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Journal of Microbiology and Related Research	Semiannual	8500	8000	664	625
Journal of Nurse Midwifery and Maternal Health	Triannual	5500	5000	430	391
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Journal of Plastic Surgery and Transplantation	Semiannual	26400	25900	2063	2023
Journal of Practical Biochemistry and Biophysics	Semiannual	7000	6500	547	508
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Otolaryngology International	Semiannual	5500	5000	430	391
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Physiotherapy and Occupational Therapy Journal	Quarterly	9000	8500	703	664
RFP Indian Journal of Medical Psychiatry	Semiannual	8000	7500	625	586
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Original Article

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Long Term Survival and Late Toxicities in Inoperable Carcinoma Esophagus Treated wth Concurrent Chemotherapy and Radiotherapy

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Abstract

Introduction: Results of treatment in carcinoma esophagus have not been very encouraging as it usually presents in an advanced stage. We treated these inoperable carcinoma esophagus patients with concurrent chemotherapy and radiotherapy and got early symptomatic relief and good long term survival. *Material & Methods:* 46 patients included in this study were treated with induction chemotherapy with methotrexate on day 1 and cisplatin on days 2 to 5 followed by radiotherapy from day 6 and further cisplatin was given on days 21, 28 and 35 concurrently with radiotherapy. *Results:* Symptomatic relief was seen during the second week and 69.56% patients had local control at 1 year. The 3-year and 5-year overall survival (OS) was 47.83% and 15.22% respectively, with a median survival period of 32 months. *Conclusion:* This regime of sequential chemotherapy followed by radiotherapy and concurrent chemotherapy has given better overall survival with acceptable toxicities.

Keywords: Survival; Esophagus; Chemo-radiotherapy; Long Term.

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Introduction

Cancer is considered a major health problem across the globe and is the 2nd most common cause of death after cardiac diseases. A significant number of cancers with various histology occurs in Gastrointestinal tract (GIT), of which, colorectal, stomach, esophagus, liver, gall bladder and pancreas are the 6 most common Gastrointestinal (GI) malignancies [1]. In the United States, esophagus accounts for approximately 1% of the overall malignancies & 6% of all the GI malignancies. With 456,000 newly diagnosed cases in 2012, it has become the 8th most common cancer in the world, though the incidence is variable with respect to geography, ethnicity and gender. In 2012, out of the estimated 1.01 million newly diagnosed cancer cases in India, 227000 were located in the GIT. GI malignancies were accountable for nearly 182000 deaths out of an approximate 682000 cancer-related deaths [2].

Esophagus is a hollow tubular structure with a length of 25 cm with most of it present in the thoracic cavity. For clinical purpose, it is divided into 3 major parts: upper 1/3rd (cervical: 15-18 cm distance from the incisors and upper thoracic: 18-24 cm), middle 1/3rd (24-32 cm) and lower 1/3rd (32-40 cm) esophagus. It is lined by stratified keratinized squamous epithelium except lower 1/3rd, which may contain glandular elements, as well. Histologically, squamous cell carcinoma is most predominant arising from squamous epithelium [3] followed by adenocarcinoma (from columnar lined distal esophagus) [4,5]. Sarcomas

and small cell carcinoma account to <1-2% of all esophageal cancers [6,7]. Moreover, esophageal melanomas, leiomyosarcomas, carcinoids & lymphomas are rare.

Carcinoma esophagus presents with the symptoms of dysphagia in 90% of the patients, odynophagia (50%), weight loss (40-70%) [8]. The incidence of adenocarcinoma is steadily on the rise in the United States. Risk factors for esophageal carcinoma are cigarette & hookah smoking, red meat, alcohol, tobacco chewing, hot tea consumption, nitrosamines in food, poor oral health, low intake of fresh fruits & vegetables, HPV, obesity, genetic alteration and low socioeconomic status [9,10,13]. Endoscopic ultrasound and CT Scan are used for proper staging & workup [11]. Despite various advances in the different modalities of treatment of carcinoma esophagus such as surgery, external beam radiotherapy (EBRT) ± chemotherapy & intraluminal brachytherapy, it still carries poor results [12]. A large number of patients succumb to the disease as a result of failure of primary lesion treatment as most of the patients present in a locally advanced stage and infiltration of disease in adjacent organs and lymph nodes. Patients who require surgery as the sole treatment have improved prognosis (owing to the evolution of surgical techniques & better postoperative care). Trials have demonstrated comparable results for concurrent chemo-radiation versus surgery in locally advanced carcinoma esophagus [22]. Here, the patients of carcinoma esophagus middle 1/3rd treated with concurrent chemo-radiation were evaluated for their clinical response, overall survival and associated late toxicities.

Materials and Methods

A retrospective observational study was carried out on 54 patients of locally advanced inoperable carcinoma esophagus who underwent definitive chemo-radiotherapy between September 2010 to 2014 and were followed up till June 2017. All the patients had histologically proven Stage III or more (locally advanced) cancer of the middle 1/3rd of esophagus with KPS ≥ 80%. After pretreatment and metastatic evaluation, all the patients were started on chemotherapy with Methotrexate (MTX) 50 mg (fixed dose) in 8 hours on day 1 and Cisplatin 20 mg/m2 on days 2 to 5 followed by radiotherapy from Day 6 combined with concurrent chemotherapy with Cisplatin 30 mg/m^2 given on days 21, 28, 35 day. CT simulation with proper immobilization in supine with arm above head position was done on SOMATOM CT Scanner. The images were then registered on Eclipse treatment planning system (TPS) version 8.9 and contouring of treatment planning volumes and organs at risk (OARs) was done as per RTOG guidelines. A repeat CT scan for replanning was done as and when required. A total of 66 Gy in 33 fractions was given to the GTV with 3DCRT or IMRT keeping the doses to OARs within tolerance limits. Overall survival (OS) was measured from start of the treatment till last follow up/death assessed till June 2017. Follow up was noted at monthly interval for initial 6 months, at 3 months for the next 12 months and 6 monthly, thereafter. Imaging and UGI Endoscopy were done on every follow up to evaluate the local control and metastatic work up. Evaluation of tumor response was done by RECIST criteria version 1.1 and of chronic toxicity was done using CTCAE version 4.0. Clinical evaluation was based on assessment of dysphagia as per RTOG/EORTC radiation morbidity grading. Pattern of failure was determined in terms of local recurrence as reappearance of primary lesion on endoscopy after treatment completion and distant metastases when there was presence of lung and liver metastases on follow up. These patients were subjected to salvage chemotherapy.

Observations and Results

In our study, the male to female ratio was approximately 2: 1. Out of 54 patients, 35 patients (64.81%) were males and 19 (35.19%) were females with median age of 55 years. Most male patients were in the age group of 51-60 years and female patients were between 61-70 years of age (Table 1). Histologically, 50 (92.59%) had squamous cell carcinoma, 3 (5.57%) had adenocarcinoma and 1 (1.85%) had small cell carcinoma esophagus. Out of 54 patients only 46 patients completed the treatment. 7 patients defaulted and did not receive complete treatment and 1 female patient who died during the treatment were excluded from the study.

Table 1: Age-wise distribution of patients

Age (yrs)	No. of Male	No. of Female	Total (%)
21-30	0 (0%)	2 (10.52%)	2 (3.7%)
31-40	3 (8.57%)	3 (15.79%)	6 (11.11%)
41-50	12 (34.29%)	2 (10.52%)	14 (25.92%)
51-60	14 (40%)	3 (15.79%)	17 (31.48%)
61-70	5 (14.28%)	6 (31.57%)	11 (20.37%)
71-80	1 (2.85%)	3 (15.79%)	4 (7.40%)
Total (%)	35 (64.81%)	19 (35.19%)	54 (100%)

Clinical evaluation was based on assessment of dysphagia as graded according to NCI CTC Toxicity Scale Version 2.0. On initial presentation, 23 (42.59%) patients had Grade 2 dysphagia and 31 (57.4%) patients had Grade 3 dysphagia. After 1 month of post-treatment follow up, 25 (54.35%) had Grade 0 dysphagia, 15 (32.6%) patients had Grade 1 dysphagia, 5 (10.87%) patients had Grade 2 dysphagia and Grade 3 dysphagia was present in 1 (2.17%) patient indicating significant relief in the symptoms of most of the patients. Symptomatic relief was seen very early during the treatment. Most of the patients were able to take oral diet during 2nd week of treatment and then it reduced mildly due to radiation esophagitis. Patients' performance status also improved during the treatment due to improved diet. After 3 years of follow up, 16 (72.72%) out of the 22 alive patients had Grade 0 dysphagia, 3 (13.64%) patients had Grade 1 dysphagia, 3 (13.64%) patients had Grade 2 dysphagia.

Out of the 46 patients, 32 (69.56%) patients had local control of the disease, 2 (4.34%) patients had local failure, 1 (2.17%) patient developed distant metastases and 11 (23.91%) patients died at the end of 1 year of follow up. 24 (52.17%) patients had local control of the disease, 1 (2.17%) patients had local failure, 4 (8.70%) patients developed distant metastases and 17 (36.95%) patients died after 2 years of follow up. After 3 years of follow up, 16 (34.78%) patients had local control of the disease, 3 (6.52%) patients had local failure, 3 (6.52%) patients developed distant metastases and 24 (52.17%) patients died(Figs. 1 & 2).

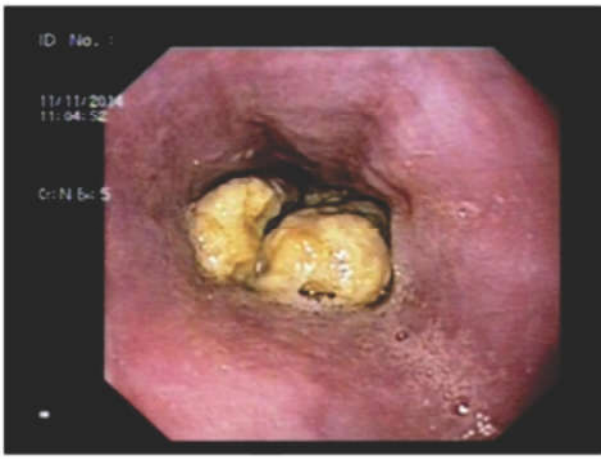

Fig. 1: Ulceroproliferative growth in esophagus

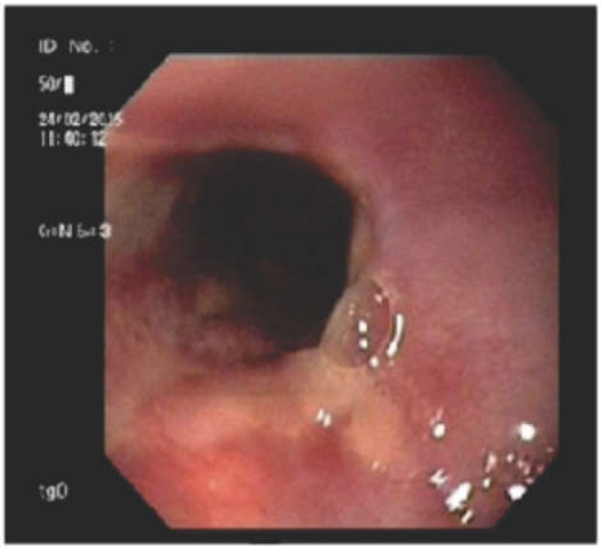

Fig. 2: Complete response after completion of chemo-radiotherapy

During follow up, seven patients developed esophageal stricture (Fig. 3), which were treated with esophageal dilatation and were able to take solid diet. Two patients developed pleural effusion and one patient had pericardial effusion, all were asymptomatic.

