carcinoma.

Key words: Carcinoma, Supraglottis, Parapharyngeal space, FNAC, Cytology

Carcinoma larynx constitutes around 25% of head and neck malignancies and around 30% of which arise in supraglottis [1]. Tobacco and alcohol consumption are important risk factors for carcinoma larynx [2,3]. Most patients with carcinoma supraglottis usually present late as the most common presenting symptom in the early stage is pain and hoarseness of voice is seen only in the advanced stage of the disease indicating the involvement of glottis. Other presenting symptoms are neck mass, dysphagia, aspiration as well as its sequelae, and airway compromise [4]. TNM staging eighth edition is the staging system for carcinoma supraglottis. Supraglottic carcinoma commonly metastasizes to the Levels II, III, and IV cervical nodal levels [5]. The incidence of distant metastasis in head and neck squamous cell carcinoma is low [6,7]. In carcinoma supraglottis, local recurrence is more common than regional recurrence and the risk of recurrence increases with advanced primary tumor stage and nodal involvement. Isolated nodal metastasis to the post-styloid parapharyngeal space (PPS) which harbors level VIIb lymph nodes is very unusual in carcinoma supraglottis with no local recurrence or regional recurrence to lower cervical nodes.

In this case report, we report an unusual case of isolated post-styloid PPS metastasis, where nerve sheath tumors are more common than nodal metastasis. It is important to differentiate between the two, which affects the patient's treatment. Obtaining tissue from such deep neck space for cytology/histopathology is sometimes difficult. We have also performed an unusual ultrasound-guided fine-needle aspiration cytology (FNAC) of this deep lesion and also discussed different access for obtaining tissue for cytology/histopathology.

CASE REPORT

A 69-year-old male patient was diagnosed with carcinoma supraglottis in 2019. Initial TNM staging at presentation was cT4N3bMo. He received nine cycles of neoadjuvant chemotherapy followed by definitive chemoradiotherapy (the last dose was on 04.03.2020). Post-treatment positron emission tomography-computed tomography (PET-CT) done in March 2020 showed complete response and the patient was on surveillance during which, he was completely

asymptomatic. Surveillance PET-CT scan done in July 2021, approximately 16 months after completion of therapy, showed a hypoenhancing FDG avid soft tissue in the left post-styloid PPS close to the skull base. Superiorly, it was extending up to the jugular foramen and carotid canal without extension into it. There was no bone erosion. It encased the left internal carotid artery (ICA) (angle of contact was 360 degrees) and mildly displaced the left internal jugular vein (IJV). There was no increase in distance between the ICA and IJV when compared to the contralateral side (Fig. 1). There was no local recurrence in supraglottis or no involvement of lower cervical lymph nodes. Nerve sheath tumors are more common in post-styloid PPS and it is very unusual to have isolated nodal metastasis in post-styloid PPS. However, since the patient had a history of malignancy, our differentials were both metastasis and nerve sheath tumors.

Since the lesion was located medial to styloid process which was densely calcified, it was difficult to do CT-guided FNAC using retromandibular or transcondylar approach. Anterior approach through the infratemporal fossa was possible under CT guidance but was limited by the parapharyngeal venous plexus (Fig. 1). Hence, we evaluated with ultrasound for a possible approach for FNAC. Ultrasound revealed a solid hypoechoic soft-tissue mass in the left suprahyoid carotid space close to the skull base involving ICA and found a safe window for FNAC using the transparotid approach. Hence, we performed ultrasound-guided FNAC (Fig. 2). Smears obtained were cellular and cytology revealed metastatic poorly differentiated carcinoma.

Although the disease was limited to suprahyoid post-styloid PPS, curative radiotherapy was not possible due to the high risk of a carotid blowout and spinal cord and brainstem myelopathy. Hence, the patient started on chemotherapy (Nanoxel, Carboplatin, and Cetuximab) and received 13 cycles. PET-CT scan done after chemotherapy showed a significant interval decrease of the lesion in the left post-styloid carotid space with mild residual soft-tissue thickening which showed no FDG uptake, suggestive of complete metabolic response (Fig. 3).

DISCUSSION

Supraglottic carcinoma is a common head and neck malignancy comprising around 30% of laryngeal cancer [1]. TNM staging eighth edition is the staging system for carcinoma supraglottis. Supraglottic carcinoma commonly metastasizes to the Levels II, III, and IV cervical nodal levels [5].

Various treatment options are available for advanced carcinoma larynx from surgery to non-surgical organ preservation therapy such as radiotherapy, chemoradiotherapy, or a combination of these. Recently, there is a paradigm shift in the management of advanced squamous cell carcinoma of the larynx, from surgical management to organ preservation non-surgical treatment such as radiotherapy and chemoradiotherapy [8]. Recurrences often occur predominantly at the primary site, while the risk of delayed regional recurrence in cervical nodal levels II, III, and IV is also higher in carcinoma supraglottis and the risk increases with advanced disease at presentation [9,10]. Isolated nodal metastasis to the post-styloid PPS which contains level VIIb lymph nodes is very unusual in carcinoma supraglottis with no local recurrence or regional recurrence to lower cervical nodes.

PPS is one of the deep neck spaces, shaped like an inverted pyramid, and extends from skull base superiorly to hyoid bone inferiorly. PPS is divided into two compartments depending on its relation with the styloid process, pre-styloid, and post-styloid compartments. Post-styloid PPS is also called as carotid space. Pre-styloid PPS contains minor ectopic salivary glands,

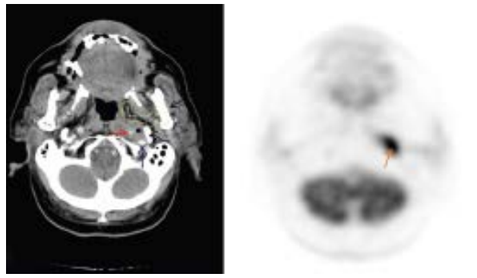

Figure 1: (a) Axial CT scan in soft-tissue window shows a soft-tissue lesion in the left post-styloid parapharyngeal space (asterisk) encasing the ICA (red arrow) and displacing the IJV (blue arrow). Yellow marked area shows pterygoid venous plexus. Black straight arrow â€“ Mandible. Black curved arrow â€“ styloid process. FDG PET image (b) at the corresponding level shows FDG uptake in the post-styloid PPS lesion (orange arrow)

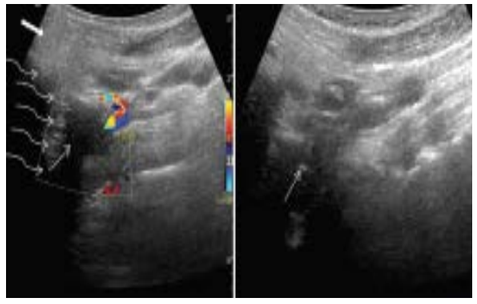

Figure 2: (a) Ultrasound shows a solid, hypoechoic soft tissue in the left post-styloid parapharyngeal space (thin arrow) close to the ICA (colored vessel). Block arrow indicates parotid gland and curved arrows indicate bone causing acoustic shadowing. (b) Ultrasound guided FNAC done with tip of the FNAC needle within the lesion (arrow)

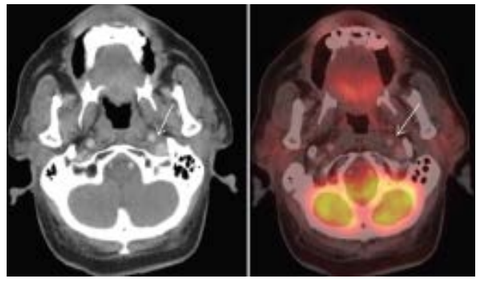

Figure 3: PET-CT scan done after chemotherapy shows significant interval decrease of the lesion in the left post-styloid carotid space with mild residual soft-tissue thickening (arrow in a) which shows no FDG uptake on corresponding fusion image (arrow in b), suggestive of complete metabolic response

mandibular division of trigeminal nerve, internal maxillary artery, ascending pharyngeal artery, and pterygoid venous plexus, where as the post (retro)-styloid compartment contains ICA, IJV, IX to XII cranial nerve, cervical sympathetic chain, and glomus bodies [11]. Post-styloid PPS also contains post-styloid lymph

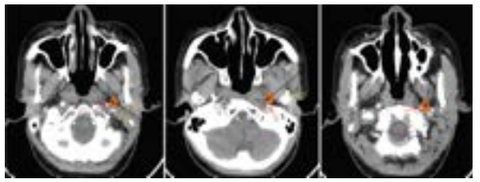

Figure 4: (a) Retromandibular approach: Orange shaded area - possible lesion in PPS, white arrow - mandible, yellow arrow - parotid gland, yellow arrow- non calcified styloid process. Red arrow - ICA, blue arrow - IJV, double black arrow - possible trajectory of needle; (b) Subzygomatic transcondylar approach: Orange shaded area – possible lesion in the left PPS close to skull base, white arrow – coronoid process of mandible, yellow arrow – condyloid process of mandible, red arrow – ICA, double black arrow – possible trajectory of needle; (c)anterior approach through infratemporal fossa: Orange shaded area – possible lesion in the left PPS, white arrow – red arrow – ICA, blue arrow – IJV, double black arrow – possible trajectory of needle.

nodes which are the cranial continuation of Level II lymph nodes and is labeled as Level VIIb in the neck node-level classification system [12]. The most common pathology of post-styloid PPS is neurogenic tumors such as Schwannoma and neurofibroma, mostly arising from the vagus nerve but may arise from other nerves. The glossopharyngeal nerve lies lateral to the ICA and ansa cervicalis is also embedded in the anterior carotid sheath which may involve or displace the ICA. Post-styloid lymph nodes receive efferent from nasopharyngeal mucosa and they are at risk of involvement in carcinoma nasopharynx and also from any other head and neck primary malignancies which have massive infiltration of the upper level II lymph nodes through retrograde lymph flow [11-13].

Many tumors show an overlap of imaging features and FNAC/biopsy is necessary for diagnosis and appropriate management. Image guidance is required to target deep non-palpable head and neck lesions, which is less time consuming, and less morbid procedure than open surgery. The proximity of lesions to major neck vessels, nerves, airways, and body structures makes biopsy/FNAC of these lesions challenging. Ultrasound-guided procedures have the advantage of real-time imaging capability, visualization of vessels without the need for iodinated contrast material, lack of ionizing radiation, and low cost. However, the lack of window due to the presence of body structures and aerodigestive tract precludes the use of ultrasound guidance in deep-seated head and neck lesions. Hence, CT guidance is preferred to target these lesions [14]. Possible approaches for CT-guided FNAC/biopsy of PPS lesion are described in Fig. 4. However, when the lesion is surrounded by the difficult to penetrate bony structures and where the oblique course is difficult, evaluating the lesion with ultrasound for FNAC/biopsy is sometimes helpful as in our case, which allows real-time visualization of the needle and makes the oblique course easier.

Our case was previously treated for advanced carcinoma supraglottis (cT4N3bMo) with complete response. Surveillance FDG PET-CT showed isolated hypoenhancing FDG avid soft-tissue lesion in the left post-styloid PPS, located lateral to the ICA and encasing it. Therefore, our imaging differentials were neurogenic tumor and nodal metastasis. It was located medial to the styloid process limiting lateral approach and the anterior approach was limited by the presence of pterygoid venous plexus (Fig. 1). Therefore, we performed ultrasound-guided FNAC using a lateral transparotid approach, which allowed oblique access through a window (Fig. 2). Retromandibular (aka "fascial vein") vein can be used as a landmark to locate facial nerve which lies lateral to the vein, to avoid injury to the nerve [15].

CONCLUSION

Head and neck cancers may present with delayed regional recurrence or distant metastasis at an unusual site where other benign tumors are more common. Often the patient can be asymptomatic during surveillance and imaging plays an important role in diagnosing locoregional recurrence and distant metastasis. Obtaining tissue for cytology/histopathology is useful to exclude other possible causes. Ultrasound and CT-guided FNAC/biopsies are useful in this regard and lesions should be evaluated with both ultrasound and CT scan for possible safest approach.

