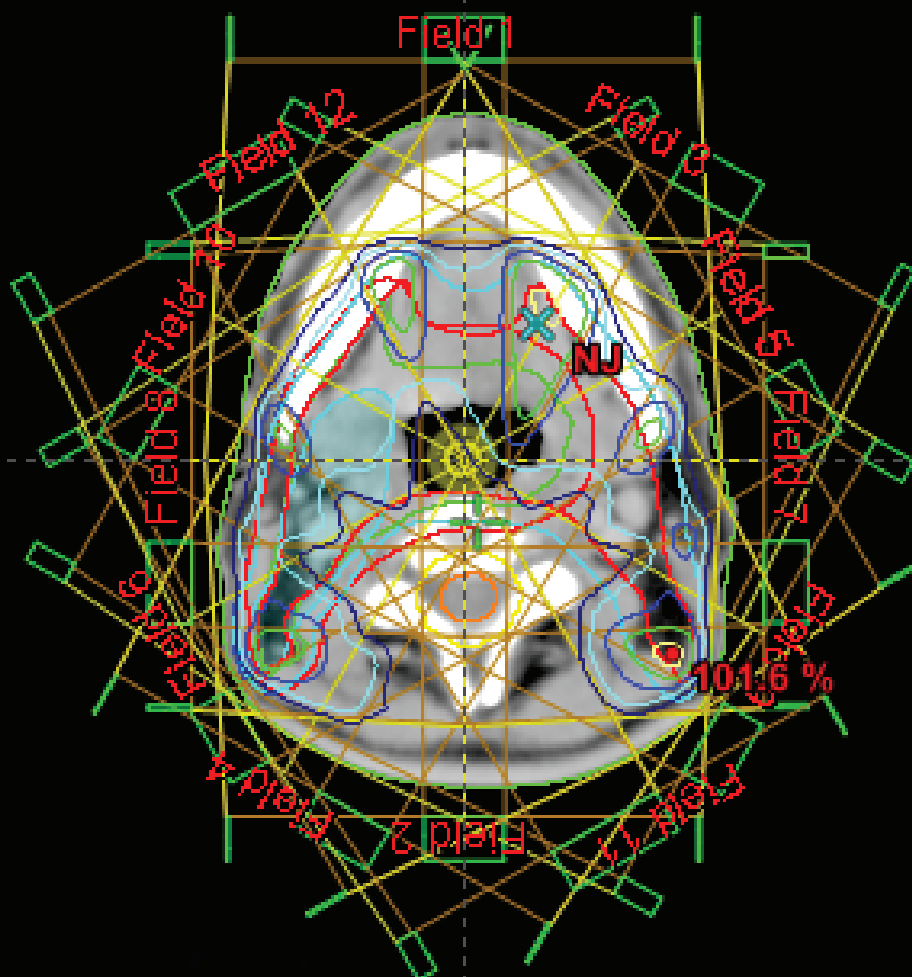




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Editorial

A case for cancer research in Sri Lanka

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It is with great pleasure that Sri Lanka College of Oncologists (SLCO) presents the inaugural edition of "Sri Lanka Journal of Cancer (SLJC)". Since its inception in 2003 the SLCO has attempted to publish a scientific journal. Infact, in the constitution of SLCO (Section 2,vi) one objective of the SLCO is, "To maintain and publish a periodical journal in the name of the college and to circulate information relating to recent developments and discoveries in oncology." Today this objective has been fulfilled with the launch of SLJC.

As Sri Lanka transits from a Low Income Country to an Upper Middle Income Country, non communicable diseases are rearing it's ugly head as a major determinant of ill health. Cancer is in the forefront of this surge with reported cancer incidence almost doubling over the last 25 years. Cancer is already the second highest cause of death in Sri Lankan hospitals and the day it rises to number one is not far away. Treatment of cancer has had significant advances in the recent past. More and more weapons are added on to the armoury we have to fight this dreaded disease. However most of these newer therapies comes with considerable "Financial toxicity". This problem takes an added significance for a country like Sri Lanka, where there is universal free health care including all forms of cancer treatment. Already cancer care places a great burden on the national health budget and this problem will only get worse in the coming years. Therefore, Sri Lanka is currently facing the dual challenge of increasing numbers of cancer patients and skyrocketing cost of cancer care. This brings into sharp focus the immediate and profound need to find innovative solutions to successfully combat not only the present day problems but also to fend off possible future challenges when it comes to cancer care in Sri Lanka.

There is no debate regarding fluidity of cancer according to geography, ethnicity and even lifestyle choices with regards to presentation, biology, outcome etc. Therefore taking clinical, policy and financial decisions on cancer care by extrapolating data from other countries has many pitfalls. This

makes it very clear why home grown research in to cancer is essential. Currently the research output from Sri Lanka related to cancer are very limited. Main objective of launching this journal is to encourage local cancer research and provide it with a platform for wider dissemination.

Cancer research mean not only discovering new drugs and developing new technologies. Equally important is research on cancer epidemiology, outcomes, barriers to care, health economics etc. Infact latter can have a far greater impact in the Sri Lankan context. Understanding priority research areas to funnel the limited resources is essential for developing cancer research in Sri Lanka. SLJC could be a valuable resource for policy makers to understand what these priority areas are.