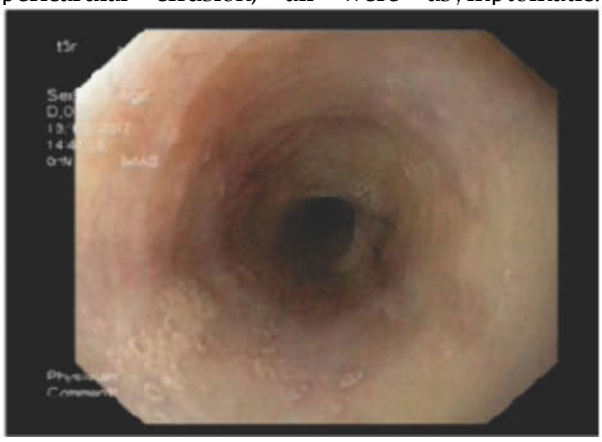

Fig. 3: Stricture post chemo- radiotherapy

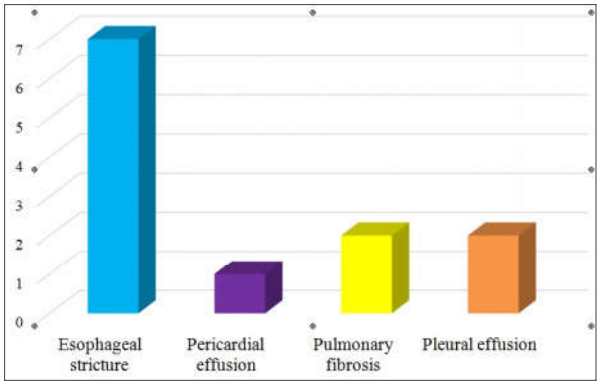

Fig. 4: Late toxicity

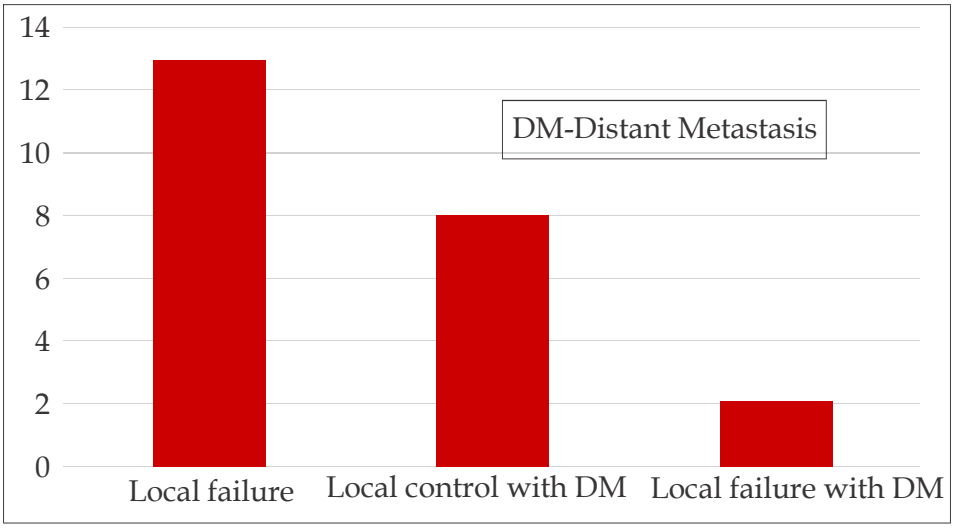

Fig. 5: Pattern of failure

Two patients had pulmonary fibrosis and they were also asymptomatic, and hence were kept on follow up (Fig. 4). None of the patients had trachea-esophageal fistula. Considering the pattern of failure in 46 patients at the time of evaluation (Fig. 5), it was seen that 13 patients (28.26%) showed local failure, 1 patient (2.17%) showed distant failure, 8 patients (17.39%) had distant metastasis and 2 patients (4.35%) had both local failure & distant metastasis.

The 3-year and 5-year overall survival (OS) was 47.83% (22 patients) and 15.22% (7 patients) respectively, with a median survival period of 32 months in this study (Fig. 6). Out of the 33 deaths, 23 were due to the complications related to disease progression (disease specific mortality – 69.7%) and 9 patients died due to other causes with controlled disease (disease non- specific mortality – 27.27%).

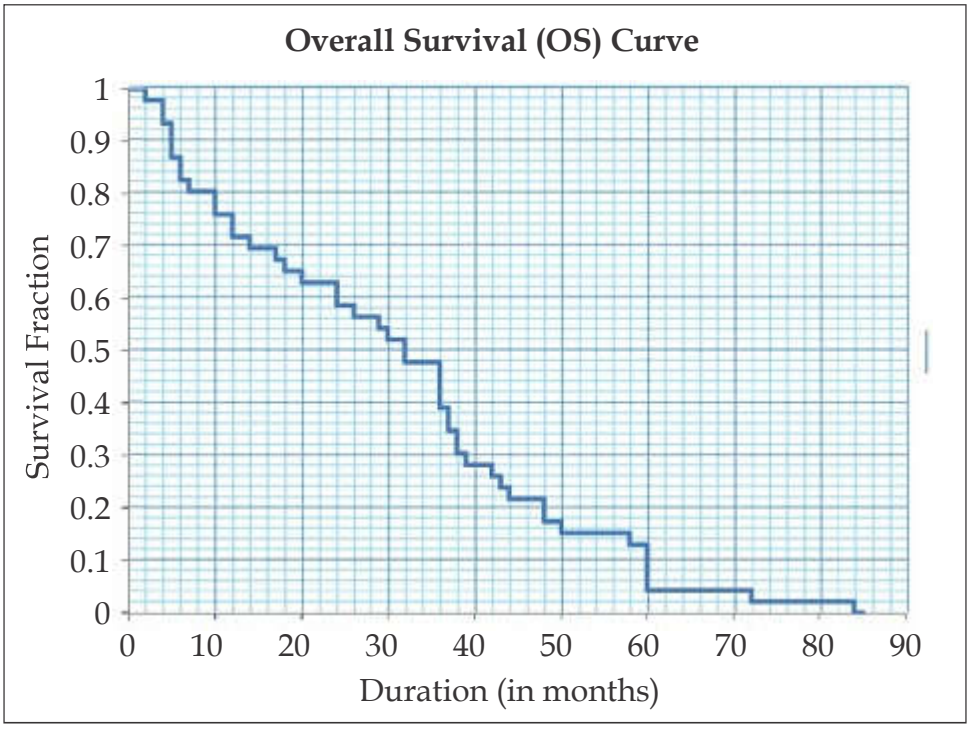

Fig. 6: Overall Survival (OS) Curve

Discussion

Cancer related deaths due to esophageal carcinoma is on increasing trends, it is the 6th leading cause worldwide and 4th in India [14,15]. Historical data suggests only 20% patients present with localized esophageal cancer, indicating that at the time of diagnosis, approximately 80% patients have either locally advanced or distant disease. 90% patients of carcinoma esophagus present with dysphagia as their main complaint leading to nausea, vomiting, cachexia, and ultimately poor quality of life. Majority of patients die due to infiltration of disease into the adjacent organs. The results of the treatment of carcinoma esophagus have been poor in spite of advances in various treatment modalities; hence, the treatment of choice for patients with carcinoma esophagus is controversial. Although surgery continues to be the standard approach for most localized esophageal cancers, cure rates after surgery alone have been poor, with 3- to 5-year survival rates ranging from 6% to 35% [16-18]. Surgery as a sole treatment carries a 2-year survival rate ranging from 35 to 42% & 5-year survival rate of 15 to 24%. As reported historically, EBRT alone carries a 5-year survival rate of 0 to 10%, owing to locoregional persistence or recurrence of the tumour, being as high as 85% [19]. The current trimodality approach, combining chemotherapy, radiation therapy (RT), and surgery, has significantly improved prognosis [20], with several studies showing improved survival rates [21,22]. However, many patients cannot tolerate surgery or decline it; for such individuals, definitive chemo-radiation is the standard approach. Combined modality treatment including radiotherapy and concurrent chemotherapy with Cisplatin and 5-Fluorouracil has lead to a long term survival rate in about 20 to 30% patients compared to surgery alone, but with increased rates of local recurrence of 77% (RT alone) [22]. FFCD 9102 trial [23] (done on 259 locally advanced esophagus cancer patients) suggested similar survival outcomes in 130 patients receiving chemo-radiation alone (2-year survival rate – 34 %) and in 129 patients treated by chemo-radiation followed by surgery (2-year survival rate - 40%) with no benefit for the addition of surgery after chemo- radiation, moreover, compromising the quality of life. Meta-analysis done by Zhu L-L et al. [40] connotes improved overall survival, reduced risk of persistence and recurrence of disease with concurrent chemo-radiotherapy compared to radiotherapy alone. The combination of radiotherapy and chemotherapy has additive effects in terms of local control and overall survival in this select population [18,24-26]. Our study is aimed at determining the 3-year and 5-year survival rates, evaluating the clinical response and observing the late oxicities. In our series, 46 patients with esophageal cancer who received definitive chemo-radiation, showed a median overall survival of 32 months and 63.04%, 47.83%, 15.22% being alive at 2-, 3- and 5-year respectively, and a median disease free survival of 25.5 months and 54.35%, 36.96%, 8.70% as 2-, 3- and 5-year disease free survival rate after diagnosis (Fig. 7).

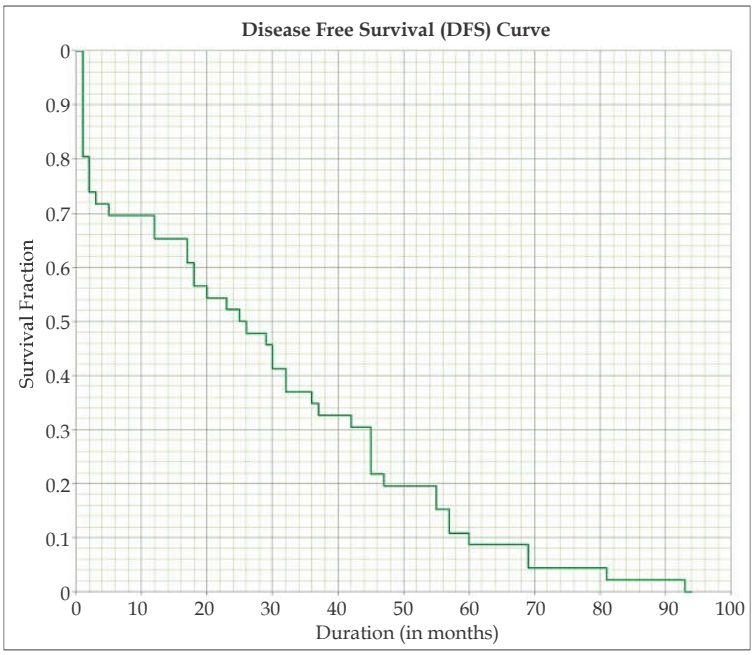

Fig. 7: Disease Free Survival (DFS) Curve

RTOG-85-01 [27] enrolled 129 patients who were treated with concurrent chemo-radiotherapy and only radiotherapy. It was found that the 3-and 5-year survival in the combined arm was 30 and 26% respectively versus in radiation only arm in which the 3-and 5-year survival was 0% each proving combined modality treatment superior to radiation alone. Although combined modality treatment has higher toxicity than radiation only arm. Similarly, ECOG [28] study in which 5FU and Mitomycin-C was used along with radiotherapy, 2 and 5 year survivals were 12% and 7% in radiation alone arm and 27% and 9% in chemo-radiation arm. Patients treated in the chemo- radiation arm had a longer median survival of 14.8 months versus 9.2 months in radiation alone group. Another study by LR Coia et al. [29] in which 90 patients of esophageal cancer were treated with definitive combined chemo-radiation therapy, 3- and 5-year overall survival rate was 29% and 18% respectively. Bhandari[30] treated a total of 31 cases of inoperable cancer esophagus with once weekly Cisplatin 30 mg/ m2 along with radiotherapy (60 Gy in 30 fractions over 6 weeks) on Telecobalt/Linear accelerator and achieved 1 year, 2 year and 3 year overall survival of 80%, 35% and 19%, respectively.