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BRAIN
Retrospective reporting of doses received by parotid glands in patients undergoing short course palliative whole brain radiotherapy

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PURPOSE

Palliative whole brain radiation is one of the fundamental modality of treatment for the patients diagnosed with brain metastasis. While the intent is to abate the symptoms it is paramount to attempt to minimize the treatment related toxicities. Parotid glands are very well established as organs at risk (OAR) in treatment of head neck cancers undergoing radiation. During palliative brain radiation, parotids may possibly receive significant radiation dose. However, in absence of routine contouring of parotid as an OAR, documentation of their doses is imperative. Here we report parotid doses and volume characteristics in our patients who were exclusively treated with short course palliative brain radiotherapy of 20 Gy in 5 fractions which isa validated regimen.

METHODS

This retrospective, single institute study included patients of both gender and all age group who were diagnosed with brain metastasis from solid tumor malignancies and planned for palliative whole brain radiation were included. Patients were immobilized in the supine position in a customized 3 clampthermoplastic mask. Conventional conformal technique with two opposed lateral fields was used and planning was done on Eclipse(version 13.2). As per the current standard of conventional palliative brain radiation, parotids were not contoured prospectively. Instead, both right and left side parotid glands were delineated separately, post treatment retrospectively. The dosimetric parameters were evaluated based on the parotid dose constraint available from head neck studies(RTOG 0615) and included mean parotid dose constraint less than 26Gy, volume constraint at 20 Gy. (V20) less than 20 cc, and dose at50% of the parotid volume (D50) less than 30 Gy. For analysis, these doses were converted to BED and equivalent doses for 5 fractions were assessed. Similarly we stratified patient data as per the lower border of the treament field (C1 vs C2 vertebrae) to analyze any difference in parotid doses received.

RESULTS

We had data of 58patients. The Average PTV volume was 1666 cc. Average volume of right and left parotid were 19.4cc (SD 6.52) and 18.9 cc (SD 7.08)respectively. Mean doses received by right and left parotid was 11.07Gy and 11.78 Gy, which is less than 14.41 Gy (BED equivalent of 26Gy). As the mean volume of parotids was 19cc, it was less than the constraints as per RTOG 0615 (V20Gy less than 20cc). The D50%for right parotid and left parotid was 11.46 Gy and 10.70 Gy. This is less than the parotid constraint of 50% less than 17.9 Gy (BED Equivalent for 30Gy). Out of which 24 patients had lower border uptoC1 vertebrae and 35 patients had lower border below C2 vertebrae. Mean Parotid doses when border is at C1 and when border is below lower border of C2 is 979.63 cc and 1255.12 cc respectively, which was significantly different (p=0.05). Similarly, D50% of parotids of C1vertebrae was 945 cc and below C2 vertebrae was 1415.17cc, which was also significantly different (p=0.05). Conclusions: Parotids should be contoured and doses documented even in palliative brain metastasis cases. In short course palliative brain radiation(20Gy/5#)the doses received by parotids are well below the known constraints. Prospective study to assess impact of hypofractionated palliative radiation on parotid toxicity and quality of life is warranted to validate these outcomes.

Inferior vena cava leiomyosarcoma with liver metastasis at presentation in a young male: A challenging diagnostic quandary

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ABSTRACT

Leiomyosarcomas of vascular origin are very rare tumors, predominantly affecting the inferior vena cava (IVC). Although vascular leiomyosarcomas are slow-growing, their non-specific and late presentation results in delayed diagnosis which portends a very poor prognosis. Here we report a case of a 24-year-old man who presented with abdominal pain since 15 days and was found to have unresectable metastatic leiomyosarcoma of the inferior vena cava at initial diagnosis.

KEY WORDS: Leiomyosarcoma, leiomyosarcoma of the inferior vena cava, sarcoma

INTRODUCTION

Sarcomas are rare malignant tumors of mesenchymal origin that comprise approximately 1% of all adult malignancies. Leiomyosarcomas (LMS) are sarcomas arising from smooth muscle cells and can originate at various locations. Vascular leiomyosarcomas account for 2% of all LMS and are difficult to diagnose due to its non-specific symptoms. Treatment includes complete surgical resection with or without chemotherapy and radiotherapy. However, prognosis for vascular leiomyosarcomas are poor and outcomes are quite dismal.

CASE REPORT

A 24-year-old man presented to our hospital with complaints of pain in the abdomen since 15 days which was insidious in onset and gradually progressive. The patient also complained of weight loss and generalized weakness. He had a past medical history of renal calculi for which he had received treatment one year back. The patient had no co-morbidities and no significant family history.

Physical examination did not reveal significant findings. Hematological investigations were normal with Carcino Embryonic Antigen (CEA) level 0.91 ng/ml (normal range, 0-5.00 ng/ml) and CA 19.9 level 6.50 U/ml (normal range, 0-37 U/ml). Liver function tests were deranged with elevated SGOT (1481 U/L), SGPT (1561 U/L) and total bilirubin (1.8 mg/dl). Serum alkaline phosphatase was within normal range (23 U/L). Serum creatinine was slightly elevated (1.59 mg/dL).

Contrast-enhanced computed tomography (CECT) of abdomen and pelvis revealed IVC to be dilated and shows a heterogeneously enhancing filling defect measuring 16 cm × 5 cm × 5 cm which is seen extending superiorly up to the level of right atrium and inferiorly up to the renal level [Figure 1]. A large conglomerating nodal thrombus with large aorto-caval nodal mass and metastatic lesions in liver.

The differential diagnoses for a solid retroperitoneal mass in an adult male without its origin from adjacent solid organs (kidney, adrenal, pancreas and bowel) are lymphoproliferative disorder, germ cell tumor, and mesenchymal tumors.

The patient underwent CT-guided fine-needle aspiration cytology (FNAC) and biopsy from the hepatic lesion. FNA cytosmears were paucicellular and showed only an occasional group of benign hepatocytes. Cytology was reported as inadequate for opinion. Histopathological examination of core needle biopsy showed multiple linear cores of hepatic parenchyma infiltrated by poorly differentiated malignant cells showing spindle cell morphology. There was extensive nuclear pleomorphism with tumor cells showing multilobated nuclei. Stroma was edematous and showed myxoid change at places. Frequent mitotic figures were noted but there was no necrosis. Histopathology was reported as metastatic poorly differentiated malignancy with spindle cell morphology [Figure 2].

Based on the radiologic and microscopic evaluation, the diagnosis of a malignant mesenchymal tumor was considered. Immunohistochemistry (IHC) was done which showed that the tumor cells were strongly and diffusely immunoreactive to Desmin, Smooth muscle actin (SMA), H- caldesmon while were immunonegative to Myo-D1, CD-31, CD-34, CK 7, CK 20 and Heppar-1 [Figure 3]. IHC was reported as leiomyosarcoma metastatic to liver.

Due to multiple metastatic lesions in liver at diagnosis, the patient was considered inoperable. Unfortunately, the patients clinical condition deteriorated rapidly and he expired within a week of diagnosis.

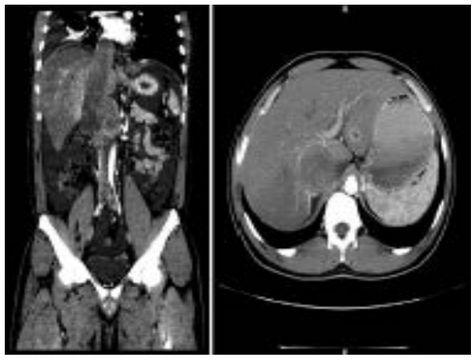

Figure 1: CECT of abdomen and pelvis shows dilated IVC with a heterogenously enhancing filling defect measuring 16 x 5 x 5 cm extending superiorly upto the level of right atrium and inferiorly upto the renal level (a). Peripherally enhancing soft tissue lesions in liver consistent with metastasis (b)

DISCUSSION

Sarcomas are rare malignant tumors of mesenchymal origin that comprise about 1% of all adult malignancies.[1] Leiomyosarcomas are of smooth muscle cell origin and vascular leiomyosarcomas account for 1-2% of all LMS, rarely affecting the Inferior vena cava (IVC).[2] Vascular LMS are usually seen in the sixth decade of life with females being more commonly affected (M:F = 1:4).[3] LMS of vascular origin forms in the tunica media and its growth pattern can be extaluminal, intraluminal or combined.

LMS can be divided into three types based on the segment of IVC affected. Lower segment involves the infra-renal area (34%), middle segment involves the region between hepatic and renal veins (42%) and upper segment involves the region from the hepatic vein to the right atrium (24%).[4] The tumor can involve more than one segment, like our case which involved the upper and middle segment and such large tumors are usually unresectable due to its extent and invasion into adjacent organs.

The most common presentation of IVC leiomyosarcoma is pain or discomfort in the abdomen. Other symptoms include lower extremity edema, weight loss and dyspnea.[5] Due to its non-specific symptoms, diagnosis is often delayed. Distant metastasis occurs in about 50% of the cases usually in the late stages involving liver, lung, lymph nodes or bone.

Computed tomography (CT) and magnetic resonance imaging (MRI) is the imaging modalities of choice that aid in the diagnosis determines the extent of disease and potential for surgical resectability.

Complete surgical resection is currently the only potential curative treatment.[6] Despite complete surgical resection, local recurrences are quite common. Surgical options available include

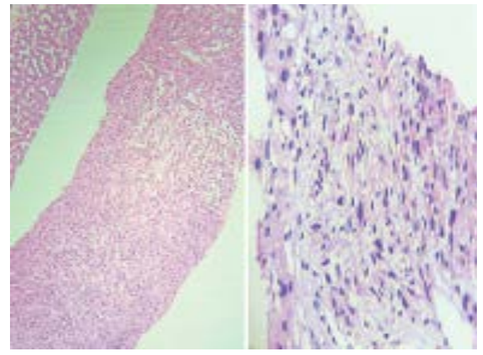

Figure 2: Histopathological examination showed multiple linear cores of hepatic parenchyma infiltrated by poorly differentiated malignant cells showing spindle cell morphology (a) with extensive nuclear pleomorphism and multilobated nuclei. Frequent mitotic figures noted but necrosis is not seen (b)

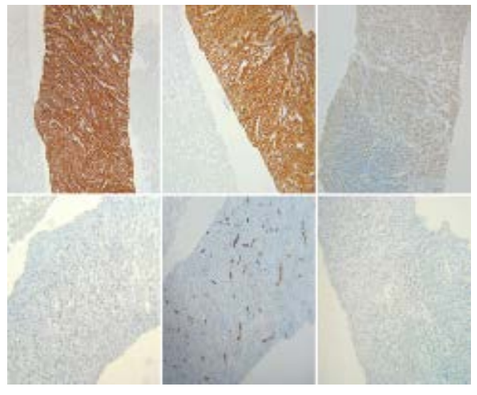

Figure 3: Immunohistochemistry showed diffuse cytoplasmic immunoreactivity to Desmin (a), SMA (b), H-caldesmon (c) while were immunonegative to Myo-D1 (d), CD-34 (e) and Heppar-1 (f)

complete resection and placement of graft, partial resection and cavoplasty and ligation of IVC. The five-year survival rate is 53% in leiomyosarcoma of IVC.[7] The efficacy of chemotherapy and radiotherapy is limited.[8] For patients who have an unresectable tumor, prognosis is very poor and survival time is measured in months as was the condition in our case. Involvement of upper segment IVC, right atrium, intraluminal growth and residual post-surgical macroscopic disease are adverse prognostic factors that result in early death, usually within 2 years.[9]

CONCLUSION

We have reported this case due to its unusual presentation in a male patient at a very young age who had metastatic disease at presentation. As surgical resection was not possible, these tumors portend a very poor prognosis. The role of chemotherapy and radiotherapy in IVC leiomyosarcoma is for palliation alone and treatment modalities for such inoperable patients' needs to be evaluated further.

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Conflicts of interest

There are no conflicts of interest.