Sri Lanka is held in high esteem for achieving and maintaining targets of health indices like Maternal mortality, Infant mortality, Immunization rates etc. These metrics are well above regional peers and are often comparable with High Income Countries. Cancer care in Sri Lanka also benefit from the same robust training of health professionals, well structured systems of health delivery, high treatment utilization rates of end users etc. However the missing ingredients in this milieu is advocacy and high quality research. I hope SLJC can fill this void so that Sri Lankan cancer care achievements can emulate its public health counterparts and become a shining beacon for other similar countries.

SLJC has been very fortunate to attract an eminent panel of international advisors and equally committed local editorial body. On behalf of the SLCO I extend my heartfelt gratitude to everyone who has contributed to make this issue a success. We hope the SLJC will go from strength to strength and would play an integral role in developing the field of oncology in Sri Lanka

Evaluation of geographic miss in conventional Radiotherapy (box technique) compared to Computed Tomography(CT) based conformal Radiotherapy in carcinoma of uterine cervix.

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Abstract

Introduction: Carcinoma of the uterine cervix is regarded as one of the most prevalent malignancies in women worldwide. In Sri Lanka, it is the 2nd most common cancer in females. Although CT-based radiotherapy is emerging as the treatment of choice, some centers continue to use x-ray based conventional radiotherapy techniques which depends on bony land marks. Uncertainty of adequate target volume coverage with conventional four field “box” is long being discussed.

Objective: This study was designed to evaluate the extent of geographic miss seen with conventional ‘box’ technique, compared to CT-based three-dimensional (conformal) radiotherapy planning (3D-CRT).

Methodology: This is a retrospective non-randomized paired observational study (n=54) in locally advanced cervical cancer patients treated at National Cancer Institute between 2010 to 2013. In this study for each subject, 2 separate “box” plans were created in the same CT simulation images. Initially conventional four field box plan was drawn according to the bony land marks on CT simulation images similar to GOG standard pelvic fields. In the conformal plan, the target volume delineation was done on planning CT scans, according to guidelines given in the literature. Primary disease and regional lymphatics were included in the Target volume. Using beam’s eye view conformal and conventional box plans were compared regarding the tumour coverage and evaluated the geographic miss.

Results: When compared with 3D-CRT, 93% of patients had geographic miss of the target volume at single or multiple borders in conventional technique. Most commonly missed borders were, Anterior (76%) and posterior (44%) borders of Lateral fields, Inferior (55%) borders of both fields.

Conclusions: Target volume coverage is highly inadequate in conventional ‘box’ technique compared to CT-based planning.

Key words: Carcinoma of Uterine Cervix, Conventional radiotherapy, Conformal radiotherapy, Sri Lanka

Introduction

Carcinoma of the uterine cervix is the second most common cancer and the third leading cause of cancer

death among females in developing countries¹The global estimated incidence of cervical cancer in 2012

was 528,000 and the annual death rate was 266,00². Age standardized Incidence rate in the world is 8.4 per 100,000 and cumulative Incidence rate (0-74 years) per 100 population is 1.02 in 2010³.

For decades, radiotherapy (RT) has been the key treatment of locally advanced cervical cancer.

Radiotherapy for cervical cancer consists of pelvic external beam radiotherapy and brachytherapy to a total dose of 80-90Gy. Concurrent platinum-based chemotherapy with RT is the best of care in advanced carcinoma of uterine cervix⁴.

Traditionally external beam radiotherapy is performed according to standard anatomical bony landmarks using X-rays. It can be delivered by anterior-posterior, posterior-anterior (AP-PA) parallel opposed fields or the four-field box (Parallel opposed anterior-posterior and posterior-anterior (AP-PA) beams and two lateral beams.)

When treating with external beam radiotherapy, it is important to achieve an optimal coverage of the draining pelvic lymph nodes to gain better disease control⁵. Several studies have demonstrated great variance in pelvic lymph node location, level of aortic bifurcation, sacral curvature and course of pelvic vessels^{6,7,12}. It raised doubts about reliability of depending on bony land marks when designing radiotherapy with four field box technique for patients with cervical cancer⁶.

With the advancements in radiotherapy techniques, 3DCRT and IMRT are widely used in affluent countries. Incorporating Computed Tomography (CT) imaging for radiotherapy planning has enabled better visualization and delineation of target volumes hence minimizing geographic miss associated with standard box plan⁷.

Unfortunately, countries like Sri Lanka do not have access to comprehensive early detection programs or robust cervical cancer prevention campaigns. As a result, most of the patients with carcinoma of the cervix present at locally advanced stage where radiotherapy is the cornerstone of treatment³. Due to limited resources and high patient number, many centers in Sri Lanka continue to use conventional anatomical landmarks for defining the target volume. Studies comparing conformal and conventional radiotherapy are rare. Even though we treat significant number of patients with advanced

carcinoma of uterine cervix with radiotherapy annually, we do not have local data about geographical miss associated with 2 dimensional conventional "box" technique.

This study aims to evaluate and estimate the magnitude of geographic miss associated with the conventional four-field "box" irradiation technique compared to CT based planning. The overall objective of the study is to evaluate the extent of geographic miss in conventional radiotherapy (four-field 'box' planning) compared to CT based conformal radiotherapy in carcinoma of uterine cervix.