Crosby TD et al. [31] treated 90 patient of esophageal cancer who were inoperable with concurrent chemo-radiation using Cisplatin and 5FU and EBRT (50Gy/25#) and observed a progression free median survival of 18 months. The 2-, 3- and 5-year overall survival rates were 51%, 45% and 26% respectively.

P. Haddad et al. [32] treated 28 patients by two courses of cisplatin and 5-FU chemotherapy with concurrent radiotherapy of 50Gy in 25#. Mean overall survival was 17 months and median survival was not reached. Compared to 283 patients treated by radiotherapy alone with a mean and median survival of 12 and 8 months, chemo radiation was significantly superior. A study done by Smit JK et al. [33] divided 287 patients who surgically unfit or inoperable into two groups. 1st group had 110 patients and they were treated by chemo-radiation the 2nd group had 177 patients and were treated by definitive radiation. They observed that the disease free survival was higher in the group treated with definitive chemo-radiation 16 and 5% at 2 and 5 years.

Bhandari et al. [34] treated 57 patients of carcinoma esophagus, of which 26 patients received sequential chemotherapy (Methotrexate & Cisplatin) followed by radiotherapy and 31 patients underwent concurrent chemoradiotherapy. The study showed a 2-year survival of 38% in sequential therapy setting and 35.5% in concurrent setting, along with a median survival of 19.5 and 18 months, respectively with comparable toxicities.

At least 7 patients in our study developed esophageal stricture out of which 5 patients required dilatation every 6 months, 2 patient developed pleural effusion and underwent pleural tapping, 2 patients developed pulmonary fibrosis, 1 developed pericardial effusion and was asymptomatic as a result of late effect of chemo-radiation. In contrast to a study done by Ito H et al. [35] in Japan after concurrent-chemo-radiation 17 late toxicities of ≥ Grade 3 were observed in 11 patients. Two patients died of late toxicities. Four Grade 3 pericardial effusions and eight Grade 3 pleural effusions and none died of it. In another study done by Ishikura et al. [36], 4 patients suffered benign esophageal strictures and required esophageal dilatation one to three times. 15 patients suffered from benign pleural effusion of grade 2 or more. Pleural effusion after thoracic radiotherapy also has been reported, mainly in Hodgkin's lymphoma [37,38]. The underlying cause of benign pleural effusion after thoracic radiotherapy is thought to be mainly due lymphatic obstruction resulting from mediastinal fibrosis and, in some cases, it may be related to heart disease, such as heart failure and pericardial effusion. There have been many reports of pericardial effusion after thoracic radiotherapy in patients with Hodgkin's lymphoma [39].

Overall 13 (28.89%) out of 45 patients had local failure, 8 (17.78%) had local control with distant metastasis and 2 (4.44%) patients had local failure with distant metastasis post treatment.

In RTOG-85-01 local failure in the form of persistence of disease was 28% in the combined modality arm and 37% in RT only arm [27]. P. Haddad et al. observed 16 (57.14%) out of 28 patients treated with chemo-radiation had recurrences after treatment [32]. TD Crosby et al. noted 21 cases (23%), recurrence after completion of chemo-radiation in 90 patients [31]. This study also shows 29% local failure rate although radiation dose was 66Gy to the primary.

RTOG-85-01 [27] which was a US intergroup trial two cycles of non-concurrent chemotherapy was given after chemo-radiotherapy; only half of the patients were able to tolerate this therapy. In contrast to our study in which Day 1-5 neo-adjuvant chemotherapy was given followed by concurrent chemo-radiotherapy which was tolerated by maximum number of patients. Similar study was done by TDL Crosby et al. [31] in which 4 cycles

of chemotherapy were given put of which 3rd and 4th cycle was given concurrently with radiotherapy and it was well tolerated with maximum number of patients. It is noted that in both studies giving neoadjuvant chemotherapy improved dysphagia to some extent prior to radiation therapy.

Conclusions

Concurrent chemo-radiation is an intensive treatment, in which combined cytotoxic effect of radiation and chemotherapy helps to control the loco-regional disease. In addition to loco-regional disease control, chemotherapy is also effective for distant metastases. There may be some severe acute side effects as seen in the studies quoted which can be managed but decreased late effects are also seen which a positive observation is.

Our study was found to be well tolerated and has given encouraging results in terms of complete and partial response with acceptable toxicities. Role of methotrexate should be further evaluated for better response as achieved in this study.

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Original Article

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A Dosimetric Study on Indigenously Developed Heterogeneous Thorax Phantom for Radiation Dose Verification in Carcinoma Lung

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Abstract

Aim: To design and study the physical and radiological properties of Heterogeneous Thorax Phantom (HTP). *Materials and Methods:* The Computed Tomography (CT) images of thorax were imported on treatment planning system and analyzed for measuring the density of chest wall tissue, lung and soft tissue behind the lung. The mean and standard deviation of these different densities were noted and analyzed. A HTP with similar density distribution was made using slabs of SP34 and pinewood. A plan was made on actual patient's CT scan and on HTP by putting 6 MV photon beam of 10x10 cm^2 field size and source to surface distance of 100 cms perpendicular to the chest wall using anisotropic analytical algorithm with grid size 0.25 cm. Depths for isodose were measured in both the mediums. The CT scan of HTP was taken at three different interface regions. The doses were planned and measured at these three interface regions using ionization chamber. Measured and planned doses were compared and analyzed. *Results:* The mean density of the chest wall, lung and soft tissue were found to be 0.94, 0.28 and 0.98 gm/cc respectively on patient's CT scan, while 0.99, 0.27 and 0.99 gm/cc respectively in HTP. Variation in planned dose and measured dose on HTP at 6 cm, 10 cm and 18 cm depths were found to be 0.47%, 0.81% and 2.4%. *Conclusion:* Phantom mimicking thorax site along with advanced third generation Monte Carlo based algorithms which are based on biological dose calculation should be used for more accurate dose calculation.

Keywords: Heterogeneous Phantom; Slab-Pinewood-Slab Phantom; Third Generation Algorithm, Monte Carlo, Across XB; Monaco.

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Introduction

Lung cancer is one of the commonest cancers and cause of cancer related deaths all over the world and is responsible for nearly one cancer death in five (1.59 million deaths, 19.4% of the total) [1]. In India, lung cancer constitutes 6.9 per cent of all new cancer cases and 9.3 percent of all cancer related deaths in both sexes, the highest reported incidence in India is in Mizoram in both men and women [2]. Radiation therapy in cases of carcinoma lung is an important modality of treatment and thorax is a complex site for radiation delivery due to different medium densities regions e.g bones, lung, air, etc. [3] and presence of other organs such as heart, oesophagus. Thorax site being a heterogeneous medium pose a challenge for accurate dosimetric calculations and radiation delivery. The precise planning and dose delivery ensures that we get the full benefit of radiation with minimal impact on other body parts i.e. Organ At Risk (OAR) and maximal permissible dose to the tumour. The dose delivery calculations on a commercial treatment planning systems (TPS) are done with the help of algorithms namely Analytical

Anisotropic Algorithm (AAA), Collapsed Cone Convolution algorithm, Pencil Beam Convolution algorithm which are not that accurate with dose calculations in complex medium like chest [4-7]. For more accurate and precise calculations, Monte Carlo (MC) code based algorithms Monaco, Acuros XB (AXB) were introduced [8-10]. To verify the dose distribution accuracy phantoms are used. Most commonly used are water phantom or water equivalent phantom which are homogeneous in nature [11-13]. So, in order to achieve better dose distribution accuracy heterogeneous phantoms should be used with advanced algorithms [14]. This study has been carried out to evaluate the dose calculated in chest wall-lung interface and dose measured in the similar kind of medium by developing a chest phantom mimicking the thorax and to verify patient specific Quality Assurance using the same.

Materials & Methods

CT scan with 3 mm slice thickness of 20 patients were performed by Siemens SOMATOM Definition AS Scanner (Siemens Medical Systems, Germany). CT set for all the patients were imported on TPS Eclipse version 13.7 (Varian Medical Systems Pvt. Ltd., Palo Alto, California, USA). These CT images were for radiotherapy planning purpose for the concerned patients. These images were analyzed for measuring the density of chest wall tissue, lung and soft tissue behind the lung. The mean and standard deviation of these different densities were noted and analyzed. Also the mean and standard deviation of chest wall thickness, lung separation and soft tissue behind the lung were measured. Keeping the above data as standard a heterogeneous phantom was made using slabs of SP34 (IBA Dosimetry GmbH, Schwarzenbruck, Germany) with dimensions 30x30x1 cm^3 and pinewood slabs cut in the dimensions of 20x30x2 cm^3. To design HTP 5 slabs of SP34 were used to represent 5 cm of chest wall, 7 slabs of pinewood were used to represent lung region and again 10 slabs of SP34 were used to represent thickness of soft tissue behind the lung. The SP34 slab is made up of polystyrene (98%) and titanium oxide (2%) which has a density of 1.045 gm/cc and that of pinewood slab was 0.30 gm/cc. In this way a heterogeneous phantom named as HTP was prepared (Fig. 1). CT Scan with 3 mm slice thickness were done for HTP as well. The CT images were imported on Eclipse TPS. First five slabs volume were marked as chest wall, next seven pinewood slabs were marked as lung and the remaining 10 slabs of SP34 were marked as soft tissue behind the lung. Hounsfield Unit (HU) were measured at multiple points in each of these three volumes created. Density was calculated using these HU numbers using the formula; Density = (1000+HU)/1000 [15]. CT data set of one of the patient was chosen for planning purpose whose average chest wall thickness was 5 cm, lung separation was 14 cm and thickness of the soft tissue behind lung was 10 cm. One plan was made on this patient's CT data set by putting 6 MV photon energy beam of 10x10 cm^2 field size and Source to Surface Distance (SSD) of 100 cms perpendicular to the chest wall surface. The plan was normalized for 100% dose as maximum dose in the entire volume which came at the depth of 1.5 cm. Another plan with same field size and SSD was made on CT images of HTP having beam perpendicular to the phantom's surface. This plan was also normalized with maximum 100% dose in the volume. Both the plans were created by using AAA with grid size 0.25 cm. Depths for isodose lines of 100%, 90%, 80%, 70%, 60%, 50% and 40% were measured in both the plans (Figs. 2,3) and were compared with each other. The CT scan of HTP was repeated thrice for 3 different interface regions using ion chamber within it viz. Ion chamber at position A (chamber at slab-pinewood interface), ion chamber at position B (chamber at 12 cm depth from the surface of the phantom i.e. within the pinewood) and ion chamber at position C (chamber at pinewood-slab interface). The arrangement of ion chamber at different positions was made possible by replacing the pinewood slab with specially designed pinewood slab of the same dimension (i.e. 20x10x2 cm^3) having cavity at its centre for the thimble chamber (IBA Dosimetry GmbH, Schwarzenbruck, Germany). These positions mimicked the soft tissue-lung, lung, and lung-soft tissue interfaces. The doses at the soft tissue-lung interface and slab-pinewood interface were measured. Similarly doses at the lung-soft tissue behind lung interface and pinewood-slab interface were measured. The dose within the lung and pinewood were also measured at 12 cm from the surface. HTP with ion chamber at position A was set on the LA couch with 100 cm SSD and matching the machine's isocenter at the surface of phantom in such a way that the central axis of the beam would go through the centre of ion chamber cavity. The plan done on phantom with chamber at position 1 was loaded for delivery. Cone Beam CT (CBCT) was taken for accurate positioning of the phantom and chamber within it. After verifying the setup plan was delivered and the

dose was measured. Similar process was repeated for measuring the dose at position B and position C (Fig. 3); The planned and measured doses at all the three positions were compared and analyzed.