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Bladder endometriosis-A great masquerader

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ABSTRACT

The bladder is the most common site affected in urinary tract endometriosis. There is a controversy regarding the pathogenesis, clinical management (diagnosis and treatment), impact on fertility, and the risk of malignant transformation of bladder endometriosis. Patients presenting with symptoms typically attributed to endometriosis might go unnoticed because of its infrequent occurrence. We, hereby, report a case of a young female who had complaints of burning micturition and dysmenorrhea. After a thorough evaluation, she was found to have a urinary bladder mass which was subjected to a biopsy. The initial histopathology report came as bladder malignancy but immunohistochemistry proved otherwise and it turned out to be urinary bladder endometriosis.

Key words: Bladder, Cystitis glandularis, Endometriosis, Infertility

Endometriosis, a very common benign gynecological condition, is defined as the presence and growth of endometrial mucosa, glands, and stroma outside of the uterus. It most commonly involves the ovaries, fallopian tubes, and sometimes may be found involving other pelvic organs such as the rectum, bladder, pouch of Douglas, and even ureters. The bladder being a very infrequent site constitutes nearly 1% cases of endometriosis. It is, however, the most common site for urinary tract endometriosis [1-3].

CASE REPORT

A 35-year-old woman was referred to our outpatient department with a positive report of bladder malignancy. She had complaints of burning micturition and painful menstruation for 5 months. All investigations were done in an outside hospital.

Per speculum examination showed a normal cervix. On pervaginal examination, a hard mass was palpated in the anterior fornix.

In view of the complaints, a computed tomography (CT) scan was done. It showed a broad-based/sessile papillary lesion of 29 X 33 X42 mm along the midline posterior wall of the base of the bladder. The lesion had an extension beyond the bladder wall (perivesical spread) toward the anterior wall of the uterus with a loss of fat planes. No appreciable lymphadenopathy was noted. Differentials on CT scan were given as vesical malignancy versus vesical papilloma. She underwent cystoscopy which showed elevated trigone of the bladder, three bladder base masses in trigone and supratrigonal area, approximately measuring 1.5 x1 cm.

Transurethral resection of bladder tumor was done. The first histopathology report suggested the lesion to be infected transitional cell papilloma. The slides were reviewed later and another diagnosis of the papillary urothelial neoplasm of low malignant potential (PUNLMP) was given.

The patient was referred to the tertiary cancer care center considering the diagnosis of PUNLMP. As per the institutional protocol, the slides were reviewed at our hospital. The superficial biopsy section showed polypoidal mucosal fragments lined by benign urothelium. Subepithelial tissue shows congested blood vessels and stroma along with multiple variably sized glands lined by urothelial, columnar, cuboidal, and mucinous types of epithelium. Chronic inflammatory infiltrate was seen, whereas the deeper biopsy showed muscle tissue infiltrated with glands formed by columnar to cuboidal cells and stromal inflammatory infiltrate (Fig. 1a-c).

In view of radiology, cystoscopy, and morphological findings, the differentials were given as cystitis cystica glandularis, endometriosis, and endocervicosis. Hence, immunohistochemistry (IHC) was advised for confirmation. On IHC, glandular cells in the muscularis propria showed immunoreactivity to estrogen receptor (ER) and the stroma surrounding the glands shows immunoreactivity to CD-10 and ER and negative for CEA. Surface epithelium shows that immunoreactivity to

uroplakin along with membranous Î²-catenin expression is seen in the urothelium and subepithelial glands (Fig. 2).

Considering history, histopathology, and IHC, the final diagnosis of polypoid cystitis glandularis with endometriosis was given. Based on this diagnosis, the patient was treated medically with antiestrogens-letrozole and was kept on a follow-up. A follow-up CT scan done after 6 months showed a reduction in the size of the bladder wall lesion and hormonal treatment was continued.

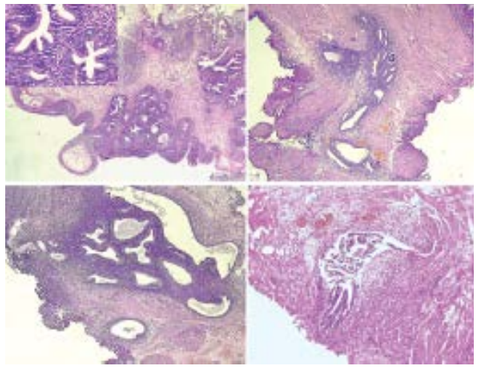

Figure 1: (a) Polypoidal bladder mucosa with subepithelial glands (inset)-cystitis glandularis); (b and c) Deeper muscle showing glands surrounded by dense stroma; (d) Initial biopsy showing similar glands in deeper muscle

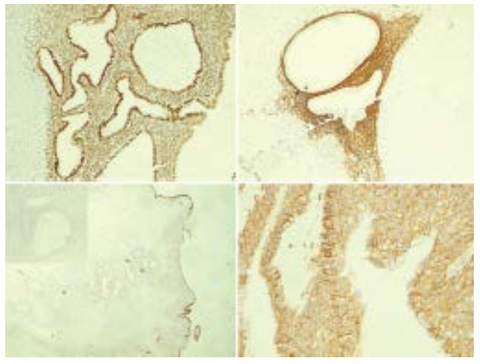

Figure 2: Immunohistochemistry images showing (a) muscle infiltrating glandular epithelium shows expression of estrogen receptor; (b) Same section where stromal cell show CD 10 positivity; (c) Uroplakin in superficial bladder epithelium (Negative deeper glands in inset); (d) Superficial glands of cystitis cystic showing membranous beta-catenin

DISCUSSION

Endometriosis of the urinary bladder is an uncommon pathology. Nevertheless, it should be taken into consideration in women with unexplained dysuria or other lower urinary tract symptoms such as frequency, hematuria, and less frequently, bladder pain, and urgency. It can also be suspected if imaging is suggestive of urinary bladder malignancy and histomorphological ambiguity [3].

The common age group affected by bladder endometriosis is women in their reproductive years (average age of 35 years). It is rare in postmenopausal women because endometriotic tissue is dependent on estrogen for continued growth and it generally undergoes regression after menopause [3].

Bladder endometriosis can be loosely categorized as primary (the one occurring spontaneously) or secondary (occurring after surgical intervention). About the origin of bladder endometriosis, the following theories have been suggested in the literature: (a) it develops from Mullerian remnants in the vesicouterine/vesicovaginal septum; (b) as an extension of an adenomyotic nodule of the anterior uterine wall; (c) as a result of implantation of regurgitated endometrium [1,3].

Up to 50% of the patients with bladder endometriosis have a history of past pelvic surgery. Bladder endometriosis lesion usually evolves from the serosal surface of the bladder toward mucosa and it is often multifocal, while the trigone and the dome are the most frequently affected sites. Cyclic sloughing of these endometrial glands along with the release of neurokinins and by pressure and traction on surrounding tissue from adhesions results in pain [2,3]. Cystitis glandularis and endometriosis both can mimic urothelial malignancy on their own.

Imaging techniques include cystoscopy, magnetic resonance imaging, ultrasonography, and urodynamics. Bladder carcinoma, angiomas, leiomyoma, amyloidosis, malakoplakia, glandular cystitis, nephrogenic adenoma, and extravesical processes such as diverticulitis should be considered in the differential diagnosis. The histopathological study is necessary in almost all cases [3,4].

A correct approach will be a detailed history regarding the type and duration of symptoms, especially in young females of childbearing age. Pathological assessment in conjunction with ancillary techniques is indispensable for the correct distinction between possible endometriosis and bladder neoplasm. The patient can either be subjected to conservative methods like hormonal therapy or surgical excision of the lesions. It is specially recommended in cases that have persistent pain or localized effect like ureteral constriction [4-6].

Histomorphology of cystitis glandularis shows cuboidal or columnar cells forming gland-like lumens, as well as cystically dilated lumens or cystic cavity. However, the cells lack significant atypia or mitotic activity or muscular invasion. Its differential can be inverted urothelial papilloma or invasive urothelial carcinoma. A thorough examination of the architectural pattern including cytological atypia and high proliferation and deeper muscular invasion can help us separate benign entities [7,8].

Endometriosis will show endometrial-type glands. There might be degenerative atypia as cells undergo regular cyclical changes. Endometrial-type stroma is seen with a fine capillary network or decidual change or fibrosis (long standing). A few cases may show only stroma (stromal endometriosis), as well as evidence of chronic hemorrhage in the form of hemosiderin-laden or foamy macrophages. Similarly, endocervical glandular component may be seen (endocervicosis) [8,9].

A combined expression of CK7, CA125, ER, and progesterone receptor along with CD10 in surrounding stromal cells helps delineate the presence of endometriosis in the bladder [8,9].

CONCLUSION

A careful assessment of suspected bladder endometriosis is very essential as it might be falsely diagnosed as a malignant pathology. As a result, the patient might be subjected to unnecessary and unwarranted testing and treatment which can be totally avoidable in cases with a high index of suspicion.

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Treatment pattern and outcomes of leptomeningeal carcinomatosis in India – a retrospective study

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SUMMARY

Background Leptomeningeal carcinomatosis (LMC), the metastatic spread of cancer to the leptomeninges, is a rare complication and has a dismal prognosis. Due to limited data available on LMC from India, we conducted a country-wise audit of LMC across 15 centres in India.

Methods The current study conducted in 2020, was a retrospective, multicentric audit of adult patients (aged 18 years) with diagnosis of LMC and who received treatment during 2010–2020. Baseline characteristics, details related to previous treatments, cancer sites, LMC diagnosis, treatment pattern and overall survival (OS) were collected. Descriptive statistics were performed, and Kaplan Meier analysis was performed for the estimation of OS.

Findings Among the patients diagnosed with LMC (n = 84), diagnosis was confirmed in 52 patients (61.9%) and 'probable' in 32 (38.1%) patients. The three most common cause of malignancy were non-small cell lung cancer (NSCLC), breast cancer and gastrointestinal cancer with 45 (53.6%), 22 (26.1%) and 9 (10.7%) patients respectively. Intrathecal therapy was offered in 33 patients (39.3%). The most common intrathecal agent was methotrexate in 23 patients (27.4%). The median OS was 90 days (95% CI 48–128). Among tested variables, intrathecal therapy administration (hazard ratio [HR] = 0.36, 95% CI 0.19–0.68) and primary in lung (HR = 0.43, 95% CI 0.23–0.83) had a favourable impact on OS.

Interpretation Prognosis with leptomeningeal carcinomatosis is poor with a significant burden of morbidity and mortality in India. This data aims to highlight the current outcomes and facilitate further research on LMC.

Funding None.

Keywords: Leptomeningeal carcinomatosis; Intrathecal; Outcomes; Pattern of care; LMIC

Research in context

Evidence before this study

We searched PubMed with the terms "Leptomeningeal disease" OR "Leptomeningeal carcinomatosis OR Leptomeningeal metastasis" for articles published from database inception to and August 31, 2022, in English. We tried to include more recent publications as references.

Added value of this study

Data on the prognosis and treatment of Leptomeningeal carcinomatosis is present across literature with varying results however data from low-middle income countries (LMIC) remains scarce. Outcomes in leptomeningeal carcinomatosis remain dismal and this necessitates further studies and trials on novel modes of therapy. However, to do so, we must first accrue robust data on prognosis and outcomes with current therapy for leptomeningeal carcinomatosis in LMICs. This is the aim of our study.

Implications of all the available evidence

Outcomes in leptomeningeal carcinomatosis remain dismal. Nearly 33% of patients received best supportive care. Despite being part of treatment guidelines, only 39% of patients were able to receive intrathecal therapy in our patient population. Intrathecal therapy was associated with improved outcomes in patients with leptomeningeal carcinomatosis. Lung cancer as primary had the better outcomes among patients with leptomeningeal carcinomatosis.

INTRODUCTION

Leptomeningeal carcinomatosis (LMC) is a rare and potentially lethal complication of cancer that occurs when cancer cells spread to the membranes surround-ing the brain and spinal cord, known as the lep-tomeninges.[1,2] The cancer cells can spread to the leptomeninges through the bloodstream or via direct extension from a nearby tumour. They are resistant to most chemotherapy options due to this being a 'sanctuary' site where they are protected by the limited fltration across the blood brain barrier.