Study Design and Method

A retrospective non-randomized cross-sectional paired study of previously untreated 54 patients with biopsy proven locally advanced (Stage IIB, IIIB, IVA) carcinoma of uterine cervix, treated in a single unit at National Cancer Institute, Maharagama between 01st of March 2010 to 31st of January 2013. Patients with involvement of the lower vagina and para aortic lymph nodes were excluded.

CT simulation was done using Toshiba CT simulator without contrast. Images were taken from T12-L1 level up to the lesser trochanter level of the femur, with the slice thickness of 3mm. The patients were immobilized supine with comfortable bladder, knee and ankle supports, and with their arms on the chest.

In routine practice, target volumes are contoured on CT simulation images considering the tumor and the uterine body as target volume, keeping adequate margins and creating a modified box plan to encompass the primary as well as pelvic lymph nodes. Pelvic lymph nodes are not routinely delineated. Due to the lack of 3DCRT time, created radiotherapy plans in CT simulation images are treated in Cobalt 60 (Co60) teletherapy machines.

In this study, for each subject, 2 separate box plans were created in the same CT simulation images (in a different image set, preserving the original radiotherapy plans).

Conventional four field box plan drawn according to the conventional anatomical bony land marks on the CT simulation images based on Gynecologic Oncology Group (GOG) standard pelvic fields. For AP-PA fields, the superior border was taken at L4-5

intervertebral space and the inferior border was taken at the inferior margin of the obturator foramen. The lateral borders were taken 2cm on both sides of the widest portion of the pelvic brim. In the lateral fields, the upper and lower borders were the same as defined for the AP-PA fields. The posterior border defined at the junction of S2-S3 vertebral bodies. The anterior border was taken at the anterior edge of pubic symphysis⁸.

Conformal plan: The conformal plan, the target volume contouring was done on CT simulation images, based on the guidelines given in the literature

^{9,10,11,12,13,14}. In this study target volume delineation was guided by the clinical findings and CT simulation images. As the Nodal Clinical Target Volume (Nodal CTV) presacral, obturator, external and internal iliac, and common iliac lymph nodal groups were included. CTV_n nodes were outlined by using a 7mm radius pearl tool, with the centre of the pearl on the edge of the vessel, and outlined the CTV nodes without delineating vessels, extending to regional areas and then excluding normal tissue on

each slice. For node negative patients the L4/5 border was used to ensure inclusion of all the iliac nodes^{10,12}. For node positive patients all the common iliac nodes were included, and contouring was started at the aortic bifurcation to ensure coverage of at least 2cm above highest positive node¹⁵. Planning Target Volume (PTV) Tumour was created adding 1cm around the CTV Tumour and Nodal PTV was created by adding 0.7cm around the Nodal CTV. Both PTVs were fused to create the total PTV. Bladder and rectum were delineated as organ at risk. Finally, in each subject by using beam's eye view (BEV) 2 box plans (conformal and conventional) were compared with regard to the tumour coverage and evaluated the geographic miss.

Results

The median age of study participants was 59 (range 41-80) years. Majority of the study candidates were included in FIGO stage IIB (68.51%). Only 4 of the participants had FIGO IVA disease. Most of the patients (43%) had moderately differentiated tumor grading(G2). Commonest histology type was Squamous cell carcinoma (SCC) (91%).

The CT based contoured PTV extended past all borders of all fields of the box plan. (Table 1)

Table 1 : PTV extension outside the borders of the fields

Radiation Fields	No of patients with PTV extending outside (%)	Length of PTV outside the border (cm) Mean 95% CI	
AP-PA Fields			
Superior border	9 (17)	1.17cm	0.89 – 1.45
Inferior border	30 (55)	0.78cm	0.58 - 0.98
Right Lateral border	18 (33)	0.32cm	0.18 – 0.46
Left Lateral border	19 (35)	0.39cm	0.27 – 0.51
Lateral Field			
Superior border	9 (17)	1.17cm	0.89 – 1.45
Inferior border	30 (55)	0.78cm	0.58 – 0.98
Anterior border	41 (76)	1.01cm	0.79 – 1.23
Posterior border	24 (44)	0.90cm	0.62 – 1.18

Only 5 out of 54 patients had adenocarcinoma. In only 4(7%) subjects, CT based target volume was fully encompassed by the conventional box plan drawn according to the bony land marks. Rest of the 50 patient's geographic miss of the target volume was seen at a single border or multiple borders.

Discussion

Current evidence shows that the pelvic failure was associated with reduced survival among patients¹⁶.

The main drawback of the conventional box planning is the uncertainty in target volume coverage and several studies have depicted failure in comprehensive primary tumor and nodal coverage with this technique^{7,9,10,11}.