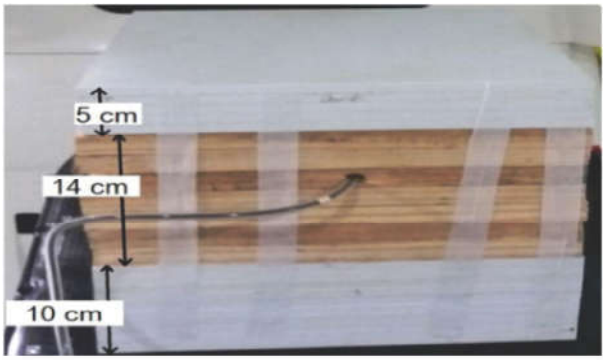

Fig. 1: Schematic representation of HTP

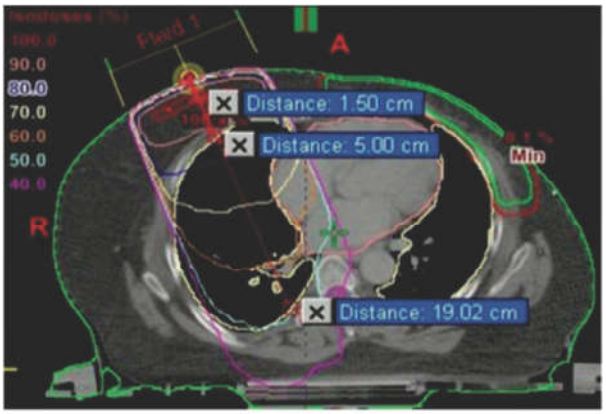

Fig. 2: Isodose curves at different depths in CT slice of patient

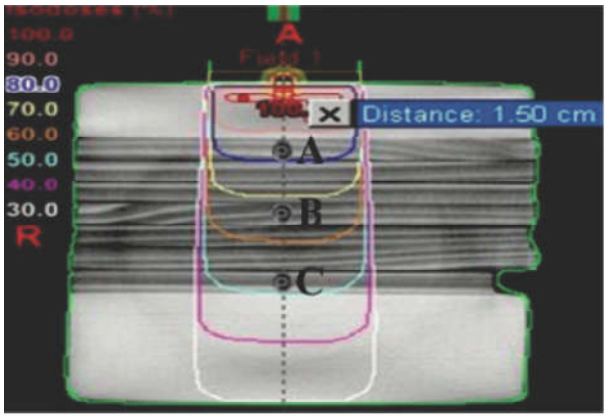

Fig. 3: Isodose curves at different depths along with different positions (A, B, and C) for placement of ionization chamber in HTP

Results

The mean density of the chest wall, lung and soft tissue behind the lung were found to be 0.94, 0.28 and 0.98 gm/cc respectively, while that of SP34 slab and pinewood slab were found to be 0.99 and 0.27 gm/cc respectively (Tables 1 and 2). Isodose curves for chest and the HTPs were almost similar for 100%, 90% and 80% depth dose. Isodose curves for 70% and 60% depth dose were more in actual patient compared to the HTP and the isodose curves for 50% and 40% dose were again similar for both (Table 3); the variation in planned dose and measured dose on HTP at 6 cm, 10 cm and 18 cm depths were found to be 0.47%, 0.81% and 2.4% respectively (Table 4).

Table 1: Hounsfield unit (HU) and density measurement of chest wall, lung and soft tissue

No of points in given medium	HU of chest wall	HU of lung	HU of soft tissue
1	-71	-683	-26
2	38	-694	-28
3	-120	-671	-94
4	-122	-743	-3
5	-100	-669	70
6	-115	-725	79
7	-30	-713	-71
8	-101	-704	-107
9	-113	-701	-72
10	53	-722	-56
11	46	-679	-106
12	10	-688	74
13	-47	-744	44
14	-64	-701	-80
15	-90	-724	-42
16	-73	-717	-59
17	-88	-798	63
18	-40	-789	-38
19	-78	-716	36
20	44	-701	21
Mean HU	-53.05	-714.1	-19.75
Density (g/cc)	0.94	0.28	0.98

Table 2: Hounsfield unit (HU) and density measurement of pine wood and SP34 slabs

No of points in given medium	HU of pine wood slab	HU of SP34 slab
1	-732	-36
2	-748	5
3	-730	11
4	-721	-18
5	-715	11
6	-740	-12
7	-709	13
8	-720	4

9	-749	-19
10	-722	-17
11	-731	-20
12	-733	8
13	-735	13
14	-718	15
15	-721	2
16	-713	15
17	-717	-36
18	-719	-5
19	-743	-6
20	-755	-35
Mean HU	-728.55	-5.35
Density (g/cc)	0.27	0.99

Table 3: Isodose depths in CT images of the patient and HTP

Isodose lines (%)	Isodose depth in patient (cm)	Isodose depth in S-P-S phantom (cm)
100	1.5	1.5
90	4.24	4.16
80	7.24	7.13
70	11.82	10.4
60	16.38	14.67
50	19.6	19.28
40	23.71	23.98

Table 4: Dose at different depths in CT image of the patient and HTP

Depth (cm)	Planned dose on TPS (cGy)	Measured dose on LA (cGy)	% variation
6 cm	83.8	83.4	-0.47
10 cm	73.6	74.2	0.81
18 cm	54.1	55.4	2.4

Discussion

The radiation therapy of carcinoma lung is a challenging task as it requires a high precision. Thorax site has different density patterns in its volume e.g chest wall consists of soft tissue which has a density of approximately 1 gm/cc, lung cavity with density near to that of air and again soft tissue behind the lung. The interaction of radiation with such a region with complex density pattern is different as it is elsewhere because of high density variation. Because of this the dose calculation and delivery becomes a tedious task. If adequate coverage of the tumour volume is not obtained and optimum dose is not delivered then it may lead to underdosing/overdosing and may lead to residual disease or recurrence.

Algorithms for dose calculation plays a pivotal role in precision radiation therapy planning and dose delivery. If a better algorithm is chosen which calculates the dose considering the heterogeneity with different density gradient then it will calculate dose more accurately. Monte Carlo based algorithms such as AXB, Monaco, etc. are latest algorithms which takes heterogeneity into account are more accurate for dose calculation in such mediums where there different density regions. If such new algorithms are used for panning then it will calculate the dose at soft tissue lung interface region more accurately and hence it will lead to better dose estimation at the edge and will also improve the treatment outcome.

Liang et al. compared AAA with Acuros XB and concluded that PTV dose was overestimated by AAA. [16]

Gurjar et al. proved that AAA doesn't calculate the dose accurately in heterogeneous medium as compared to homogeneous medium [17]

However, if newer Monte Carlo based algorithms are not available at the centre in the TPS and second generation algorithm like AAA is available then the drawbacks of such an algorithm should be kept in mind and appropriate corrections should be made at the time of planning which will help in accurate dose delivery to the target and it can also avoid underdosing or overdosing.

Current study has evaluated the dose calculated by AAA and its comparison with measured dose and its implementation in approving dose planned. The study was carried out by using heterogeneous chest phantom with same density pattern as of chest region after confirming the similarity in density pattern in both the media i.e. HTP and actual chest region.

The mean densities of soft tissue of the chest wall, lung and the soft tissue behind it were found to be 0.95, 0.28 and 0.98 gm/cc respectively. The phantom (SP34) which is routinely used for patient specific QA, is made up of water equivalent material and have an average density of 1.034 gm/cc which is similar to that of chest wall region and also to the soft tissue behind it. Similarly the calculated density of pinewood slab is 0.30 gm/cc which is nearly equal to density of the lung region. In this way HTP is representing the density pattern with equivalent thickness regions of each density type as the chest i. e. chest wall-lung-soft tissue. Therefore choice of using HTP for dose calculation purpose for chest region is rational.

Now, the selection of HTP is important as compared to using a phantom with uniform density across its volume.

The radiological property of HTP and the chest

site was checked for isodose depths with a beam of 6 MV photons with field size 5x5 cm2, Source to Surface Distance (SSD) of 100 cm and perpendicular to the surface in both the cases.

The isodose depths of 100% and 90% have almost similar depths in both the plans (one on the patient's CT image and another on the HTP) while the 80%, 70% and 60% have different depths in both the plans, this is significantly because density of the lung is low, hence there is low backscattering of electrons and also the density of the slab is slightly higher than the chest wall and then again 50%, 40% isodose depths matches.

Dubey et al. reported that if phantoms resembling the actual chest are used for QA in IMRT plans then it would yield better results [18].

The planned doses which were calculated by AAA at the interface regions and in the middle of the wood region were compared with the measured doses at the concerned points. The results indicates that AAA over-calculates the dose at interface region, it is because number of secondary electrons produced in SP34 are higher and number of backscattered electrons in the wood are lower due to low density of the medium, while the AAA under calculated dose at wood-SP34 region and in the wood.

Rana [19] have published a study which shows AXB is better than AAA for dose calculation in heterogeneous medium.

The difference in calculated doses and measured doses is a good reference in understanding the actual dose distribution pattern in carcinoma lung cases, it is different from what we see on TPS as calculated by AAA.

So, understanding from the study, it is explainable that if PTV is the target, L is the lung region and S is the soft tissue region (Fig. 4).

What we see here is AAA calculates lesser dose at point P1 and greater dose at point P2. If the plan is approved with 95% of the planned dose coverage then based on the results of this study, approximately 2.5 % dose will be higher at the point P1 and lesser at the point P2 as compared to what we see on the TPS.

So, the dose at P1 is not a problem if it is lesser than 105% to <2 cm^2 area and higher than 95% dose as the maximum dose at hotspot acceptable as per ICRU-83 is 105% to a 2 cm^2 area. But if the planned dose at P2 is 95% then there is a high probability that it will receive lesser dose and if the lesser dose covers the bigger target then it might result in underdosing. Therefore, based on the current study, it is highly recommended that the minimum of 97% or above dose coverage should be achieved at the region which is similar to P2 on the TPS as per the calculations shown by AAA, so that at least 95% plus dose can be practically delivered to the whole PTV.