LMC can cause a range of neurological symptoms, such as headache, nausea, vomiting, seizures, altered sensorium, memory loss and difficulty speaking or walking. The non-speciïcity of these symptoms could initially be mistaken for other conditions, making LMC challenging to diagnose. If left untreated, LMC can lead to severe and potentially life-threatening complications. Diagnosis of LMC is typically made using cerebrospinal fuid (CSF) analysis and imaging modalities.

LMC is observed in approximately 10% of patients with solid tumour cancer.[3] Breast cancer, lung cancer and melanoma are three malignancies commonly associated with LMC.[4,5] With recent developments in systemic therapies, there is a significant improvement in the extra cranial control of the above three mentioned malignancies.[6-10] As a result of this improvement in extra cranial control, there is an increase in relapse seen in sanctuary sites such as the central nervous system.11 In general, there is an increase in incidence of both brain parenchymal lesions as well as LMC. It is hypothesised that in addition to improvement in systemic control and prolonged survival, a combination of other factors like improved imaging techniques and a lower threshold for initiating diagnostic work-up have led to increase the incidence and prevalence of LMC. Median time between diagnosis of systemic cancer and diagnosis of LMC is around 1â€“2 years. Developments in management of leptomeningeal metastasis of solid tumours majorly include systemic chemotherapy,[12] intrathecal therapy and irradia-tion.[13] However, impact of these management modalities on prognosis currently varies widely. LMC has a dismal prognosis and hence there is a need for improvement in outcomes. Till now, only few randomised trials were conducted and previous observational studies are mostly retrospective. Also, very limited literature is available from India and other low-income and middle-income countries (LMIC). The applicability of retrospective studies' from high-income countries in LMIC is questionable and warrants further review. The advances in systemic treat-ment in solid tumours that have led to improved out comes have become in accessible to a-large-proportion of patients in India and other LMICs. We aimed to under-stand the current prevalence of LMC and management in India. Hence, we did a retrospective country-wide analysis to determine the pattern of care and outcomes in solid tumour patients with LMC.

METHODS

A multicentric retrospective analysis was conducted across 15 centres in India.

The study was conducted after Ethics Committee clearance and in accordance with the standards of Declaration of Helsinki, International Council for Har-monisation (ICH)–Good Clinical Practice (GCP), and the Indian Council of Medical Research (ICMR). The study was conceptualised in December 2019 and the data collection was done in January to March 2020. The study was presented at the American Society of Clinical Oncology (ASCO) annual conference of 2021. The study adhered to Strengthening the Reporting of Observa-tional studies in Epidemiology (STROBE) guidelines.[14] The flowchart is depicted in Fig. 1.

Patient selection

Adult patients (age > or = 18 years) with LMC, treated between January 2010 and December 2019 were selected

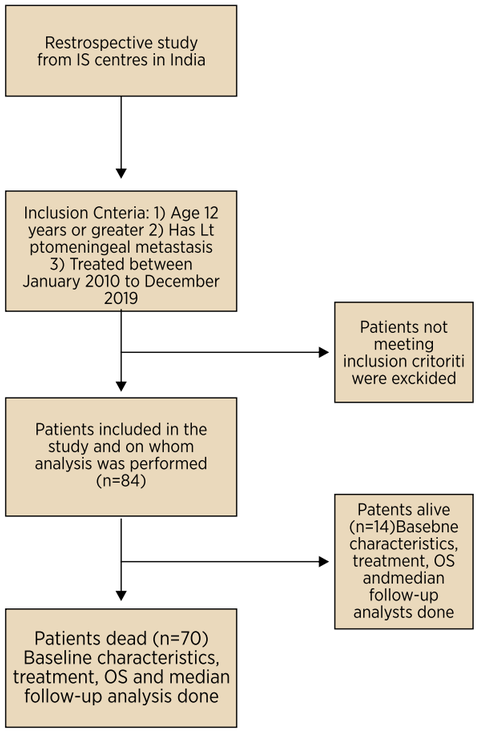

Fig. 1: STROBE flowchart for this study.

for this analysis. The diagnosis of leptomeningeal carcinomatosis was per European Association of Neuro-Oncology (EANO)15 guidelines as confirmed, probable or 'possible'. The definition of 'confirmed' LMC was if there was the presence of positive cerebrospinal fluid (CSF) cytology. In the absence of positive CSF cytology, if there was a presence of typical MRI features of lep-tomeningeal carcinomatosis with typical clinical features, it was labelled as probable LMC. A diagnosis of possible LMC was made if the CSF cytology was negative with absence of typical features on MRI but with the presence of typical clinical features. Patients with LMC due to leukaemia were excluded.

Data collection

The data was collected on a predefined data collection sheet which was shared with all investigators. The data collected was of baseline characteristics at the time of diagnosis of LMC, previous treatment re-cords, disease status with molecular details, the pattern of care, the treatment offered, response and overall survival.

Outcomes

Overall survival was defined as the time in days from date of diagnosis of LMC to date of death or date of last follow up whichever was applicable.

Data analysis

Descriptive statistics were used for data analysis and statistical software SPSS version 26 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp) and RStudio version 1.4.1106 (RStudio Team (2021). RStudio: Integrated Development Environment for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/.) were used. Medians with range were provided for continuous variables while percentages with 95% CI were provided for non-continuous variables. Imaging Response was assessed by Response Assessment in Neuro-Oncology (RANO). Response Evaluation Criteria in Solid Tumors (RECIST) was used to assess response the primary and the type of assessment was local. Agresti-Coull Interval Method was used for the calculation of 95% CI. Overall survival was estimated using Kaplan Meier analysis. Cox regression analysis was performed to identify factors impacting survival. A p-value of 0.05 was considered statistically significant. The assumptions of Cox regression analysis were checked before performing the analysis and were met. Cox proportional hazard model was constructed, and the proportional hazard assumption was tested us-ing Schoenfeld residuals. The median follow-up was calculated using Reverse Kaplan–Meier method.

RESULTS

Baseline characteristics

Eighty-four patients were included in the present study. The baseline characteristics, tumour details and previous treatment details are shown in Table 1. The number of lumbar punctures required to get positive CSF cytology was 1 in 44 (52.4%), 2 in 6 (7.1%) and 3 in 2 (2.4%). In 32 (38.1%) patients the CSF cytology was either not done or was negative. The commonest site of primary leading to LMC was lung in 46 patients (54.8%). The number of lumbar punctures required to get positive CSF cytology was 1 in 44 (52.4%), 2 in 6 (7.1%) and 3 in 2 (2.4%). In 32 (38.1%) patients the CSF cytology was either not done or was negative. It was equivocal in 2 patients which was considered as negative. Fifty-three patients (73.1%) had cerebrospinal MRI at baseline. Out of these 33 (39.3%) had only cerebral MRI while the rest 20 (23.8%) had cerebrospinal. Furthermore, Ommaya reservoirs were not used in any of the patients. Four patients (16.7%) had hydrocephalus at diagnosis of Leptomeningeal metastasis. Nineteen patients (16.7%) had received WBRT.

All patients had clinical symptoms of LMC such as headache, nausea and vomiting, seizure, altered sensorium and difficulty with walking or speech. Leptomeningeal metastasis was discovered at the time of diagnosis in 9 patients (11%) and within 30 days in 12 patients (14%). The median time-period between met-astatic diagnosis and LMC diagnosis was 360 days (range 0–1800). The median OS from diagnosis of metastatic disease was 587 days (95% CI 472–702)

Variable	Value (N=84)
Age in years-No (%)	
Median (Range)	52.5 (21-75)
Non-Elderly	61 (72.6)
Elderly	23 (27.4)
Gender- No (%)	
Male	38 (45.2)
Female	46 (54.8)
ECOG PS- No (%)	
1	41 (48.8)
2	28 (33.3)
3	9 (10.7)
4	6 (7.1)
Disease site-No (%)	
Breast	22 (26.2)
Lung (NSCLC)	45 (53.6)
Lung (SCLC)	1 (1.2)
Gastrointestinal	9 (10.7)
Other	6 (7.1)
NSCLC-Molecular type-No (%)	
EGFR mutation	36 (42.9)
ALK rearrangement	3 (3.6)
No mutation	7 (8.3)
Breast cancer-Molecular types-No (%)	
TNBC	11 (13.1)
ER/PR + & Her-2 negative	9 (10.7)
ER/PR + & Her-2 positive	1 (1.2)
ER/PR + & Her-2 positive	1 (1.2)
Number prio r therapies-No (%)	
Nil	2 (2.4)
1	43 (51.2)
2	20 (23.8)
3	15 (17.9)
>4	4 (4.8)
LMC diagnosis-No (%)	
Confirmed	52 (61.9)
Probable	32 (38.1)
Ectracranial disease status at diagnosis- No (%)	
Progressive disease	39 (46.4)
Stable disease	31 (36.9)
Partial response	8 (9.5)
Complete response	5 (6)
Missing data	1 (1.2)

ECOG PS- Eastern Coviatne OrKok.0 Group Ple riormarice Status. NSCLC- Pica sirnal sell lun9 cancer,. SCLC-small cell lung carKer, EFfi-epilerrnal q rowth factei receptim ALK-Anickastk gympharna kinase, ER-Estrogen receptor. PR-PiotyKtercike receptor, Her-2-human epidemial growth factor receptor 2, LMC- Leptorneininеal carcirpornatoss. 'Retrict to 22 pat pents wfth breast 4arKer and 45 patients with IVSCLC 6 Brleny was &fined as age =>60 years

Table1: Baseline details of the pa-ticipants

Treatment pattern

The treatment pattern administered is shown in Table 2. The two most common treatment algorithms chosen were best supportive care and in trathecal with systemic. therapy in 24 (28.6%) patients each. In EGFR mutated tumours, osimertinib was used in 1 and afatinib in 1 patient, respectively. Rest all EGFR mutated patients were exposed to only first-generation tyrosine kinase inhibitors. Similarly, in ALK-rearranged patients, none of the patients had exposure to 3rd generation ALK in-hibitors. None of these patients had received immuno-therapy. Intrathecal therapy was offered in 33 patients (39.3%). The most common intrathecal agent was methotrexate in 23 patients (27.4%).

Response

The response assessment with respect to cerebrospinal fluid (CSF) studies and radiological response is shown in Table 3. The main reasons that follow-up CSF cytology analysis or MRI analysis was not available were progression or death prior to the first follow-up assessment: progression and death before 2 months were observed in the majority of patients. The 30 days and 60 days OS were 73.5% (95% 62.6-"81.7) and 56.9% (95%CI 45.3-"66.9).

Overall survival

The median follow-up was 763 days (95% CI 316-"1211). There were 70 deaths, and the estimated median OS was 90 days (95% CI 48-"128) (Fig. 2). The 1-year and 2 years OS were 8.7% (95% CI 3.3-"17.3) and 5.2% (95%CI 1.4-"12.9%) respectively. The results of multivariate

Variable	Value (N=84)
Treatment	
Best supportive care only	24 (28.6)
Systemic therapy only	17 (20.2)
Intrathecal + Systemic therapy	24 (28.6)
Intrathecal only	9 (10.7)
Radiation only	10 (11.9)
Radiation-No (%)	
Yes	18 (21.4)
No	66 (78.6)
Radiation type-No (%)	
Focal	15 (17.9)
CSI	3 (3.6)
Systemic therapy-No (%)	
Targeted	21 (25)
Chemotherapy	16 (19)
Chemotherapy + Targeted	4 (4.8)
Type of intrathecal therapy-No (%)	
Methotrexate	23 (27.4)
Triple	10 (11.9)
Duration of therapy	
Median (Range)	4 (1-14 weeks)

Triple–methotrexate, AraC (cytosine arabinoside) and hydrocortisone. CSI-Craniospinal irradiation. aln 8 patients it was given along with systemic therapy and in 10 it was administered as the sole therapy.

Table 2: Table depicting pattern of treatment.