This study evaluated the borders involved in geographic miss and quantify the geographic miss with the conventional box plan with regard to CT-based planning. In present study, only 4 (7%) patient's CT based target volume (PTV primary and nodes) was fully encompassed by the conventional box plan drawn according to anatomical land marks. A study conducted in India with 50 patients, in only 2 patient's target volumes were adequately covered by the conventional four field box.⁵ Therefore, it indicates that the majority of patient's tumour and regional lymph node groups are not appropriately covered with the conventional radiation fields; hence the Target Volume (TV) would receive suboptimal doses. According to our study most commonly missed borders were, Anterior (76%) and posterior (44%) borders of the Lateral field and Inferior (55%) border of AP-PA and Lateral fields. In most studies TV was predominantly missed at the anterior border of the lateral portal^{17, 6, 9, 11} and similar pattern was detected in this study. The mean miss at the anterior border was 1.01cm (95% CI- 0.79 - 1.23cm). Geographic miss at the anterior border of the lateral field was due to the extension of contours of PTV for external iliac lymph node groups (N-PTV) extended beyond conventional bony land marks in 41 out of 54 study participants (Annexure:03). N-PTV was missed in 14 out of 54 patients (26%) at this border and T-PTV was missed due to the bulky anteverted uterus according to CT simulation images.

Gulia et al. has noted 54% (23 out of 50) of the study subject's TV has failed to encompass by anterior

border and in 24% miss was due to bulky anteverted uterus (5). MRI based American study has demonstrated Uterine fundus was incompletely encompassed in 62.5% of the patients at anterior border of the lateral portals¹⁸. Detected difference in results with the western and Asian studies may be due to difference in ethnicity or difference in imaging techniques. Russell et al. highlighted inadequacy of the lateral fields in conventional box plan and concluded that the bony land marks are inaccurate way of defining radiotherapy portals in locally advanced carcinoma of uterine cervix¹⁸.

In the present study PTV was missed at the Posterior border of the lateral portal in 24% of stage IIB, 25% of stage IIIB and 13% of stage IVA (Table-01). Not only PTV, even gross tumour volume was not encompassed by the posterior border of the conventional "box" in 7% (4 out of 54) of patients in the current study. Another study has detected, Posterior border of the lateral fields were inadequate in 8% of stage IIB, 27% of stage IIIB and 22% of stage IIIB/IVA disease¹¹. Russell et al. indicated 24% (6/25) of patient's GTV was failed to encompass by the posterior border of the conventional lateral portals²¹. These findings have depicted marked inadequacy in the posterior border of the lateral portals of the standard "box" technique.

Bonin et al. also noted 45% (10 out of 22) of the patients would have missed the target volume in lateral fields if followed the standard "box" plan according to bony land marks. In the present study PTV was missed at the inferior border of both fields in considerable number of patients (55%) and the geographic miss at this border has been sparsely discussed in the literature this finding in the current study may be due to the involvement of upper vagina in significant number of patients (26%) in the study cohort as well as the margins recommended by the current guidelines to adequately encompass the TV.^{13, 14} Geographic miss at the left and right lateral borders of the anterior portals were seen in 35%¹⁷ and 33%¹⁶ of the study subjects. In all the subjects miss was due to extension of the external iliac lymph node contours (N-PTV) beyond the standard anatomical landmarks of anterior field. An Indian study showed inadequacy of lateral border in

54% the of participants^[7]. Median miss at the lateral border in the present study and the Indian study were more or less similar, which are 0.25cm and 0.27 respectively⁷.

This study shows marked inadequacy in target volume encompassment with conventional four-field “box” technique compared to CT-based planning. In centers where CT based planning is not achievable, could consider modification of x ray based conventional land marks balancing the toxicities of radiotherapy. A correction factor needs to be determined and validated by larger prospective studies.

Conclusions and Recommendations

- With the evidence from this study, we conclude that CT- based radiotherapy planning offers better visualization of the Target volume and minimizes geographic miss associated conventional x-ray-based radiotherapy. The study results suggest necessity of increase accessibility to CT based radiotherapy planning to improve outcomes.
- Larger prospective studies are needed to calculate correction factor for conventional fields to ensure same tumour coverage as conformal plans.

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A novel and simple three-dimensional conformal radiotherapy technique for treatment of the posterior cervical lymph nodes in resource limited settings

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Abstract

Introduction

Intensity modulated radiotherapy (IMRT) is now standard of care in the delivery of radical radiotherapy for squamous cell carcinoma of the head and neck (SCCHN). However, in many parts of the world where SCCHN is highly prevalent, access to linear accelerators capable of delivering IMRT is limited. In such settings, delivery of radical doses, in excess of spinal cord tolerance, to the posterior cervical nodes is not possible. We performed a planning study to evaluate a simple conformal technique which permits the delivery of a higher dose to the posterior cervical lymph nodes in resource limited settings.

Methods

Ten patients with SCCHN where the planning target volume for 70Gy included the posterior cervical lymph nodes bilaterally were included in the study. Tumour volumes and organs at risk were contoured as per institutional protocol. Phase I comprised two parallel opposed lateral fields treated to a dose of 40 Gy. For the second phase the novel technique uses 12 equi-spaced fields with conformal shielding of the spinal cord. The prescribed dose to PTV for phase II was 30 Gy. A dosimetric and tumour control probability comparison was performed between the two techniques in addition to

Results

Using conventional treatment, the mean minimum dose to PTV and posterior cervical lymph nodes was 45 Gy (range 44-46). With the novel technique the mean minimum dose to the PTV was 60 Gy (range 57-61) while the mean minimum dose to the posterior cervical lymph nodes was 62 Gy (range, 61-63Gy). Mean tumour control probability was nearly zero with the conventional technique and 0.42 (range, 0.22-0.62) with the novel technique.