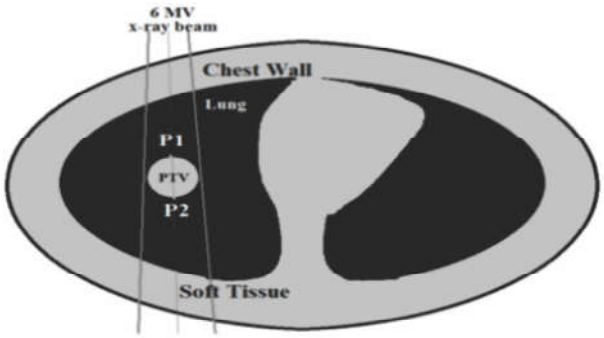

Fig. 4: Schematic diagram of chest region

Conclusion

The current study was done by using S-P-S heterogeneous chest phantom for the the verification of doses calculated by AAA at interface regions. As the density and isodose depths profiles of the HTP were found to be equivalent to the actual chest region. Thus the use of heterogeneous phantom for patient specific QA is justified. Based on the results of current study it can be concluded that that the heterogeneous chest phantom should be used for verifying the dose calculated in the chest site planning instead of homogeneous phantom.

Besides heterogeneous phantom there is a need of Monte Carlo based algorithm which can calculate accurate dose at the interface region. Hence newer algorithm like acuros XB should be used for dose calculation in heterogeneous medium instead of AAA.

Combination of such heterogeneous phantom and Monte Carlo based algorithm will definitely improve the patient specific QA practices and thus help in improving treatment outcome.

Sources of support: NIL

Ethical Issues: NIL

Conflicting Interest : NIL

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Original Article

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Chromosomal Abnormalities in Multiple Myeloma: An Observational Study from South India

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Abstract

Recurrent cytogenetic abnormalities are noted throughout the course of multiple myeloma (MM) from the premalignant stage of monoclonal gammopathy of undetermined significance to end-stage disease. The prospective, observational study evaluated the frequency of structural and numerical chromosomal abnormalities in a cohort of 118 patients diagnosed with MM from south India using conventional cytogenetics. Chromosomal analysis was carried for both fine needle and bone marrow samples and the karyotypes were interpreted as per the International System for Human Cytogenetic Nomenclature. The study identified 6 hyperdiploidy, 2 hypodiploidy and 3 pseudoploidy. The most common numerical abnormalities noted were gain of chromosomes 3, 5, 6 ,7, 11, 15, 16, 18, 19 and 21, and loss of 10, 12, 14, 17 and 22. The study validated the role of CC in conducting primary screening of MM, especially in the resource-poor settings and in remote areas with limited diagnostic facilities

Keywords: Chromosomes; Cytogenetics; Karyotype; Multiple Myeloma.

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Introduction

Multiple myeloma (MM), a cytogenetically heterogenous plasma cell disease, is marked by the presence of several frequent cytogenetic abnormalities throughout the disease course [1]. In terms of disease prognosis, cytogenetic alterations has been identified as an important risk factor and abnormal karyotypes are noted in 30-50% of the patients, especially in the advanced stages of the disease [2]. According to the 2018 systematic analysis published in JAMA Oncology, the mean incidence of MM increased by 126% worldwide and mortality by 94%. The study has underscored that the lack of diagnostic facilities is adding to the increased incidence rate of the malignancy in countries with lower sociodemographic index [3].

Based on the chromosome numbers in the tumor clone, the malignancy can be broadly classified as hyperdiploid MM (≥47 and <75 chromosome) and non-hyperdiploid MM. Non-hyperdiploid MM is further divided into 3 subgroups: hypodiploid (≤44 chromosomes), pseudodiploid (45–46 chromosomes) and near tetraploid (>75 chromosomes). The hyperdiploid clone marked by a distinct pattern of chromosome gain (+3, +5, +7, +9, +11, +19, +21) is associated with better survival, whereas deletions of 1p, 12p, 16q and 17p may have poor outcome or disease progression [4].

Apart from these major chromosomal abnormalities breakpoints at the loci of tumor suppresser

gene, proto-oncogenes or immunoglobulin-related gene especially involving 1p13, 11q13, 6q21, 7p11.2, 14q13, 17p11, and 19p13.3 regions have also been noted in rare cases of MM. [5]

The present study investigated the frequency of structural and numerical chromosomal abnormalities in a cohort of patients with MM from south India. It also explored the feasibility of using conventional cytogenetics (CC) as a primary screening technique for multiple myeloma.

Materials and Methods

The prospective, non-interventional, observational study involved 118 patients newly diagnosed with MM at a super specialty center in south India. The subjects were enrolled between January 2006 and September 2010. The diagnosis was concluded on the basis of the International Myeloma Working Group criteria [6,7]. Informed consents were obtained from all patients prior to the study.

Bone marrow and fine needle aspirations (2 cases) were carried out for all the enrolled subjects. Bone marrow samples were collected according to the standard procedures followed for hematology and cytogenetic investigations. The aspirates were cultured as direct, 24- and 48-hour cultures, without mitogens, in RPMI-1640 medium supplemented with 15% fetal bovine serum at 37^0C. After incubation, the cells were exposed to colcemid (0.10µg/ml) for 30 minutes, followed by hypotonic treatment (0.075 M KCl) for 20 minutes. The cells were subsequently fixed with Carnoy's fixative (methanol-glacial acetic acid, 3:1) and kept in refrigerator overnight. On the following day, chromosomal analysis was performed on the air dried bone marrow samples using the standard G-banding technique (Seabright 1973). [8] Metaphases of good morphology were captured and analyzed by Image Analysis System. The karyotypes were interpreted according to the International System for Human Cytogenetic Nomenclature (2005). [9]

With reference to the modal number, hyperdiploidy and hypodiploidy have been used to describe cells with 47–57 chromosomes and 35–45 chromosomes respectively. The corresponding terms near triploidy, near tetraploidy, and pseudodiploidy have been used to define chromosomes 58–80, 81–103 and 46 with numerical and/or structural aberrations [9].

Results

The recruited subjects included 74 males and 44 females between the age range of 31 to 80 years. Conventional cytogenetic analysis of bone marrow (BMA) and fine needle aspirate (FNA, 2 cases) cultures revealed successful karyotype in 77 (87.5%) and complex abnormal karyotypes in 11 patients (12.5%). The numbers of patients noted with hyperdiploidy, hypodiploidy and pseudoploidy were 6, 2 and 3 respectively. The most common numerical abnormalities noted were gain of chromosomes 3, 5, 6, 7, 11, 15, 16, 18, 19 and 21, and loss of 10, 12, 14, 17 and 22. The break points (X) (q13), 3 (q12), 3 (p12), 6 (q23), 9 (q22), & 11 (q13) were involved in deletion and (1) (q21), 19 (p13) & 8 (q24) in addition. The characteristic translocations noted were t (1;6) (q23;q11), t (1;9) (p12;q34), t (11;14) (q13;q32) and t (11;16) (q13;q22). Abnormalities noted during chromosome analyses of the bone marrow and peripheral blood cells are briefed in Table 1 and Figure 1.

Table 1: Abnormalities noted during chromosome analysis of the bone marrow and peripheral blood

Age/ Sex	No. of patients	Samples used	Karyotype
50/M	1	BMA	51, XY, t(1;?)(q21; ?) x2, del (3) (q12), +5, +5, +7, der (9), t (1; 9)(q34; q12), -12 ,der (16), t (11; 16) (q13; q22), -19, +21, -22,+mar/ 55XY, add (1) (q21) x2, dic t (1;9) (p12; q34), del (3) (p12), +5, +5, +7, -14, -17, add (19) (p13),+21, -22, +6mar
17/M	1	FNA	46XY, add (19) (q13)
42/F	1	BMA	46XX, t (2;3) (p23;p27)
68/F	1	BMA	55, X, del (X) (q13), +3, +5, +5, +5, i (8)(q10), add (9) (p24), +11, +11, del (11) (q13),-14, +15, add (16) (q24), -17, +18, +19, +21, +mar/ 46, XX
54/M	1	BMA	46XX, t (11; 14) (q13; q32)
61/M	1	BMA	54XY, +5, del (6) (q21) x2, +6, +7, +7, add (8) (q24) x2, -10, +15,+15, derdic (16), t (1; 16) (p12; p13) x2, +16, +19, +19
48- 50 /M	4	BMA	47XY, +mar/ 46, XY
55/M	1	BMA	78, XY, +X, t (1; 6) (q23; q24), +2, +3, +3, +6, +6, +7, +8, +8, +9, +9, +10, +10, +11, +12, +14, +15, +15, +16, +16, +17, +17, +18, +18, +19, +19, +19, +21,+ 21, +4mar

Cells

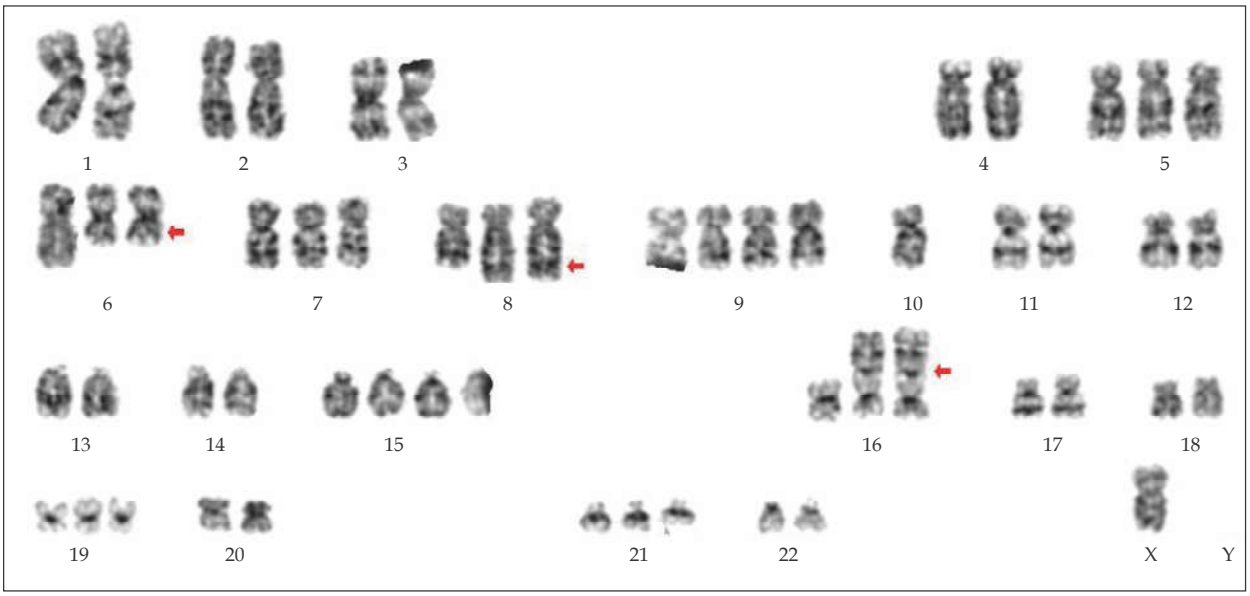

Fig. 1: Karyotyping results of multiple myeloma patients

Discussion

The present study reports CC as an important tool in elucidating the complex and diverse genetic abnormalities associated with MM. The cytogenetic findings helped in identifying two distinct groups of MM: hyperdiploid associated with better prognosis (6 patients) and non-hyperdiploid with poor survival (5 patients). It also helped in establishing the presence of prognostic chromosomal markers such as t (1; 6), t (1; 16), t (11; 14), t (11; 16), and 16(q) abnormalities.