Variable	Value (N=84)
CSF response	
Not assessed	59 (70.2)
CSF negative	13 (15.5)
CSF positive	11 (13.1)
Missing data	1 (1.2)
MRI response	
Not assessed	67 (79.8)
Complete response	1 (1.2)
Partial response	6 (7.1)
Stable disease	6 (7.1)
Progressive disease	3 (3.6)
Missing data	1 (1.2)

CSF-cerebrospinal id. MRI-Magnetic resonance imaging.

Table 3: Response assessment details.

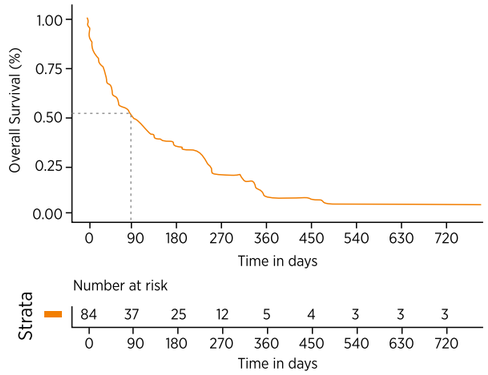

Fig. 2: Overall survival curve.

analysis are shown in Table 4. The median OS in breast cancer was 571 days (95% CI 335-"807), that in NSCLC was 647 days (95% CI 561.0-"733.0) and in other sites was 317 days (95% CI 102-"533).

DISCUSSION

To our knowledge, this is one of the first multicentric data collection efforts in LMC from any LMIC across the globe. The data throws light on multiple aspects of LMC in LMIC which were previously unknown. Melanoma is not one of the commonest malignancies associated with LMC in India. It is possibly a reflection of the lower incidence of melanoma in tropical countries where it is not even within the top 10 commonest malignancies as per GLOBOCAN data.[16] The commonest three malig-nancies associated with LMC in our present study were non-small cell lung cancer, breast cancer and gastroin-testinal malignancies. The corresponding sites in west-ern literature from the Americas region are melanoma, breast cancer and non-small cell lung cancer.[17-"20] Thus suggesting different demography of LMC as opposed to that reported from western literature. Even in other studies reported from the Indian subcontinent the pre-dominant disease is either non small cell lung cancer or breast cancer. In a LMC experience reported from Kochi (State of Kerala), the commonest site leading to LMC was breast (45%) followed by lung cancer (35%). [21] Other large experiences from India (>1100 patients) by Patil and colleagues[22] and Abraham and colleagues,[23] were in lung cancer and breast cancer respectively.

A significant proportion of patients (>50%) have presented in ECOG PS 2-4 state. This reflects the pattern of practice of Indian oncologists where limited scanning of the brain and CSF axis is performed due to constraints of resources. Multiple guidelines, including National comprehensive cancer network (NCCN), sug-gest that imaging of the brain needs to be performed in NSCLC stage IV.[24] However brain imaging is rarely done due to less accessibility to MRI and its associated cost. Further, this information often does not influence the treatment decisions as irrespective of presence or absence of central nervous system (CNS) involvement, CNS penetrating tyrosine kinase inhibitor (TKI) cannot be selected due to their prohibitively high cost. Hence multiple oncologists choose to scan the neural axis or do a CSF examination only when the patient is symptom-atic. This is reflected also in the fact that all patients in the current study already had CNS symptoms. Similar experience was reported by Abraham and colleagues in breast cancer[23] where nearly all patients were symptomatic with headache (47%), vomiting (47%), diplopia (20%), and seizure (20%) being the most common symptoms. In a large experience from prospective studies in NSCLC, the symptoms of leptomeningeal disease were symptoms of altered higher mental func-tions (48.4%) or seizures and Headache and dizziness (32.2%).[22] Similar experience was published from Kochi, where the commonest presenting features were head-ache, vomiting, loss of consciousness, cranial nerve palsies and seizures.[21]

The treatment pattern suggested that a significant proportion of patients were offered the best supportive care in our study. This is in line with multiple guide-lines suggesting that poor PS patients or patients with uncontrolled progressive disease should be offered the best supportive care.[25] The survival in this group of pa-tients is dismal as seen in our study where the median OS in patients with Eastern Cooperative Oncology Group Performance Status 3–4 (ECOG PS 3–4) was 29 days and in patients with the extra cranial progressive disease was 64 days. Hence it is imperative that these patients are diagnosed early in the disease course. Probably, following guidelines and doing imaging to detect CNS involvement might lead to improvement in outcomes however that presents its own challenges in LMICs. While prevalence of leptomeningeal carcinomatosis has been seen to be around 3–7% with solid tumours, its incidence is often 15–20% on autopsy

Variable	Median OS in days (95% CI)	Univariate Hazard ratio	Log rank p value	Multivariate Hazard ratio	95% CI of Hazard ratio	p-value
Age	Not applicablea	0.99	Not applicablea	1.00	0.97-1.02	0.764
Gender						
Male Female	64 (34–223) 104 (43-136)	0.97	0.98 Reference	1.14	0.68-1.91	0.630
ECOG PS						
1 2–4	61 (38-186) 104 (43–142)	0.93	0.46	0.66 Reference	0.37–1.18	0.159
Site						
Lung Non-Lung	90 (47-227) 70 (34-128)	0.78	0.69	0.54 Reference	0.29-1.014	0.055
Extracranial disease status Progressive disease Non-progressive disease	64 (29-172) 107 (43-183)	1.13	0.012	1.22 Reference	0.72-2.03	0.467
LMC diagnosis Confirm Probable	74 (38-142) 94 (43-223)	0.81	1.000	0.43 Reference	0.23–0.81	0.009
IT received						
Yes No	142 (70-245) 51 (29-94)	0.69	0.13	0.35 Reference	0.19-0.66	0.001

LMC-Leptomeningeal carcinomatosis, ECOG PS- Eastern Cooperative Oncology Group Performance Status, IT-Intrathecal.
a Continuous variable. Elderly = Age >60 years.

Table 4: Table depicting factors influencing overall survival.

suggesting a large number of these are being missed owing to delayed imaging and/or poor survival before CNS symptoms become evident.

Intrathecal therapy (IT) is one of the recommended therapies for LMC.[26-28] Multiple established guidelines recommend it. However, the utility of IT is tested mainly in two trials for breast cancer. One study was negative for OS benefit however had its own limitations while the second study was able to show beneficial effect on progression-free survival (PFS) in LMC in breast cancer.[29-31] Such randomized data is not available for lung cancer. However, recent large retrospective anal-ysis suggests that giving IT probably wont improve outcomes, at least in driver mutated NSCLC.[32-35] How-ever, our results suggest that IT improves overall sur-vival. This might be a result of the limited exposure to 3rd generation tyrosine kinase inhibitors (TKIs) seen in our patients. Third generation TKIs have CNS penetration ability[36] and might not need IT. However first-generation TKIs have limited CNS penetration and the addition of intrathecal therapy might improve out-comes. The utility of triple IT was seen in a study re-ported from Kochi.[21] Symptomatic improvement was noted in 70% of patients and the 6 month-OS was 38%. However the median PFS was a dismal of 2.0 months only. Dismal median OS of 2.0 months was reported by Patil et al. in a prospective study of NSCLC who had developed LMC. In that study there was trend towards improved outcomes in patients who were treated with third generation TKI with a median OS of 245 days (95% CI: 215.48-274.52) versus 52 days (95% CI: 22.62-81.38) in favour of third generation TKI.[22] Similar dismal median OS of 3 months was reported in breast cancer patients from Thiruvananthapuram (State of Kerala).[23]

This data indicates that despite a substantial pro-portion of patients having targetable driver mutations, outcomes of LMC remain dismal in LMIC.[37,38] This suggests that the current treatment landscape in LMICs is insuficient to adequately treat leptomeningeal carci-nomatosis as outcomes have remained low even in those with targetable mutations. There is a need for the development of new treatment options like CNS-penetrating immunotherapy acknowledging that the evidence of existing treatment modalities like radio-therapy (RT) does suggest that it improves outcomes however this is scant and unsubstantiated at this point in time.

Another important facet is the cost-effectiveness of early screening modalities to screen for and identify LMC before symptoms with solid tumours in LMICs. A high percentage of LMC is seen only at autopsy compared the reported numbers with a definitive diag-nosis coupled with the poor prognosis from lep-tomeningeal carcinomatosis suggests that early, widespread and periodic screening would very likely play a role in lowering mortality from it. However, on the other hand, the high-cost burden of this screening via imaging modalities coupled with the barrier of financial access to effective CNS-penetrating therapy raises the question of the feasibility of this strategy in LMICs. The optimal strategy lies somewhere on this spectrum where cheaper, more easily accessible screening strategies with good sensitivity would allow a smaller number to require the resource-burdening confirmatory test of high specificity to allow the most fertile situation for shared decision making of treatment between patient and doctor.

The strength of the current study is the multicentric real-

world data across multiple primary tumours. The study also had few limitations, viz. treatment algorithms were heterogeneous and very few patients had exposure to 3rd generation TKIs. Unfortunately, we have not collected data on progression-free survival. The data generation for the current study was possible because of wide collaboration between clinicians at different cen-tres. Thus, clinicians could have had differing protocols for follow-up procedures and timing. Due to this, we did not gather data on progression-free survival (PFS) as we could not maintain uniformity for reliable PFS data.

LMC has a grave prognosis and nearly one-third of the patients are treated with the best supportive care due to dismal prognosis. Intrathecal therapy, though part of guidelines, is administered in only 39% of patients with leptomeningeal carcinomatosis. IT therapy and lung primary are associated with relatively improved out-comes. This data can serve as a benchmark for further improvement to facilitate studies for further improving the outcomes.

Contributors Conceptualisation, study design, literature search, data acquisition, data analysis, statistical analysis, manuscript preparation, writing—review and editing: all authors. Guarantor: AK.

Data sharing statement De-identified data may be shared on a case-by-case basis upon reason-able requests to the corresponding author for a period of 5 years.

Declaration of interests Authors declare no conflicts of interest.

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Ultrasound Guided FNAC / Biopsy of Small Liver Lesions: Its Importance and Difficulties Encountered in the Field of Oncology

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ABSTRACT

Introduction : Liver is a common site of primary and secondary malignant tumors, secondary involvement / metastasis being more common. There are small liver lesions which may not demonstrate typical morphology and are sometimes difficult to characterize. Definitive diagnosis of these small liver lesions is important which aids in better patient management and avoids un-necessary follow up. Here ultrasound guided FNAC/biopsy plays an important role to obtain tissue for cytological/histopathological diagnosis.

Objective: Primary objective is to describe the importance of ultrasound guided FNAC/biopsy of small liver lesions and various difficulties encountered. Also, based on the authors experience, some technical difficulties in the procedure and how to deal with them, are also described in this paper.

Methods : The study is a single institution based retrospective analysis of data of cancer patients with small liver lesions whose ultrasound guided FNAC/biopsy were done. Data was obtained from the institutional database. Ultrasound guided FNAC was done using a 9.8cms 25G spinal needle/15cms 23G Chiba needle and biopsy was done using 18G BARD coaxial biopsy gun. Local anesthesia was given at the puncture site. Final cytology/biopsy reports were obtained.

Results: Total 28 nodules in 26 patients were targeted. Out of these 28 nodules, FNAC was performed from 26 nodules and biopsy was performed from 2 nodules. Liver lesion sizes range from 5 mm to 20 mm, with mean size of 12.88 mm and median size of 13 mm. Of these nodules, 24 (85.71%) out of 28 nodules turned out to be metastatic. 4 nodules were benign out of which one was bile duct adenoma, 2 were regenerative nodules and 1 nodule showed reactive atypia.

Conclusion: Ultrasound guided FNAC / biopsy of the small liver lesion has an important role in the field of oncology. It helps in obtaining the tissue for cytology / histopathology and thus helps in better management of cancer patients.
Keywords: Liver, metastasis, FNAC, biopsy, too small to characterize (TSTC).