Conclusion

Our technique permits the delivery of a substantially higher dose to the posterior cervical while still maintaining dose to the spinal cord within tolerance.

Key words : Squamous cell carcinoma head and neck, posterior cervical lymphnodes, radical radiotherapy

Introduction

Squamous cell carcinoma of the head and neck is the commonest malignancy among males, and the fourth commonest among females in Sri Lanka¹. According to data from the national cancer registry around 3000 new cases are diagnosed each year¹. Even though oral visual examination by primary health care workers has been shown to be a highly sensitive method of detecting oral cancers, utilisation of screening services is low mainly due to a lack of awareness amongst those at high risk of developing these cancers^{2,3}. Furthermore, malignant tumours of the oropharynx, supraglottis and hypopharynx have very vague symptoms and often present with more advanced disease⁴. As a consequence, more than 40% of all new cases of squamous cell carcinoma of the head and neck present with advanced nodal disease¹. Although surgery is the treatment of choice for early stage oral cancers, its high morbidity makes curative-intent radiotherapy a more suitable option for most cases of squamous cell carcinoma of the oropharynx, larynx, hypopharynx and nasopharynx⁵. As common with all tumours treated with radical radiotherapy, dose delivered to tumour is limited by the tolerance of adjacent organs at risk, most significantly, the spinal cord. Radiation myelitis has a devastating impact on quality of life of patients and is a complication which should be avoided at all costs in the modern era. Therefore, most radiotherapy protocols require dose delivered to the spinal cord to be kept below 44-48 Gy.

Apart from early glottic tumours, primary cancers of these sub-sites have a high predilection for nodal metastases and therefore often require treatment of the cervical lymph nodes for gross or occult disease.⁶ The posterior cervical lymph nodes lie bilaterally adjacent to the spinal cord, and its inclusion in high risk treatment volumes results in a concave shape with the planning target volume (PTV) surrounding the spinal cord. Conventionally, squamous cell cancers of the head and neck requiring treatment of bilateral neck lymph nodes were treated with two lateral parallel opposed fields with a matched anterior lower neck field to spinal cord tolerance in the first phase (40-44 Gy) followed by a second phase comprising two lateral parallel opposed fields where the posterior border of the beams are placed anterior to the spinal cord with the total dose delivered to PTV being 66-70 Gy⁷. Therefore if the posterior cervical lymph nodes are included in the PTV,

treatment with doses beyond spinal cord tolerance is not possible with conventional photon fields.

Before the advent of intensity modulated radiation therapy, an attempt was made at treating these regions to meaningful doses with the use of matched electron beams⁸. Even so, the dose delivered to the PTV could as low as 80% in certain regions, and the dosimetry of electron beams makes matching with photon fields a difficult task fraught with a high degree of uncertainty⁸. Furthermore, it requires a linear accelerator capable of delivering electrons at multiple energy levels. Several other three dimensional conformal techniques have been previously assessed but these techniques are in effect variants of forward planned intensity modulated radiotherapy^{7,9}.

Dynamic multi-leaf collimators made it possible to treat concave PTVs using inverse planned intensity modulated radiation therapy. However intensity modulated radiation therapy requires more stringent quality assurance protocols and a greater depth of expertise from the medical physics department. In many centres in the developing world, single energy linear accelerators with static multi-leaf collimators and cobalt teletherapy units are still widely used and these machines are incapable of delivering either intensity modulated radiotherapy nor matched electron fields¹⁰. In Sri Lanka, presently only two linear accelerators are available in the state health sector with both machines operating at the National Cancer Institute of Sri Lanka. Three other machines are due to be commissioned shortly, but even so the radiotherapy departments of Anuradhapura, Badulla and Kandy would still be equipped with only cobalt teletherapy units in the foreseeable future. Given the high incidence of nodal involvement of patients with squamous cell carcinoma of the head and neck it would not be possible to refer all patients requiring irradiation of posterior cervical lymph nodes to the National Cancer Institute.

In this paper, we describe a novel but simple treatment technique that aims to deliver higher doses to the posterior cervical lymph nodes than would otherwise be possible with conventional techniques using simpler radiotherapy units. We performed a radiotherapy planning study to assess the dosimetric differences of this technique in comparison to standard techniques.

Materials and Methods

Patients

10 patients with laryngeal, oropharyngeal and hypopharyngeal tumours with involved bilateral

posterior cervical lymph nodes (level V) were included in the study. Patients with involved supraclavicular lymph nodes were excluded from the study.

Definition of treatment volumes and organs at risk.

The gross tumour volume, clinical target volume and planning target volumes were contoured as per institutional protocol. The posterior cervical lymph nodes were defined as the lymph node target volume posterior to the sternocleidomastoid muscle and was contoured separately. The true spinal cord excluding the subarachnoid space was contoured from two centimetres below the level of the inferior border of the clavicular head to the level at which the cerebellum disappears superiorly. A 5mm margin was added to create the planning organ at risk volume (PRV) for the spinal cord.

Treatment techniques

The Phase I treatment is common to both techniques and comprised two parallel opposed equally weighted lateral fields with wedges prescribed to a dose of 40 Gy at the centre of the planning target volume. In the conventional technique, the posterior borders of the lateral fields were adjusted to the anterior half of the vertebral body to avoid irradiation of the spinal cord.