Traditional approaches such as cytogenetic analysis, molecular genetic studies, and fluorescence in situ hybridization (FISH) provide crucial diagnostic and prognostic information in patients with MM. CC plays a paramount role in identifying the chromosomal abnormalities that demarcates patients with good prognosis from poor in relation to therapeutic response. It also holds the advantage of conducting whole genome analysis in a single experiment, whereas FISH targets only specific genes and is expensive when large panel probes are necessary [2].

In concurrence with the current findings, a 2016 single-center study conducted in Korea has highlighted the need of including CC as a part of initial diagnostic work-up in patients suspected with MM. The study considered cytogenetic results obtained from 222 patients with newly diagnosed MM. Among the abnormalities detected, hyperdiploidy with structural aberrations was the predominant finding (44%), followed by hypodiploidy with structural aberrations (28%) [2].

A more recent cytogenetic study conducted by Royal et al. in Indian population has added a few more numerical, structural and clonal abnormalities to the previously reported literature evidence on MM. The researchers noted the existence of a combination of ploidies, i.e., clones of hyperdiploidy, hypodiploidy, hypotetraploidy, and hypertetraploidy, in addition to the commonly reported monosomies. The study also documented the presence of other monosomies such as − 2, −6, −9, −10, −20, −21, and two cases with −Y, and one with −X [5].

Although, cytogenetic analysis provides more valuable information on prognosis, the low proliferation activity of terminally differentiated plasma cells, especially in the early disease stages, is one of the major limiting factors of this technique. In addition, interpretation of the result may be challenging, if the aberrations are cryptic and the chromosomal morphologies obtained through karyotyping are of poor quality [2]. The complementary molecular cytogenetic techniques such as FISH may be required in such cases. The major limitations of the current study are reduced sample size and not introducing FISH data to compare with conventional karyotyping.

A retrospective study from western India has concluded on the necessity of conducting interphase

FISH study along with CC for detecting specific chromosomal aberrations with major prognostic significance in MM. The researchers carried out CC and interphase FISH on 58 subjects and the CC could identify only abnormal karyotype in 8 cases. Whereas, the FISH identified 50 patients with complex genetic aberrations and 8 with normal karyotypes [10].

Conclusion

The present study corroborates the role of CC in conducting initial screening and the primary diagnosis of MM. Owing to the cost-effectiveness; it is highly beneficial for patients belonging to the resource-poor settings and in remote areas with limited access to newer diagnostic facilities.

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Case Report

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Carcinoma Cervix with Extensive Scar Site Metastasis after Simple Hysterectomy: A Rare Scenario

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Abstract

Recurrences after surgery or radiation for Carcinomas of uterine cervix are most commonly locoregional with the parametrium, lymph nodes and vagina as the most frequent sites of relapse. The occurrence of scar site metastases from carcinoma cervix is reported to be extremely rare ranging from 0.1 to 0.2%. We report here an unusual case of extensive scar site metastasisin patient with squamous cell carcinoma cervix operated earlier for simple hysterectomy and did not receive any adjuvant treatment. 60 year old female presented with 17x 10cm lower abdominal mass over the midline scar with multiple excavated ulcers on the surface. She was operated a year back for simple hysterectomy with bilateral salpingo-oophorectomy. Final histology came out as moderately differentiated squamous cell carcinoma of the cervix. Biopsy was taken from skin ulcer which was suggestive of squamous cell carcinoma. CECT scan was suggestive of a solid mass involving anterior abdominal wall and extensive areas of skin of around size 17 x15 x 12 cm and multiple omental metastasis. She was given taxane based chemotherapy after which she was also given palliative radiation to stop the bleeding ulcer but she succumbed to the disease. Scar site metastasis are an uncommon occurrence, with frequency of less than 5%. These have been frequently reported in cancers of colon, kidney, and bladder. The most common histopathology is adenocarcinoma and undifferentiated carcinoma, whereas squamous cell carcinoma is been rarely reported. The intent of treatment in advanced recurrent disease is palliation by surgery, chemotherapy, radiation therapy alone, and/or in combination.

Keywords: Carcinoma Cervix; Hysterectomy; Adenocarcinoma; Uterine cervix

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Introduction

Recurrences after surgery or radiation for Carcinomas of uterine cervix are most commonly locoregional with the parametrium, lymph nodesand vagina as the most frequent sites of relapse. Distant metastases which although rare are observedin the lungs, bone, and liver [1]. Cutaneous metastasis most commonly arises from primaries of cancer of breast, large intestine, lung, and ovary. The occurrence of scar site metastases from carcinoma cervix is reported to be extremely rare ranging from 0.1 to 0.2% [2]. We report here an unusual case of extensive scar site metastasisin patient with squamous cell carcinoma cervix operated earlier for simple hysterectomy and did not receive any adjuvant treatment

Case Report

Sixty (60) year old female presented with complains of lower abdominal mass since 8 months.

On examination she had a huge 17x 10 lower abdominal mass over the midline scar. The mass was hard, mobility restricted covering the hypochondrium, right and left iliac fossa, right and left lumbar regions with multiple excavated

ulcers on the surface. There was inguinal or supraclavicular lymphadenopathy.

She was operated a year back for simple hysterectomy with bilateral salphingo-oophrectomy. Final histology came out as moderately differentiated squamous cell carcinoma. She was advised for adjuvant radiotherapy but patient defaulted on it.

Biopsy was taken from skin ulcer which was suggestive of squamous cell carcinoma. CECT scan was suggestive of a solid mass involving anterior abdominal wall and extensive areas of skin of around size 17 x 15 x 12 cm and multiple omental metastasis.

In view of extensive abdominal wall involvement and omental metastasis patient was started on docetaxel, cisplatin and 5 FU based chemotherapy. Patient initially responded (Fig. 1) but again defaulted on treatment.

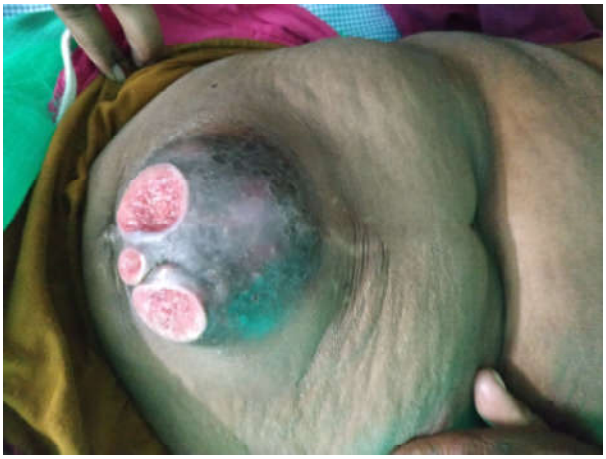

Fig. 1: Showing extensive scar site metastasis after 2 cycles of chemotherapy

Patient again presented with bleeding ulcer from anterior abdominal wall. She was given palliative radiation over the abdominal wall but she succumbed to disease about 5 days later.

Discussion

Scar site metastasis are an uncommon occurrence, with frequency of less than 5% [1]. These have been frequently reported in cancers of colon, kidney, and bladder [2]. Even after R0 surgical resection, solid cancers may recur locally up to 50% [3]. Scar recurrences are mostly regarded to be the result of the interaction of residual occult cancer with the surgical wound while contained inside a defined tissue plane or organ compartment [4].

Tumor implantation of malignancy at the time of surgery could be one of the mechanism for skin incision metastasis [5], whereas the retrograde spread of tumorsecondary to the lymphatic obstruction is believed to be mode of spread by other authors [6].

The most common histopathology is adenocarcinoma and undifferentiated carcinoma, whereas squamous cell carcinoma is been rarely reported [7]. There has been no difference in the incidence of skin metastasis among the clinical stage [7]. The most common site of skin metastasis in carcinoma cervix is anterior abdominal wall (especially at the drain site), vulva, and anterior chest wall [7].

The current principles of surgical oncology have to be revisited. A radical tumor operation must remove not only the macroscopic and microscopic tumor but also a maximum of the microscopically occult local cancer with a minimum of tissue trauma [8].

The intent of treatment in advanced recurrent disease is palliation by surgery, chemotherapy, radiation therapy alone, and/or in combination. Cis-platinum-based chemotherapy has been found to be an effective treatment in controlling the symptoms [6].

Conclusion

Scar Site metastasis are seen few and far in solid malignancies but mostly seen for breast colon and kidney. Common histology is adenocarcinoma. Cutaneous Metastasis from squamous cell carcinoma cervix is very rare situation described in only few case reports. Usually such stage represents advanced stage of malignancy and requires palliation.

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Case Report

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Sebaceous Gland Carcinoma of Upper Eyelid with Parotid Metastasis: A Case Report

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Abstract

Sebaceous gland carcinoma is a rare malignancy which usually arises from periocular region. It accounts of 1–5.5% eyelid malignancies and represents third most common eyelid malignancy. It mostly occurs in elderly women and is characterized by high rate of local recurrence along with regional and distant metastases. A delay in diagnosis, often leads to inappropriate management with increased morbidity and mortality rates. This is a rare case report of sebaceous gland carcinoma of right upper eyelid that presented with metastasis to parotid lymph node.

Keywords: Sebaceous Gland Carcinoma; Parotid metastasis.

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Introduction

Sebaceous gland carcinoma (SGC) is highly malignant tumor of eyelids, arising from the meibomian glands, gland of Zeis or glands associated with the caruncle. Sebaceous glands are most commonly present in the dermis of periocular skin, caruncle, tarsal plate and skin follicles of eyebrow while the glands of Zeis are mostly found at the eyelash's base.

The upper eyelid is the most common site of origin seen in 63% of cases, the lower lid in 27% of cases, and both in 5% of cases [1]. Extra ocular manifestation comprises of about 25% of sebaceous gland carcinoma [2] involving mainly the head and neck region which has abundance of sebaceous gland followed by external genitalia, parotid and submandibular glands, external auditory canal, trunk, upper extremity, sole, larynx and pharynx [3].

Case History

A 55 year old male known case of sebaceous gland carcinoma of right upper eyelid, presented with swelling at right side of face in parotid region. On examination prior to surgery there was a diffuse swelling over the upper eyelid laterally covering almost 40% of right eyelid. The lid margin was distorted and tumor was firm and fixed. A wide excision of eyelid along with anterior orbital tissue biopsy was done. Histopathology confirmed it as sebaceous carcinoma. In past he had underwent excision of tumor from same site thrice.

During followup after one year, he developed swelling over right parotid. PET CT scan reported no evidence of FDG active disease at primary operated site with no internal visceral malignancy, but FDG avid mildly enlarged right preauricular node/ intra parotid node was noted. Patient underwent right superficial parotidectomy with sampling of level II nodes. Post OP HPE- poorly differentiated sebaceous carcinoma in parotid gland as well as

intra parotid node. Surgical margins negative, level II lymph nodes negative. Then patient was given radiation 60 Gray (Gy)/30 fractions (#) with IGRT technique to right parotid and draining nodes of the neck on right side. Now patient is on regular follow up since 2011 with no evidence of disease.