INTRODUCTION

Liver is a common site of primary and secondary malignant tumors, secondary involvement / metastasis being more common. The most common site of primary malignancy metastasizing to the liver being carcinoma breast, lung and colon. (1)(2) In oncology, in diagnostic / staging as well as surveillance CT scan of patients, small liver lesions are frequently found. These lesions may not show typical morphology to characterize them into either benign or malignant categories and FNAC/biopsy is sometimes difficult in inexperienced hands. In patients with known malignancy, definite characterization of these lesions into benign vs malignant is crucial in determining the prognosis and treatment. Jones et al (3) reported in their study that liver lesions less than or equal to 15 mm were found in 17% of the cases and were benign in 51% of the 82% of patients with known malignancy. Schwartz et al(4) in their study reported that hepatic lesions less than or equal to 1 cm, deemed too small to characterize, are most often benign, but approximately 11.6 % of these lesions were malignant. Schwartz et al also reported in their study that when these too small to characterize liver lesions were followed, the average reported time for increase in size of these TSTC liver lesions was 13 months if malignant in etiology.

Colin et al(5) reported that almost all of the malignant liver lesions were diagnosed within four weeks, but required long term follow up and un-necessary increased imaging for benign lesion. In patients with liver cirrhosis or focal fatty lesions, it was difficult to differentiate between regenerative nodules or focal fatty lesions from hepatocellular carcinoma (HCC) and such lesions required longer follow up (range of follow up was 2 – 42 weeks). More likely diagnosis in cirrhotic liver is HCC, followed by the high and low grade dysplastic nodules. In cirrhotic liver, liver nodules less than 1 cms require follow up with ultrasound every 3 months while nodules between 1 to 2 cms size require histopathological correlation if imaging findings are atypical. (6)

Stacey et al(7) in their study found that upto 30% of liver lesions, deemed too small to characterize on CT scan, remained indeterminate on MRI. However, follow up imaging and histopathology diagnosis (in few) showed no significant interval change/resolved and benign nature of these lesions respectively. However, when followed up, mean follow up was 60.6 weeks. Unnecessary follow for small lesions increases patient's anxiety and more repeated imaging studies were performed for benign than malignant lesions. White paper of the ACR on management of incidental liver lesion describes that most of the liver lesions less than 1 cms are benign; however suggests follow up MRI after 3 – 6 months in high risk patients for further characterization of these lesions. They also suggest hepatic MRI for liver lesions between 1 – 1.5 cms with suspicious features on imaging. (8)

However, when patient has known extra-hepatic malignancy, it becomes important to characterize these small liver lesions into benign and malignancy, especially when imaging findings are atypical. Sometimes it becomes difficult to differentiate new onset small liver lesion into benign or malignant, if malignant then labeled as disease progression. Timely intervention of liver metastasis in selected patients has favorable prognosis and delay in diagnosis has poorer prognosis and reduced survival.(9)(10)(11)(12)(13) When solitary or few, as seen often in colorectal cancer where metastatectomy/ RFA/ intraarterial chemotherapy can be performed(14)(15), to characterize these TSTC liver lesions into benign and malignant, tissue diagnosis is important. Also resection of isolated liver metastasis in carcinoma breast which can be the site of isolated recurrence (16) tissue diagnosis prior to surgery is important.

So if these lesions are intervened early with USG guided FNAC / biopsy which is cost effective, reliable and easily available, early diagnosis is possible with early treatment and this long follow up without appropriate treatment can be avoided.

Therefore, when the suspicion of liver metastasis is high, even when the lesion is small, it is essential to sample it and to get a final cytological / histopathological diagnosis that will aid in precise patient management and in turn improve the outcome.

MATERIALS AND METHODS

This is a single institution retrospective study performed at National Cancer Institute, Nagpur, Maharashtra, India. Retrospective data was collected of patients who have undergone FNAC / biopsy of small liver lesions during 01.01.2019 to 31.10.2021. Data was collected from the radiology dataset of patients available at the institute. During this period, total 1455 USG guided FNAC and biopsies were performed, out of which 899 were FNACs and 556 were biopsies. Of these, total 53 procedures were performed on liver nodules including 34 FNAC and 19 biopsies, out of which 28 nodules in 26 patients met out study criteria, i.e., liver lesion size less than or equal to 20 mm. Out of these 28 nodules, FNAC was performed on 26 nodules and biopsy on 2 nodules.

Ultrasound guided percutaneous aspirations were done in 26 nodules. For FNAC, 25 G spinal needles were used and for deep lesions in segment VII/VIII which were beyond the reach of the spinal needle that is 9.8 cm long, 23G 15 cm chiba needle was used to obtain tissue. Slides prepared from the aspirate and transferred to the coplin jar containing 95% ethyl alcohol solution. Few dry smears were also prepared.

Biopsy was done using an 18 G BARD coaxial biopsy needle and 17 G BARD biopsy gun. Multiple cores, at least 4 cores in 4 different positions of the cutting edge, were obtained. Also more cores were obtained by changing the needle position if required.

Samples were sent to the pathology department for further cytological / histopathological reporting.

TECHNIQUE:

Prior to FNAC/biopsy, liver lesion is evaluated with ultrasound, approach decided and point of entry is marked on skin. FNAC / biopsy can be done using either intercostal, subcostal or transabdominal / sub- xiphoid approach depending upon the location of the liver lesion. (Fig. 1) Then entry site and surrounding area is cleaned with alcohol / betadine. Transducer and wire is covered with sterile probe cover with jelly inside over the transducer, which is important to avoid soiling of the probe and to maintain proper aseptic technique. Local anesthesia with 2% lignocaine is given at the site of entry involving skin and underlying soft tissue along the proposed needle trajectory. Then under ultrasound guidance, a FNAC / biopsy needle is inserted into the lesion avoiding the vessels. Keep the tract of the needle tangential to the ultrasound beam, with this entire tract of the needle can be visualized and, vessels can be avoided using color doppler technique. It is always preferred to put the needle parallel to the vessels and not perpendicular to it, to avoid transection of vessels while taking cores with a gun. (Fig. 2, 3 and 4) We prefer to do the procedures during normal breathing and the needle can be advanced in whichever phase of respiration the lesion is more conspicuous. However, for smaller lesions, those located beneath the rib and deeply seated lesion in segment VII/VIII, breathhold (either during inspiration / expiration) is required. (Fig. 5) While doing FNAC, move the needle to & fro and let the sample collect in the needle with the capillary action and check for the same by looking at the needle hub. If the sample does not collect in the needle, then gentle suction with a syringe is given. Care should be taken not to give excessive negative pressure in the syringe to prevent hemorrhagic aspirate. Generally it requires 2-3 passes for FNAC. Slides are prepared from the aspirate and transferred to the coplin jar containing 95% ethyl alcohol solution. It is better to perform the procedure under the presence of cytologists who can check for the adequacy of the sample obtained and

avoiding inconclusive FNAC and repeat procedures. For biopsy, after confirming the position of the needle in the lesion (preferably at the periphery in larger lesion), semiautomatic biopsy gun is inserted and cores are taken. At least 4 cores in 4 different directions of the curing edge are taken and transferred to the container containing formalin.

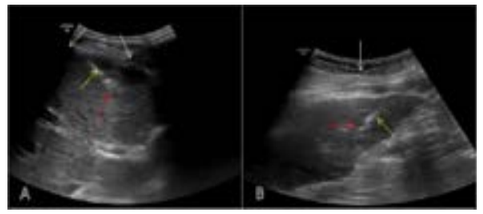

Figure 01: (A) Intercostal Approach USG guided FNAC of segment IV liver lesion (red arrow). White arrow denoted ribs and yellow arrow FNAC needle. (B) Transabdominal / Sub-xiphoid Approach USG guided biopsy of segment III liver lesion (red lesion). White arrow denoted anterior abdominal wall and yellow arrow biopsy needle.

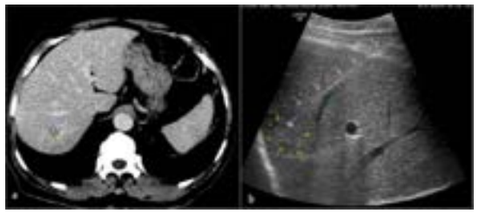

Figure 02: In this treated case of carcinoma rectum, surveillance CT scan reveals a 13 mm nodule in segment VII of liver (yellow arrow in a). USG guided FNAC was performed from this small liver lesion (as shown in b, yellow arrows). Entire course of the 15 cms 23G chiba needle (white arrows) is seen when the needle is parallel to the transducer. Tip of the needle is seen in mildly hyperechoic liver lesion in segment VIII (yellow arrows). Blue arrow shows hepatic vein. Cytology report suggestive of metastasis.

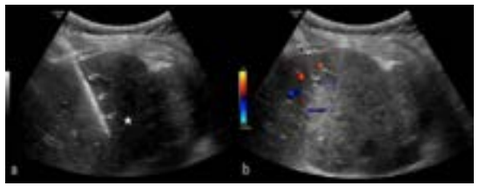

Figure 03: USG guided biopsy has been performed from the right lobe liver lesion in this suspected case of carcinoma gall bladder with liver metastasis. Almost entire needle (arrows) is seen in a with its tip in liver lesion (asterisk). Color doppler image shows vessels (in red and blue colors) on either sides of needle (arrow) which is carefully inserted avoiding the vessels.

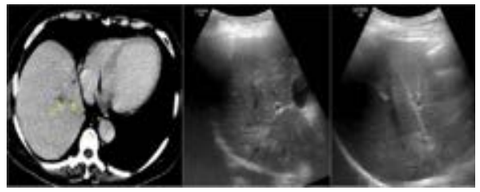

Figure 04: 69 Y / Male, operated case of carcinoma colon, on observation. Surveillance CT scan shows an irregular hypodense lesion in right lobe of liver (black arrow in a) and associated focal IHBR dilatation (yellow arrow in a). Correlative ultrasound shows an irregular hyperechoic lesion in right lobe of liver (black arrow in b). USG guided FNAC was done (c) with needle close to the branch of portal vein (white arrow in c) and is avoided.

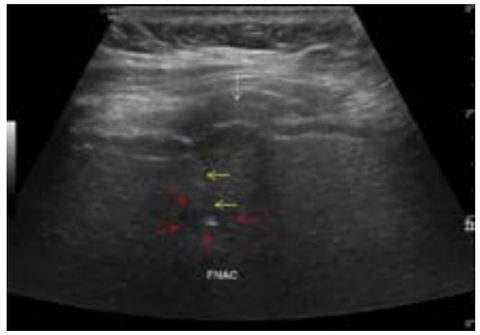

Figure 05: 42Y/Female, known case of carcinoma breast with new onset 5 mm lesion in segment VIII of liver. Note the location of the lesion beneath the rib. Needle was inserted in this small lesion in breathhold during inspiration. White arrow denotes rib, red arrows denote the liver lesion and yellow arrow denotes the spinal needle with its tip inside the liver lesion. Background liver shows fatty infiltration. Cytology report suggestive of reactive atypia in the liver lesion.

Primary & Secondary Outcome

Primary outcome is to describe the importance of ultrasound guided FNAC/biopsy of small liver lesions.

Secondary outcome is to address technical difficulties in the FNAC / biopsy of small liver lesions and methods to deal with them.

Inclusion & Exclusion Criteria

Inclusion Criteria:

1.Patient with known malignancy with small liver lesions of size less than 20 mm

2.Biopsy / FNAC was performed at our institution and histopathology / cytology report available.

Exclusion Criteria:

1. Patient with known malignancy with liver lesions of size more than 20 mm

Statistical Analysis

In this research paper, the collected data has been methodically categorized into distinct groups, allowing for a comprehensive and systematic analysis of the research subject. The subsequent presentation includes a detailed breakdown of data distribution, expressed in terms of percentages. This quantitative approach not only elucidates the prevalence of each category but also uncovers significant trends and patterns within the dataset, thereby enhancing the overall depth and clarity of the findings.