In the novel technique, a total of twelve equispaced equally weighted fields at the following gantry angles were used during the second phase of treatment—0°,30°,60°,90°,120°,150°,180°,210°,240°,270°,300° and 330°. The collimator angles and the multi-leaf collimators were adjusted to ensure shielding of the spinal cord PRV in each field. As shown in Figure 1 this results in twelve equispaced parallel opposed treatment fields. Figure 2 shows a “beam’s eye view” of the shielding technique.

The dose for the second phase of treatment was 30 Gy prescribed to the centre of the PTV resulting in a total dose to the PTV was 70Gy.

Dosimetric analysis

The dose delivered to the PTV, posterior cervical lymph nodes and spinal cord with the novel technique was compared with the conventional

treatment. The paired t-test was used to test for statistically significance fixed at two-sided p value of 0.05.

Analysis of tumour control probability

For the purposes of this study, it will be assumed that tumour control probability is determined by the minimum dose to the PTV. The Biological effective dose (BED) to the PTV will be calculated using the following formula based on the linear-quadratic model as described by Fowler et al¹².

$$BED = \left(D \cdot \left(1 + \left(\frac{d}{(\alpha/\beta)} \right) \right) \right) - K \cdot (t_{overall} - t_k)$$

where D = total dose delivered, d = dose per fraction, $\alpha/\beta = 10$, $t_{overall}$ = overall treatment duration (45 days), t_k = kick off time for repopulation (28 days). and K = BED equivalent repopulation rate (0.4 Gy/day).

Thereafter the survival fraction (SF) will be calculated using the following formula

$$SF = \exp^{-\alpha \cdot BED}$$

Where α is the radiobiological parameter of radiosensitivity and a value of 0.3 Gy⁻¹ is used for the purposes of this study.

Finally, the tumour control probability (TCP) will be determined by the using Poisson statistical formula¹³.

$$TCP = \exp^{-N_0 \cdot SF}$$

Where N_0 is the initial number of clonogens and since the minimum dose to the PTV is considered here a conservative value of 10^8 will be used to determine TCP¹⁴.

Results

Using conventional treatment the mean minimum dose to PTV and posterior cervical lymph nodes was 45 Gy (range 44-46). With the novel technique the mean minimum dose to the PTV was 60 Gy (range 57-61) while the mean minimum dose to the posterior cervical lymph nodes was 62 Gy (range, 61-63Gy). The mean maximum dose to the spinal cord was 43 Gy (range, 42-44) with the conventional technique and 44 (range, 43-45) Gy with the novel technique.

The mean minimum biological effective dose to PTV after accounting for repopulation was 44.8 Gy₁₀

(range 43.6 – 45.9) while it was 61.9 Gy₁₀ (range, 60 – 63.8) for the novel technique. Mean tumour control probability was nearly zero with the conventional technique and 0.42 (range, 0.22-0.62) with the novel technique.

Table 1 lists the characteristics as well as the dosimetric and tumour control probability analyses for both techniques in each patient.

Discussion

Our results show that significant dose escalation can be achieved by using the described novel technique of equispaced fields with conformal shielding of the spinal cord, in the treatment of the posterior cervical lymph nodes of patients with advanced squamous cell carcinoma of the head and neck, with no significant increase in the dose received by the spinal cord. Tumour control probability was virtually zero with the conventional technique and therefore, delivering higher doses to the rest of the PTV will have no clinical benefit. On the other hand, with the novel technique, tumour control probability reached modest values justifying the use of high dose radiotherapy to achieve meaningful results.

This technique can be applied to both cobalt-60 teletherapy units as well as linear accelerators, provided basic three-dimensional planning is available. While the presence of a multi-leaf collimator is certainly desirable, it can also be utilised even with rectangular shielding blocks. At least in theory, it is also possible to deliver this treatment with only two-dimensional planning using an integral volume for the spinal cord and tumour. However, our technique has several limitations of its own. Practically, delivering 12 fields in a busy radiotherapy department would prove to be difficult, especially if a multi-leaf collimator is not available as the shielding blocks would require adjustment for each field. This can be readily overcome by treating two pairs of fields each day, thereby ensuring a compromise between easy of delivery and under-dosing large portions of shielded volumes during each fraction.

In comparison to intensity modulated radiation therapy, our technique results in under-dosage of the PTV by about 15-20% and sparing of the parotid gland is not possible. However, limiting parotid gland dose to tolerance values can be challenging in

patients with involved bilateral posterior cervical lymph nodes even with modern inverse-planned intensity modulated radiation therapy since often the

PTV extends to the parotid glands. While most linear accelerators have capabilities to deliver intensity modulated radiotherapy as well as multiple energies of electrons, some vendors offer a low-cost single energy linear accelerator with static multi-leaf collimators.

Given the high cost of replacement of the Cobalt-60 teletherapy source, there is a high demand for low-cost linear accelerators. Even if more sophisticated machines capable of delivering intensity modulated radiotherapy are available, it requires more detailed quality-assurance and maintenance, resulting in the need for trained human resources to ensure safe treatment. Since our technique could be successfully delivered with a single energy linear accelerator with a static multi-leaf collimator, it is an alternative strategy that can be used to improve tumour control.