Discussion

Sebaceous Gland carcinoma though rare, is a highly aggressive malignancy with a mortality rate second to malignant melanoma [4]. Irrespective of its location and nature of local spread, probability of regional and distant metastases is high. Surgery is the main stay of treatment, ranging from local wide excision of tumor along with the margins extending beyond the palpable tumour with excision of regional lymph nodes to orbital exenteration due to diffusely infiltrating nature of neoplasm [5]. Other modalities also includes radiotherapy or chemotherapy depending upon the staging at the time of initial presentation of tumor. Before surgery, careful assessment of the patient is very important for the evidence of pagetoid spread, multicentricity of tumor or for any conjunctival alteration such as telangiectasia, papillary change, or any mass.

Radiation therapy has been recommended only as an adjunctive or palliative mode of treatment, while surgery remains as main treatment of choice. Indications for radiation in sebaceous gland carcinoma are poor surgical candidates, advanced age or disease, and in patients who refuse exenteration for advanced local disease [7].

Chemotherapy has also been tried but the role is doubtful as there is not much study supporting its benefits due to rare occurrence of this malignancy. In a study by Sheilds, effective results of using topical mitomycin-C for pagetoid invasion of conjunctiva by sebaceous gland carcinoma was reported [8]. Bhandari suggested, use of systemic chemotherapy has no effect on local and distant control of the disease rather the disease progression was noted [9].

Conclusion

This rare report is presented with the aim that sebaceous gland carcinoma can also metastasize to parotid gland and should be kept in mind on follow up of the patients.

Sources of support: NIL

Ethical Issues: NIL

Conflict of Interest: NIL

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Case Report

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Carcinoma Oesophagus with Subcutaneous Metastasis: A Rare Case Report

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Abstract

Metastases to skin from primary internal malignancies are rare with the incidence ranging from 0.7% to 10%. Cutaneous metastasis are frequently found in melanoma, breast cancer, or mucosal cancers of the head and neck. Subcutaneous metastases from squamous cell carcinoma of the esophagus are extremely rare (less than 1% cases reported). A 55 year old male a known case of carcinoma oesophagus presented with one subcutaneous nodule over the left ala of nose, another was found incidentally on anterior abdominal wall below umblicus. FNAC from both nodules revealed metastatic squamous cell carcinoma.

Keywords: Carcinoma Oesophagus; Subcutaneous Metastasis; Squamous Cell Carcinoma.

How to cite this article:

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Introduction

Esophageal cancer ranks seventh in terms of incidence and sixth in mortality overall [1]. Patients with esophageal cancer usually present with locally advanced disease at the time of initial diagnosis. Extra-nodal metastases are seen in most of the patients and the liver and lungs are the more common sites of distant metastasis [2]. Subcutaneous metastasis in carcinoma oesophagus are very rare and has been seen reported in less than 1% cases [3]. In general, skin metastases from malignant tumors of the internal organs are rarely seen, with range between 0.7 and 9%. Metastatic spread to the skin occurs either hematogenously or via the lymphatic system and presents in the form of rapidly growing papules or nodules [4,5]. Here, we report an uncommon case of skin metastases from squamous cell carcinoma of upper oesophagus.

Case Report

A 55 year old male presented to us with one subcutaneous nodule, present on the left ala of nose and cough since last 20 days .Cough which was productive, not associated with any blood in sputum. In past he was diagnosed as high grade squamous cell carcinoma (SCC)–upper 1/3 oesophagus, stage III (T4bN2M0) in 2015. MDCT Thorax with abdomen revealed circumferential wall thickening of upper oesophagus extending from D1 to D4 vertebral level with length of approx 7cm causing significant luminal narrowing, with involvement of posterior wall of trachea with multiple enlarged perilesional lymph nodes and left cervical II lymphnode. He received concurrent chemo-radiotherapy with 50Gy / 25# along with 5 cycle of chemotherapy with cisplatin 50mg given once weekly. He was then on regular follow up. Now he presented with a swelling on the left ala of the nose from last 20 days.

On examination, a subcutaneous nodule was present on left ala of nose measuring approx 2 cm x 1 cm firm, fixed, tender, fixed to skin with no ulceration and discharge (Fig. 1). On abdominal examination another nodule was found which was 1 cm x 1 cm firm ,mobile, non tender present on anterior abdominal wall around 10cm below umblicus, with no increase in local temperature. There was no evidence of ulceration or discharge from the nodule. FNAC from both nodules revealed Metastastic Squamous cell carcinoma (Fig. 2). Following this a metastatic workup of the patient was done and a mass in left middle lobe of lung was found, possibly suggestive of lung metastasis. Rest of organs did not show any sign of metastasis or disease. Patient is now started on palliative chemotherapy with Paclitaxel and Carboplatin combination.

Fig. 1

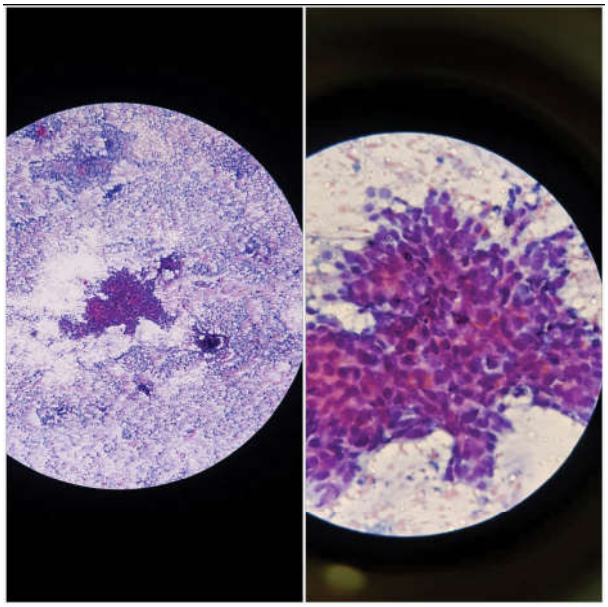

Fig. 2:

Discussion

Subcutaneous metastases are the uncommon and accounts for 0.7-9% of all malignant tumors of internal organs. Out of various cancers documented, most common cancers with this presentation are malignant melanoma, followed by breast cancer and other mucosal tumors of head and neck [6]. Esophageal carcinoma carries a poor prognosis with 5-year survival rates of 5-35% usually representing with lymph node and distant metastases at the time of diagnosis [7]. In distant metastasis, liver and lung are most commonly involved via hematogenous route [2]. Skin metastases from esophageal cancer affect less than 1% of all cases usually reported [3] and indicate rapid disease progression with poor prognosis. It can be found both in squamous and adenocarnimos of oesophagus (more commonly in adenocarcinomas variant of carcinoma oesophagus) [8-10]. Distant metastasis can occur via three pathways: lymphatic, arterial or venous routes. The metastasis at unexpected sites can be explained by arterial route, since arterial blood has been proved to be a better source of circulating tumor cells than venous blood [11]. Cutaneous manifestations of esophageal carcinoma may clinically represent as dermal papules, indurated nodules, inflammatory patches or rapidly growing subcuatenous masses. A metastatic workup should be done in patients who represent with skin soft tissue mass as they frequently presents as a painless, dermal tumor. Appropriate workup should include detailed medical history, physical examination, imaging, and histopathological analysis. In our patient, both skin lesions were evaluated by biopsy examination and imaging tests were used for metastatic workup. Only after the histopathological conformation the diagnosis of a skin metastasis in our patient was made which itself presents a rare entity of metastasis.

Conclusion

With the advancement of treatment facility in radiotherapy and improvement in survival in cases of carcinoma esophagus it becomes mandatary to look for subcutaneous metastasis during follow up along with other routine investigations.

Sources of support: NIL

Ethical Issues: NIL

Conflict of Interest: NIL

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Case Report

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Male Breast Cancer with Skeletal Metastasis: A Case Report and Review of Literature

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Abstract

While it is the most common malignancy in women, breast cancer is rare in men and thus often ignored or overlooked, which leads to delayed diagnosis for the already fulminant condition. Bone is the most common location for metastasis from breast cancer, and there is a particular affinity for the spine. Despite the high incidence of spinal metastasis from breast cancer, only around 10 cases of breast cancer with spinal secondaries in male patients have been reported. Management of spinal metastases is palliative, with treatment aimed at restoring or preserving neurological function and relief of symptoms such as pain and incontinence. Here we report the case of a male patient with breast cancer and extensive metastasis to the axial skeleton and review the relevant literature.

Keywords: Breast Cancer; Male Breast Cancer; Spinal Metastases.

How to cite this article:
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Introduction

Breast cancer is extremely rare in men and is a biologically more aggressive malignancy than breast cancer in women. Diagnosis is often delayed too, due to late presentation, and low index of suspicion. Bone is the most common site for secondary deposits from breast cancer, the majority of which localize to the axial skeleton. Spinal involvement has the dreaded complications of pathological fractures, instability, cord compression and resulting intractable pain, paralysis and incontinence. Treatment is multi-modal, and palliative surgery may have to be undertaken. This is only the 10th report of male patient with breast cancer complicated by spinal metastases.

Case Report

A 55-year-old male patient presented to the Orthopedic OPD with complaints of progressively worsening back pain for the last 6 months, with an acute exacerbation of lower back pain when lifting farm equipment a few days earlier. He had taken over-the-counter pain medication but did feel sufficient symptomatic relief. Orthopaedic examination did not reveal any specific abnormality, and spinal and neurological evaluation were normal except for tenderness noted along multiple paravertebral spaces (positive Sign of Delitala, Lasegue or Valleix). Bilateral lower limb power, bulk, muscle tone and reflexes were symmetrical and normal, and sensory system examination was also normal. Special tests including SLRT (straight leg raising test) and FABER (Flexion, Abduction, External Rotation) were unremarkable.

MRI of the Lumbar Spine showed bony erosions with multiple lytic and sclerotic foci in the iliac bones and lumbar vertebra, suggestive of malignant etiology, following which the search for occult primary began, and the patient referred to General

Surgery Department for evaluation.

Head to toe examination clinched the diagnosis, with nipple retraction noted on the right side (Fig. 1). On enquiry, the patient confessed that the nipple retraction had been present for over a year,and he had ignored it as it did not give him any discomfort. There was no significant past or familial history, and no history of any discharge from the nipple. The nipple was almost completely retracted, the nipple-areolar complex destroyed and induration was present. An ill-defined hard mass fixed to the chest wall was palpable on the affected side. The contralateral breast and nipple areolar complex were normal, and bilateral axilla did not have any palpable lymph nodes.