ETHICS

The study was approved by the Ethics Committee, National Cancer Institute, Nagpur, Maharashtra, India, on dated 13.08.2021 Approval number is NCI /EC / 2018 / 017 / 08 //2021. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

RESULTS

Patient demographic are given in table 1. There are a total 28 nodules in 26 patients, out of which biopsy was done on 2 nodules and FNAC was done on 26 nodules. Out of 26 patients, 11 were male patients and 15 female, with 8 cases of carcinoma breast (30.76%), 7 cases of colo-rectal cancer (26.92%) 3 cases of lung cancer (11.54%), 1 carcinoma buccal mucosa (3.84%), 1 carcinoma cricopharynx (3.84%), 1 case of carcinoma soft palate (3.84%), 1 carcinoma esophagus (3.84%), 1 carcinoma pancreas (3.84%), 1 case of carcinoma urinary bladder (3.84%) and 1 carcinoma cervix (3.84%). 1 patient (3.84%) was being evaluated for liver SOL. (Table 2) Liver lesion sizes range from 5 mm to 20 mm, with mean size of 12.68 mm and median size of 12.5 mm. 1 out of 28 lesions was located in segment II (3.57%), 11 in segment III (39.28%), 3 in segment IVA (10.71%), 2 in segment IVB (7.14%), 3 in segment V (10.71%), 1 in segment VI (3.57%), 3 in segment VII (10.71%) and 4 in segment VIII (14.28%). (Table 3) Of these nodules, radiologically 25 (89.28%) nodules appeared metastatic, 1 (3.57%) nodule regenerative while 2 nodules (7.14%) were suspicious for metastasis as were new onset on follow up imaging and were small (5 mm in size). Out of the 26 patients, 8 (30.77%) patients had single liver lesion, 6 (23.07%) patients had 2 liver lesions, 3 (11.53%) patients has 3 liver lesions, 1 (3.85%) patients had 4 liver lesions, 1 (3.85%) had 5 liver lesions and 7 (26.92%) patients had more than 5 liver lesions. (Table 4) Median number of passes for FNAC was 2. Aspirate from 22 nodules was cellular (84.61 %) while aspirate from 4 lesions was sparsely cellular (15.38%). Two of the 4 sparsely cellular smear were metastatic, 1 nodule showed reactive atypia while 1 showed necrotic aspirate which on repeat FNAC turned out to be metastatic. Biopsy samples obtained for histopathology were adequate for histopathological examination and for immunohistochemistry. On cytology report, 1 (3.84%) nodule was bile duct adenoma, 22 (84.61%) nodules were metastatic, 1 (3.84%) nodule showed reactive atypia and 2 (7.69%) nodules were regenerative nodules. Two nodules, which were biopsied, turned out to be metastatic. In total, 24 (85.71%) out of 28 nodules turned out to be metastatic. In the nodules, which turned out to be regenerative nodules, background liver showed fatty changes in one case and cirrhotic changes in another case. Size of the nodule which showed reactive atypia was 5 mm and the liver showed grade III fatty changes. None of the patients had complications related to the procedure. We have reported accuracy of USG guided FNAC of small liver lesions to be 100%.

Sr. No.	Age	Sex	Primary diagnosis	Liver Segment	Liver Lesion Size in mm	FNAC or Biopsy Done	FNAC Biopsy report	No. of liver lesions	Smear Cellularity	Radiologica 1 Diagnosis
1	66	M	Lung	III	16	Biopsy	METASTASIS	>5	Adequate	Metastasis
2	66	F	COLON	V	19	Biopsy	METASTASIS	5	Adequate	Metastasis
3	62	F	BREAST	III	5	FNAC	REGENERATIV E NODULE	3	Cellular	Suspicious
4	42	F	BREAST	VIII	5	FNAC	REACTIVE ATYPIA	1	Scanty cellularity	Suspicious
5	69	M	RECTUM MELANOMA	III	6	FNAC	METASTASIS	>5	Cellular	Metastasis
6	44	M	RECTUM	IVB	6	FNAC	METASTASIS	>5	Cellular	Metastasis
7	48	M	LUNG	III	8	FNAC	METASTASIS	>5	Cellular	Metastasis
8	64	M	LUNG	IVA	8	FNAC	METASTASIS	2	Cellular	Metastasis
9	65	F	URINARY BLADDER	VIII	8	FNAC	METASTASIS	2	Cellular	Metastasis
10	56	F	COLON	VII	10	FNAC	METASTASIS	4	Cellular	Metastasis
11	55	M	PANCREAS	II	11	FNAC	METASTASIS	1	Cellular	Metastasis
12	36	F	BREAST	III	11	FNAC	METASTASIS	>5	Scanty Cellularity	Metastasis
13	38	F	CERVIX	III	12	FNAC	METASTASIS	>5	Cellular	Metastasis
14	50	M	BUCCAL MUCOSA	VIII	12	FNAC	METASTASIS	1	Scanty Cellularity	Metastasis
15	41	M	RECTUM	VII	13	FNAC	METASTASIS	2	Cellular	Metastasis
16	46	F	RECTUM	VIII	13	FNAC	BENIGN BILE DUCT LESION (BILE DUCT ADENOMA)	1	Cellular	Metastasis
17	75	F	COLON	V	13	FNAC	METASTASIS	2	Cellular	Metastasis

Sr. No.	Age	Sex	Primary diagnosis	Liver Segment	Liver Lesion Size in mm	FNAC or Biopsy Done	FNAC Biopsy report	No. of liver lesions	Smear Cellularity	Radiologica 1 Diagnosis
18	61	M	CRICOPHA RYNX	IVB	14	FNAC	METASTASIS	2	Cellular	Metastasis
19	41	F	BREAST	IVA	14	FNAC	METASTASIS	1	Cellular	Metastasis
20	66	M	LUNG	III	16	FNAC	METASTASIS	>5	Cellular	Metastasis
21	60	F	BREAST	IVA	16	FNAC	METASTASIS	3	Cellular	Metastasis
22	45	F	ESOPHAGUS	III	19	FNAC	METASTASIS	1	Cellular	Metastasis
23	66	F	COLON	V	19	FNAC	METASTASIS	5	Cellular	Metastasis
24	53	M	UNDIAGNOSED	III	20	FNAC	CIRRHOTIC NODULE	3	Cellular	Regenerativ e nodule
25	49	F	BREAST	VII	20	FNAC	METASTASIS	1	Cellular	Metastasis
26	59	M	SOFT PALATE	VI	20	FNAC	METASTASIS	1	Necrotic Material	Suspicious for metastasis
27	69	F	BREAST	III	8	FNAC	METASTASIS	>5	Cellular	Metastasis
28	49	F	BREAST	III	12	FNAC	METASTASIS	2	Cellular	Metastasis

Table 1

Sr.No.	Primary neoplastic site	Total no. of Patients	%
1	Breast	8	30.76
2	Buccal Mucosa	1	3.84
3	Cervix	1	3.84
4	Colon	3	11.54
5	Cricopharynx	1	3.84
6	Esophagus	1	3.84
7	Lung	3	11.54
8	Panereas	1	3.84
9	Rectum	4	15.38
10	Soft Palate	1	3.84
11	Undiagnosed	1	3.84
12	Urinary Bladder	1	3.84

Table 2

Sr.No.	Liver Segment	Number of nodules	Percentage %
1	II	1	3.57%
2	III	11	39.28%
3	IVA	3	10.71%
4	IVB	2	7.14%
5	V	3	10.71%
6	VI	1	3.57%
7	VII	3	10.71%
8	VIII	4	14.28%

Table 3

Sr.No.	No. of liver lesions	Total no. of patients	Percentage %
1	1	8	30.77%
2	2	6	23.07%
3	3	3	11.53%
4	4	1	3.85%
5	5	1	3.85%
6	>5	7	26.92%

Table 4

DISCUSSION

Liver is a common site of primary and secondary malignant tumors, secondary involvement / metastasis being more common. The most common site of primary malignancy metastasizing to the liver being carcinoma breast, lung and colon. (1)(2) In oncology, in diagnostic / staging as well as surveillance CT scan of patients, small liver lesions are frequently found. There are studies in the literature which showed that most of these small liver lesions are benign, however, significant number can be malignant.(3)(4) If these lesions are followed up, follow up time is significantly high with un-necessary increased imaging for benign lesions.(4)(5)(7) Significant number of these lesions remain indeterminate on MRI (7) and 18F FDG PET may have limitations in evaluation in these small lesions(17). When patient has known extra-hepatic malignancy, it becomes important to characterize these small liver lesions into benign and malignant, especially when imaging findings are atypical. Timely intervention of liver metastasis in selected patients has favorable prognosis and delay in diagnosis has poorer prognosis and reduced survival. (9)(10)(11)(12)(13) New onset liver lesions in patients with known malignancy are looked with suspicion, but may not always be metastatic. Figure 6 describes a 64 years male patient, a case of carcinoma left lung on chemotherapy. Response evaluation CT scan shows a new onset 8 mm liver lesion while primary neoplastic lung mass was stable. The small liver lesion was FNAed and on cytology, it was metastatic, suggestive of disease progression. Figure 7 describes a 46 years female patient, a treated case of carcinoma rectum, on surveillance. Surveillance CT scan shows a new onset 13 mm liver lesion and appears metastatic on imaging; however, on cytology features were suggestive of bile duct adenoma which is a benign tumor. In our study, 3 out of 4 benign nodules were new onset on follow up imaging.

In our study, 19 (67.86%) out of 28 nodules were less than 1.5 cms and 9 (32.14%) nodules were less than or equal to 1 cm in size. 16 out of these 19 nodules (less than 1.5cm) (84.21%) were metastatic, 1 nodule (5.26%) was regenerative nodule, 1 (5.26%) nodule showed reactive atypia on cytology and 1 nodule (5.26%) turned out to be bile duct adenoma. 7 out of 9 (77.78%) nodules which were less than 1 cm turned out metastatic on cytology. The nodule, which turned out to be bile duct adenoma, was new finding on follow up CT scan in a known case of carcinoma rectum. Since new onset, radiologically, it was metastatic, but it did not show uptake on PET-CT. So USG guided FNAC was done and turned out to be bile duct adenoma of cytology. (Fig. 7) The small nodule, which turned out to be regenerative nodule, was 5 mm in size, background liver showed fatty changes and was resolved on follow up triphasic CT scan after 3 months. Size of the nodule which showed reactive atypia was 5 mm, the background liver showed grade III fatty changes and it was stable on follow up ultrasound after 3 months. All of these 3 benign nodules on cytology were new onset and all of them showed delayed enhancement on equilibrium phase of the contrast enhanced CT scan. This delayed enhancement is likely due to fibrous stroma in these nodules. Therefore, though most of new onset small liver lesions can be metastatic in patients with known primary malignancy, not all are. Thus, USG guided FNAC is extremely useful in differentiating between small benign and malignant liver lesions which has significant impact on patient management.

8 out of 26 patients (30.77%) had single liver lesion, out of these 6 were metastatic. 6 patients (23.07%) had 2 liver lesions, all were metastatic. So, in total 14 out of 26 patients (53.85%), just more than half of the patients, has either 1 or 2 liver lesions and turned out to be metastatic in 12 out of 14 patients (85.71%). 8 out of 26 patients (3.76%) had 5 or more nodules and all were metastatic. 4 patients (15.38%) had 3 to 4 liver lesions, the nodules in 2 patients turned out to be benign.

In our study, we found that 84.21% of liver nodules less than 1.5 cms and 77.78% of liver nodules less than 1 cms size were metastatic. 53.85% of patients had only 1 or 2 liver lesions and were metastatic in 85.71%. However, our findings are limited by the small sample size and our study does not calculate the prevalence of the small liver lesions. We emphasize on the importance of liver FNAC/biopsy of small liver lesions. In our study, FNAC was done in liver nodules, which had suspicious or indeterminate features on imaging. Un- necessary long term follow up and repeated imaging was avoided in these patients. Some patients may drop out on long follow up which can also be avoided by obtaining final cytological / histopathological diagnosis with FNAC or biopsy. Final tissue diagnosis on samples obtained with USG guided FNAC/biopsy helped in appropriate patient management.