Intensity modulated radiation therapy enables the delivery of highly conformal doses and permits curative treatment of patients with squamous cell carcinoma of the head and neck and advanced lymph node metastases. However, in centres without such facilities, these tumours are doomed to fail with conventional fields and are often treated with a palliative approach. Our technique, on the other hand offers some hope in mitigation, as a minimum dose of around 60 Gy can be delivered to the gross tumour.

Conclusion

We have described a simple but novel three dimensional conformal radiotherapy technique to treat the posterior cervical lymph nodes of patients with squamous cell carcinoma of the head and neck in settings where facilities to deliver intensity modulated radiotherapy are not available.

Table : Characteristics, dosimetric data and tumour control probability of patients included in the study

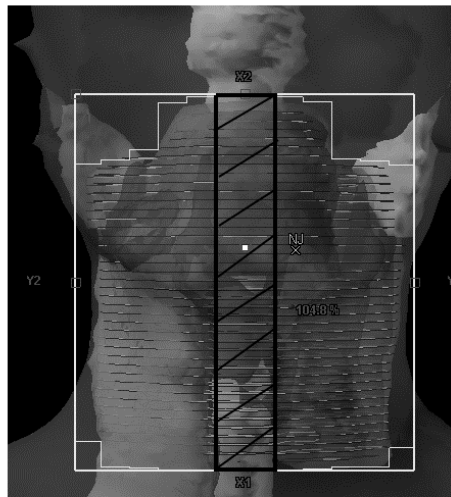
	Tumour site	Minimum dose to PTV		Minimum dose to CTV		Maximum dose to Spinal Cord		Tumour Control Probability	
		Conv	Novel	Conv	Novel	Conv	Novel	Conv	Novel
1	Supraglottis	44.6	58.2	45.2	61.0	43.0	43.7	<0.001	0.22
2	Hypopharynx	45.1	60.4	45.8	61.9	43.7	44.1	<0.001	0.52
3	Oropharynx	44.8	59.9	45.3	62.1	42.6	43.3	<0.001	0.45
4	Oropharynx	46.1	61.1	47.1	62.4	44.2	44.7	<0.001	0.60
5	Supraglottis	43.9	57.4	45.5	60.2	42.1	42.9	<0.001	0.13
6	Hypopharynx	44.2	60.4	45.1	61.8	42.8	43.1	<0.001	0.52
7	Supraglottis	45.6	58.8	46.2	60.3	43.3	43.4	<0.001	0.30
8	Oropharynx	45.9	60.3	46.4	62.4	44.0	44.4	<0.001	0.50
9	Oropharynx	46.0	59.9	47.2	62.0	44.2	45.1	<0.001	0.45
10	Supraglottis	44.2	61.2	45.1	62.5	42.7	43.7	<0.001	0.61

PTV, Planning Target Volume. CTV, Clinical Target Volume. Conv, Conventional Technique. Novel, Novel Technique.

Figure 1:
Axial dose map showing the placement of the 12 equi-spaced fields with shielding of the spinal cord.



Figure 2:
Beams eye view showing conformal shielding of the spinal cord as indicated by shaded region.



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Hypoxic radiosensitisation with carbogen: The Tellipalai Trail Cancer Centre Experience

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Key words: Hypoxia, Carbogen, Radiosensitisers Introduction

Introduction

Hypoxia is a well recognised cause of tumour radioresistance¹. Carbogen is a gas mixture of carbon dioxide and oxygen, in concentrations of 2-5% and 98-95% respectively, which improves tumour oxygenation by increasing the intra-tumoural partial pressure of oxygen, enhancing tumour blood flow and reducing the affinity of haemoglobin to oxygen by shifting the haemoglobin oxygen dissociation curve to the right². High dose nicotinamide is often given concomitantly with carbogen to target acute hypoxia, but many patients are unable to tolerate it due to severe bowel toxicity^{3,4}. In the BCON trial of carbogen and nicotinamide in muscle-invasive bladder cancer, nearly 30-40% of patients discontinued nicotinamide, but still derived clinical benefit from carbogen alone^{4,5}.

Carbogen and nicotinamide have proven benefit as hypoxic radiosensitisers in squamous cell carcinoma of the head and neck in addition to muscle-invasive bladder cancer^{4,5,6}. Furthermore, a meta-analysis has confirmed the benefit for radiosensitisation with hypoxia modification independent of modality in cancers of the head and neck, cervix and lung¹. In spite of being highly cost-effective with robust evidence of efficacy, hypoxic radiosensitisation has not translated into widespread clinical practice¹.

Treatment with carbogen as a radiosensitiser was commenced at the Tellipalai Trail Cancer Centre in Jaffna, Sri Lanka in February 2018, and we report our initial experience of its use.

Methodology

Carbogen, prepared as a gas mixture of 3% carbon dioxide and 97% oxygen, was procured from the supplier of medicinal gases to the hospital. The

breathing system was locally assembled and carbogen was administered 5 minutes prior to commencement and during radiotherapy at a flow rate of 15 litres per minute. Radiotherapy was delivered with conventional fields according to the institutional protocol by Cobalt-60 teletherapy unit. Since high dose nicotinamide was not available in the country, all patients were treated with carbogen alone.