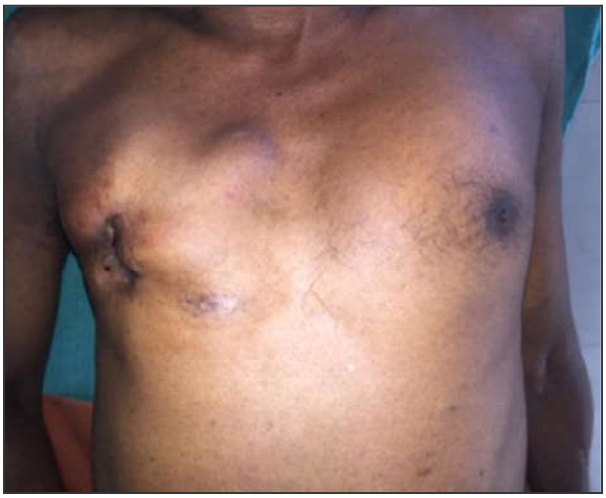

Fig.1: Nipple retraction right breast

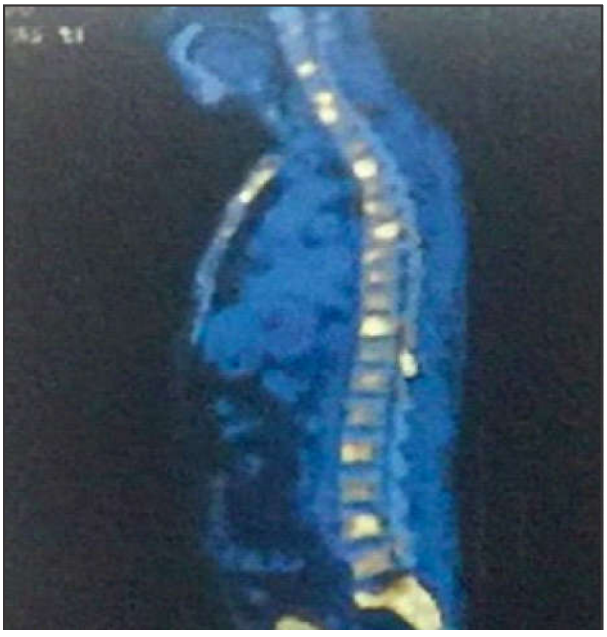

Fig. 2a: PET CT showing involvement of axial skeleton

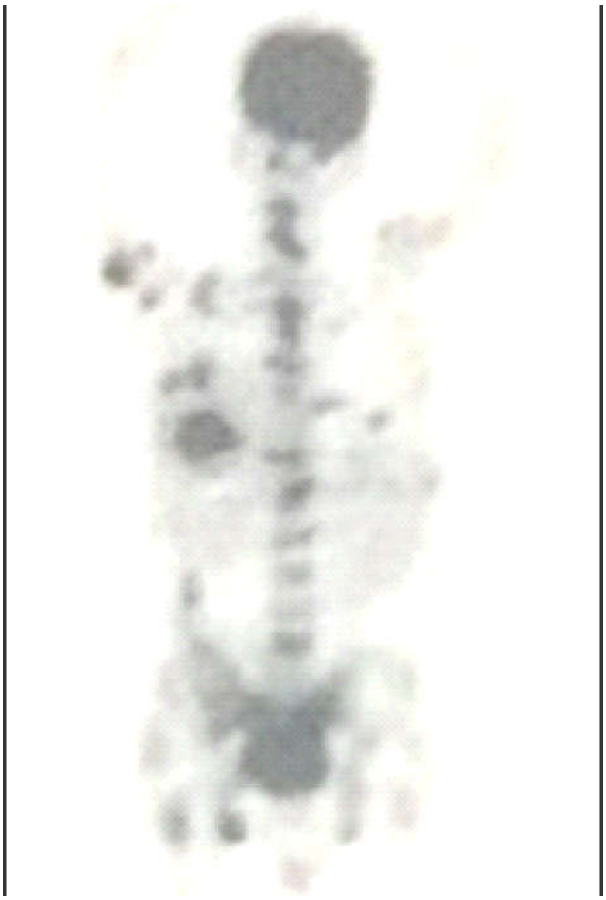

Fig. 2b: PET CT showing carcinoma of right breast with extensive skeletal metastases

PET CT was done, which demonstrated carcinoma of the right breast involving the skin and pectoralis major muscle and right axillary lymphadenopathy with extensive skeletal metastases (Figs. 2a and b).

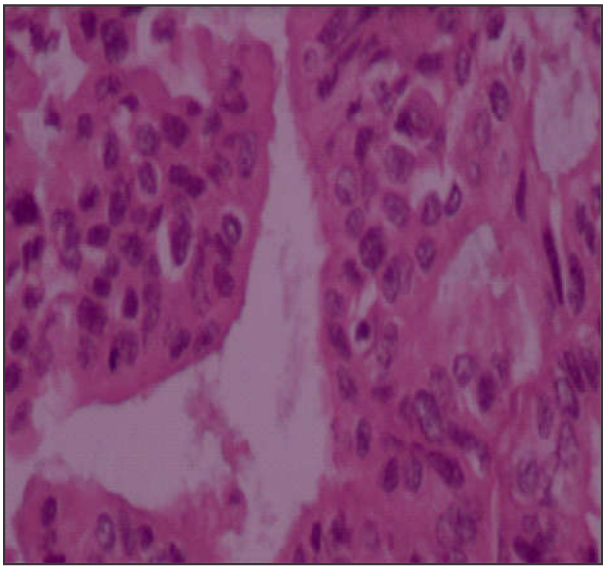

Fig. 3: Ductal carcinoma

Histopathology revealed infiltrative ductal carcinoma (Fig. 3), with ER PR positivity and Her2 negative.

The patient underwent a modified radical mastectomy with axillary clearance. Post-operatively, Tamoxifen as an oral chemotherapeutic agent was used, in addition to which, bisphosphonates were given in view of the spinal metastasis. The patient was doing well 6 months postoperatively, with no evidence or recurrence.

Discussion

Accounting for less than 1% of all malignancies in men, and 0.5% of all cancer-related deaths, male breast cancer is a rare disease [1]. However, like the female counterpart, the incidence has been rapidly increasing, estimated to have risen 26% in the last quarter century [1]. The contrasting prevalence of the disease between men and women is evident from the Surveillance, Epidemiology, and End Results (SEER) registry which lists 5494 cases of male breast cancer and 835,000 cases of female breast cancer between 1973 and 2005 [2].

In a retrospective German study that included 160 male patients diagnosed with breast cancer in a district with a population of 1.5 million over a 16 years period, 41 patients (25.6%) had metastatic disease at the time of presentation, with bone being the most frequently involved site (23 patients) [1].

Bone involvement occurs in 8% of patients with breast cancer, and a whopping 69% of patients with advanced disease. There is a strong affinity for the spine, which accounts for two-thirds of the secondary deposits [3]. This is facilitated by the valveless Batson's venous plexus, which includes the Azygous Vein which through the intercostal veins receives blood drained form the breast [3].

The complications of osseous metastases include pathological fractures, reduced hemopoieses, hypercalcemia (which in itself is a dreaded paraneoplastic syndrome), and spinal cord compression causing intractable pain, neurological deficits, incontinence, instability and paralysis [3]. Pain may be biological, caused by periosteal stretching; radicular, due to nerve involvement or cord compression; or mechanical, due to instability resulting from osteolytic lesions.

The prognosis of male breast cancer is significantly worse than that of the disease in women, due to greater biological aggressiveness of the disease itself, and delay in diagnosis due to low index of suspicion of the disease in both the patient and physician [2].

Treatment requires a multidisciplinary approach, and a combination of hormonal therapy, radiotherapy and surgery as the circumstance demands. Emergent situations where fragility of the spine causes impending cord compression requires urgent intervention, in the absence of which there can be a spinal "stroke" with irreversible neurological damage [3]. The Spine Instability Neoplastic Score (SINS), a 6-point scale that accounts for the location of pathology, pain, type of bony lesion, spinal alignment, extent of vertebral body collapse and posterior element involvement is an effective and reliable tool to guide decision-making and treatment [3].

Hormone therapy includes selective estrogen receptor modulators and aromatase inhibitors, and depends on the receptor status of the tumor. Bisphosphonates along with Vitamin D and Calcium limits osteoclastic tumor activity, and corticosteroids have oncolytic effects [3].

On immunohistochemistry, male breast cancers tend to be positive for estrogen receptor (ER) and negative for HER2 receptor [4]. ER positivity allows the use of Tamoxifen [5] as oral chemotherapeutic agent, as was done in our cases. Additionally, bisphosphonates were given to the patient in view of the spinal metastasis.

The median survival of patients with breast cancer is 10 months after the diagnosis of spinal metastases, but surgery is still an important modality of palliative care to manage instability and for decompression, tasks that cannot be achieved by chemotherapy or radiation [2].

Despite the high incidence of breast cancer metastases to the spine, to the best of our knowledge, only 9 cases of breast cancer with spinal secondaries in male patients have been reported [2] prior to this, and only 2 where surgical management (one case of vertebroplasty and the other decompression followed by screw and rod fixation) was undertaken [2].

Conclusion

Breast cancer is rare in men; however, it must be kept in mind when the search for a relevant occult malignancy is being done. Breast cancer in men tends to be more aggressive and carries an overall worse prognosis compared to the disease in women. Bone is the most common site for the seeding of breast cancers, the spine being a favoured location, and patients may suffer debilitating pain and neurological dysfunction. Patients are also prone

to pathological fractures, spinal cord compression, bowel and bladder disturbance, and paralysis. Timely diagnosis is thus essential to prevent the development of serious complications. Treatment is mainly palliative and aimed at preserving neurological function, ensuring spinal integrity and relieving pain so that reasonable quality of life can be maintained.

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Conflict of Interest: None declared

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The text of observational and experimental articles should be divided into sections with the headings: Introduction, Methods, Results, Discussion, References, Tables, Figures, Figure legends, and Acknowledgment. Do not make subheadings in these sections.

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The title page should carry

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The second page should carry the full title of the manuscript and an abstract (of no more than 150 words for case reports, brief reports and 250 words for original articles). The abstract should be structured and state the Context (Background), Aims, Settings and Design, Methods and Materials, Statistical analysis used, Results and Conclusions. Below the abstract should provide 3 to 10 keywords.

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Present your results in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat in the text all the data in the tables or illustrations; emphasize or summarize only important observations. Extra or supplementary materials and technical details can be placed in an appendix where it will be accessible but will not interrupt the flow of the text; alternatively, it can be published only in the electronic version of the journal.

Discussion

Include summary of key findings (primary outcome measures, secondary outcome measures, results as they relate to a prior hypothesis); Strengths and limitations of the study (study question, study design, data collection, analysis and interpretation); Interpretation and implications in the context of the totality of evidence (is there a systematic review to refer to, if not, could one be reasonably done here and now?, What this study adds to the available evidence, effects on patient care and health policy, possible mechanisms)? Controversies raised by this study; and Future research directions (for this particular research collaboration, underlying mechanisms, clinical research). Do not repeat in detail data or other material given in the Introduction or the Results section.

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Standard journal article

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Article in supplement or special issue

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Corporate (collective) author

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Reference from electronic media

[9] National Statistics Online—Trends in suicide by method in England and Wales, 1979-2001. www.statistics.gov.uk/downloads/theme_health/HSQ20.pdf (accessed Jan 24, 2005): 7-18. Only verified references against the original documents should be cited. Authors are responsible for the accuracy and completeness of their references and for correct text citation. The number of reference should be kept limited to 20 in case of major communications and 10 for short communications.

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Tables should be self-explanatory and should not duplicate textual material.

Tables with more than 10 columns and 25 rows are not acceptable.

Table numbers should be in Arabic numerals, consecutively in the order of their first citation in the text and supply a brief title for each.

Explain in footnotes all non-standard abbreviations that are used in each table.

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