At out institute, cost of USG guided FNAC INR 2750/-, INR 2750/- for USG guided biopsy, INR 3500/- for CT guided FNAC and INR 7500/- for CT guided biopsy. Also many times, for CT guided FNAC/biopsy, intravenous iodinated contrast material (ICM) needs to be injected to locate major vessels. ICM has adverse reactions which can range from mild urticaria to severe anaphylactic shock. (18)(19) Also, there is risk of acute kidney injury with the use of intravenous ICM. (20) Ultrasound color Doppler helps in evaluating the vascular anatomy and avoid the use of ICM. Ultrasound guided FNAC/biopsy is a real time procedure where FNAC/biopsy needle can be monitored real time with accuracy. While performing procedure under CT guidance, breathing movement and small size of lesion along with intermittent CT cuts taken for the guidance makes it difficult to target the lesion. Therefore, USG guided FNAC/biopsy is cost effective and safer as compared with CT guided FNAC/biopsy.

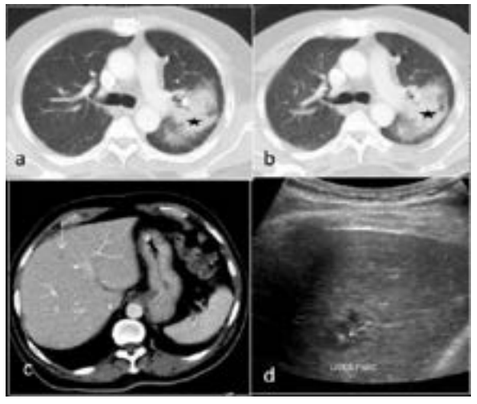

Figure 06: 64 Y / Male patient, known case of carcinoma left lung (asterisk in a) on chemotherapy. Follow up CT scan revealed stable left lung mass (asterisk in b), but developed new 8 mm liver lesion (arrow in c). USG guided FNAC of the liver lesion was done (arrow in d showing bright tip of spinal needle in liver lesion). Cytology report suggestive of metastasis.

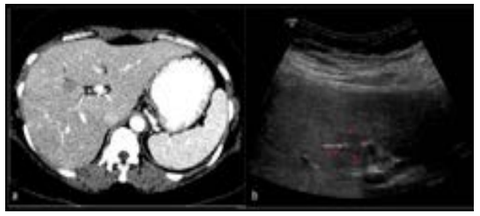

Figure 07: 46 Y/ Female patient, treated case of carcinoma rectum (post NACT-RT, post exenteration). She developed new onset 14 mm liver lesion on surveillance CT scan, 9 months after the surgery and also appeared metastatic on CT scan (arrow in a). USG guided FNAC was done from the liver lesion (red arrow in b denotes liver lesions and white arrow denotes tip of spinal needle in the lesion). Cytology report was suggestive of bile duct adenoma, which is a benign lesion.

Difficulties Encountered

There are some difficulties with ultrasound guided FNAC/biopsy procedures and most are patient related.

1. Deep seated hepatic lesions in segment VII/VIII: These deep seated lesions are sometimes beyond the reach of spinal needles which are routinely used in FNAC. Long 23 G 15 cms chiba needle should be used for FNAC. Some lesions are seen only during deep inspiration, so after breath hold during inspiration needle can be advanced. Similar technique can be used for biopsy. (Fig. 2)

2. Patient unable to breathhold: It is preferable to do procedure during normal breathing and to advance the needle either during normal inspiration or expiration, in whichever the phase the lesion is more conspicuous.

3. Proximity of lesions to the vessels: It is preferable to insert needle parallel to the vessels, if the lesion is in close proximity to the vessels. Putting needles parallel to the vessels help prevent vessel transection while taking cores in biopsy. Also since it is a real time procedure, needle course can be modified /manipulated if required so that the vessels are avoided. (Fig. 2, 3 and 4)

4. Patients with abnormal coagulation profile and low hemoglobin (Hb): Usually blood coagulation profiles are not required for FNAC, unless the patient has history bleeding disorder, compromised liver function or obstructive jaundice. Blood coagulation profiles are must if biopsy is to be performed. Most of the cancer patients receive chemotherapy which suppresses the bone marrow and also cause hepatotoxicity with resultant low counts and deranged coagulation profile. Therefore, it is important to order fresh investigations in these patients.

a. Deranged INR (International Normalised Ratio): INR less than or equal to 1.5 is acceptable. If INR is more than 1.5, vitamin K can be given. Generally, low dose oral vitamin K is sufficient to achieve INR below target level. (21) If INR is not corrected with vitamin K or in case of urgent biopsy, fresh frozen plasma can be given. It is preferable to do the biopsy while the transfusion is going on due to short life of clotting factors. (22)

b. Low platelet: There are variations in the different studies about the minimum platelet count required for surgery and ranges from 50,000/mm3 to 1,00,000/mm3. (23) We prefer minimum platelet count more than 80,ooo/mm3 and is safer for liver biopsy. If low, then RDP / SDP can be infused. SDP raises platelet counts more than the RDP. (24)

c. Low hemoglobin: It is preferable to have Hb value of 8 gm% and above. If Hb is low, then blood can be transfused and taken for the procedures after desired level is achieved. (25)

5. Patients on anticoagulant: If patient is on warfarin or other vitamin K antagonists, they should be stopped 5 days before biopsy.(26) If patient is on antiplatelet therapy (like aspirin, clopidogrel), stop them for 5 days before the procedure.(27) Some advice to continue low dose aspirin in low risk patient. But since we are solely dependent on the patient's hemostasis status to prevent bleeding complications and also we don't have dedicated vascular interventional setup at out institute, we prefer to stop aspirin. LMWH (low molecular weight heparin) should be stopped 24 hrs before the biopsy.(21)

6. Requires expertise: It definitely requires expertise to target small liver lesions, particularly for those located underneath the ribs and deep seated lesions.

CONCLUSION

Ultrasound guided FNAC / biopsy is cost effective, easily available and safer, less morbid procedure than open / surgical biopsy.(28)(29) However, there are some difficulties encountered when performing these procedures in cancer patients, which can be related to patient factors, like coagulation profile, liver lesions size / location or could be related to the operator performing the procedure, like expertise, localization of small liver lesions and deciding the correct needle path avoiding the vessels. We have also described the measures to be taken for these difficulties.

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Phase 3 randomized study for evaluation of physician choice Rx and triple metronomic as second-line therapy in head and neck cancer (CRSF 2021-HN-001)

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BACKGROUND

There are multiple options of treatment in second-line therapy in locally advanced head and neck squamous cell carcinoma (LAHNSCC) with recurrent or metastatic disease. However triple metronomic chemotherapy is oral, affordable, and requires minimal resources. Hence in this study, we compared NCCN-recommended physician choice of standard systemic therapy versus triple metronomic therapy in the second-line treatment of head and neck cancer.

METHODS

This was a phase 3, multicentric (16 sites), randomized study with a superiority design that was approved by the insti-tutional ethics committees and registered with CTRI (CTRI/2021/08/036002) conducted in India under the aegis of Cancer Research Statistics Foundation. The study recruited LAHNSCC with a recurrent and metastatic disease that either was platinum-refractory or was planned for second-line chemotherapy. The key inclusion criteria were: Age $18 years, ECOG PS 0-2, and the presence of normal hematological and biochemical parameters. These patients underwent 1:1 central stratified randomization (Stratification - site of disease & ECOG PS) to either triple metronomic chemotherapy (methotrexate 9 mg/m2 PO weekly, celecoxib 200 mg PO twice daily and erlotinib 150 mg PO once daily) or physician choice therapy (nivolumab or pembrolizumab or cetuximab or taxane or afatinib or 5-FU or capecitabine). The study drugs were administered either till disease progression or the devel-opment of intolerable side effects. The primary endpoint of the study is overall survival (OS). The secondary endpoints are adverse events (CTCAE version 5.0), progression-free survival (PFS), and quality of life (EORTC). The sample size required was 114. The OS and PFS were estimated using Kaplan-Meier method and were compared using the log-rank test. Cox proportional hazard model was constructed for the calculation of the hazard ratio. The adverse events were compared using Fishers test. A p-value of 0.05 was considered significant.

RESULTS

At a median follow-up of 258 (95% CI 209-306) days. The median overall survival of the triple metronomic chemotherapy was 181 days (95%CI 142.7-219.2) versus 123 days (95%CI 94-152) in the physician choice therapy arm (P=.0.002). The corresponding hazard ratio of death was 0.58 (95%CI 0.33-0.79, P=0.003). The 6-month OS was 52.9% (95%CI 36.9-65.1) versus 14.8% (95%CI 6.4-26.4). The median progression-free survival was 120 days (95%CI 89.2-150.8) versus 70 days (95% CI 58.2-81.8) in metronomic chemotherapy and in the physician choice therapy arms respectively (P=0.000). The corresponding hazard ratio of progression was 0.5 (95%CI 0.33-0.74, P=0.001).

CONCLUSIONS

In this phase 3 multicentric study, triple metronomic chemotherapy as second-line therapy had an overall survival and progression-free survival advantage over NCCN-recommended physician choice therapy. Clinical trial information: CTRI/ **2021/08/036002. Research Sponsor: Individual Donor.**

DIBH: a gift of technological advancement to spare heart in left sided breast cancer patients undergoing radiotherapy.

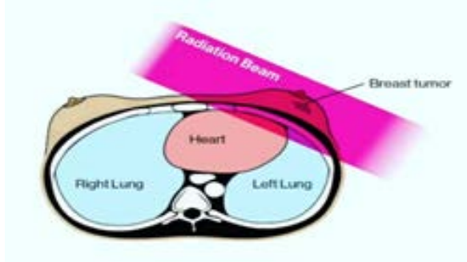
MR. PARIMAL PATWE

Medical Physicist - Department of Radiation Oncology

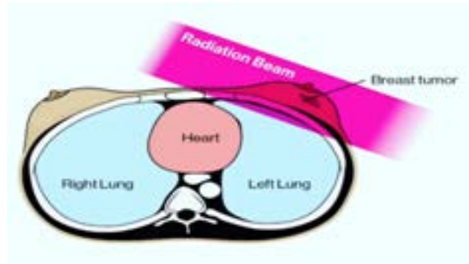
Breast cancer is the most common cancer amongst women in urban and second in rural India. As per GLOBOCAN 2020 projection, the new cases of breast cancer among Indian women will be around 1,70,000 per year. Breast cancer is typically treated with a combination of surgery, chemotherapy, hormone therapy, biological therapy, and radiation therapy based on the stage, hormonal status, and molecular and the genetic nature of the disease.

Radiation therapy (RT) plays vital role in the management of patients with breast cancer. However, breast radiotherapy inevitably delivers some radiation to the heart. Older RT methods often exposed the heart to significant doses of radiation, particularly in patients receiving radiation to left breast. A retrospective population based study from Norway shows that the relative risk for ischemic heart disease is increased by 7.4% for every 1Gy increase in mean heart dose.

Improvements and advances in radiation technology and delivery system over time have opened up doors for new treatment techniques. There are RT methods like APBI, Proton Therapy, IMRT, VMAT & DIBH to reduce the heart doses for the patients with left sided breast cancer. Out of these, Deep Inspiration Breath Hold (DIBH) is a simple, reproducible &well established treatment technique. The RT technologist guides the patient to breathe to the required threshold through intercom. When patient hold her breath as guided, her lungs expand and so heart is further from the treatment beam as shown in picture. This reduces the risk of X-rays damaging heart.



Heart position during free breathing



Heart position during DIBH

Radiation Oncology Department at NCI, Nagpur is equipped with Varian's trueBEAM SVC linac which has advanced RPM gating system to facilitate DIBH radiotherapy. Department launched its DIBH program in 2018. By end of year 2021, the department had treated about 50 patients with DIBH. Radiation Oncology team is working in tandem to improve and harmonize clinical practice in order to offer this heart sparing technique to more patients.

AS PATIENTS LIVE LONGER AND OFTEN CURED OF THEIR CANCER, TECHNOLOGIES LIKE DIBH WILL MAKE SURE THAT THEY DON'T SUFFER FROM LONG TERM CRITICAL ORGAN TOXICITIES DUE TO TREATMENT

Dr. Mahesh Upasani
Consultant Radiation Oncologist

BONE MARROW TRANSPLANT UNIT AT NATIONAL CANCER INSTITUTE, NAGPUR