Results

Carbogen was administered to ten patients with head and neck and cervical cancer, treated with curative-intent radiotherapy but deemed unsuitable for concurrent chemoradiotherapy and their characteristics and acute toxicity are listed in table 1. The mean age was 70 years (range 59-76) and most patients were Eastern Cooperative Oncology Group performance status 2. Two patients reported initial discomfort due to tightness of the breathing apparatus, which improved with reassurance and counselling as treatment proceeded. Patient numbers and follow up are inadequate to report outcomes in terms of tumour control. Although there was a high incidence of acute grade 3 mucositis in patients with head and neck cancer, such toxicity is expected in patients treated with conventional fields using a Cobalt-60 teletherapy unit. All patients completed the full course of treatment with radiotherapy without interruption.

Discussion

These preliminary data confirm that carbogen is a well-tolerated, low-cost and easily deliverable hypoxic radiosensitiser highly suited as an alternative to chemotherapy in resource limited settings.

We used carbogen without nicotinamide, but as mentioned previously there is sufficient data to suggest that it is effective as hypoxic radiosensitiser as a stand-alone agent. Although a number of biomarkers of hypoxia have shown promise in retrospective studies none have been validated prospectively⁷. If robust biomarkers are available, a more personalised approach to hypoxic radiosensitisation could be applied. The advent of radiosensitising chemotherapy relegated the use of hypoxic radiosensitisers to patients unsuitable for chemoradiotherapy. However, even in these patients clinicians have tended to opt for more expensive options such as the monoclonal antibody cetuximab in squamous cell carcinoma of the head and neck⁸. This is of particular relevance to regions in the country with a high incidence of chronic kidney disease, which renders many patients ineligible for cisplatin⁹.

While we restricted the use of carbogen to patients unsuitable for concurrent chemoradiotherapy, its low

toxicity and mechanism of action suggests that a synergistic benefit could be derived if it is combined with radiosensitising chemotherapy. A small single institutional study of carbogen and nicotinamide administered concurrently with cisplatin-based chemoradiotherapy in cervical cancer patients conducted in Indonesia reported that this treatment was well tolerated without excess toxicity¹⁰. However, the numbers were too small and follow-up was inadequate to make any conclusions about efficacy. Therefore, further work is needed to confirm the benefit combining hypoxia modifiers such as carbogen with radiosensitising chemotherapy.

Conclusion

Hypoxic radiosensitisation with carbogen is a low cost easily deliverable option that merits further application, at least in patients with cancers of the head and neck, cervix and bladder who are unsuitable for concurrent chemoradiotherapy.

Table 1 : Tumour sites and characteristics of patients treated with carbogen

No.	Tumour site	Stage	Age (in years)	Performance status	Acute Toxicity
1	Supraglottis	T3N0	72	2	Grade 2 mucositis Grade 2 skin toxicity
2	Oropharynx	T4N2	75	1	Grade 3 mucositis Grade 2 skin toxicity
3	Hypopharynx	T3N2	76	2	Grade 3 mucositis Grade 2 skin toxicity
4	Cervix	IIIB	59	2	Grade 1 Gastrointestinal toxicity
5	Oral Cavity	T4N1	68	2	Grade 3 mucositis Grade 2 skin toxicity
6	Oropharynx (Re-irradiation)	T3N0	71	1	Grade 3 mucositis Grade 2 skin toxicity
7	Cervix	IIIB	75	2	Grade 1 Gastrointestinal toxicity
8	Oropharynx	T4N2	75	1	Grade 3 mucositis Grade 2 skin toxicity
9	Cervix	IIIB	68	2	Grade 1 Gastrointestinal toxicity
10	Cervix	IVA	62	2	Grade 2 Genitourinary toxicity Grade 1 Gastrointestinal toxicity

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Case Report

Pulmonary and Hepatic Metastasis of Mandibular Ameloblastoma

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Keywords : Ameloblastoma, metastasis, rare cancers

Introduction

Ameloblastoma, a benign locally aggressive tumour accounts for 11% of all odontogenic tumours. It constitutes 1% of all jaw tumours and the most common site is the mandible (80%)¹. It has a propensity to recur locally (50-62%) but metastasis is rare (2-5%). Here we report a case of ameloblastoma of mandible recurring after 7 years of primary excision with metastatic disease in the liver and lungs with no evidence of disease at the primary site.

Clinical Report

Our patient was a 63 year old female who had a local excision of a tumour of left mandible in 1973 (at the age of 18 years), which was found to be an inflammatory mass. No further histological details were available. In 2011 She developed another mass (at 55 years) at the same site and she underwent re-excision of the tumour. This time the histology revealing a plexiform ameloblastoma in 2011. She remained disease free for seven more years and then presented with loss of appetite, weight loss and exertional dyspnoea worsening over six months.

On examination, primary site was normal. She was not dyspnoeic at rest and there was mild reduction of breathing sounds in left mid and lower zones. No abdominal masses or icterus was seen. Rest of the general and systemic examinations were normal.

Her chest x-ray revealed two, coin shaped lobulated soft tissue opacities in left mid and lower zones (Figure 1). Chest CT showed two large left sided lung masses in left lingular lobe peripherally (6.8cm x 6.7cm x 7.4 cm) and in posterior segment of the left lower lobe (5.6 cm x 4.4 cm x 5.3 cm). Ultrasound abdomen showed multiple liver lesions without hepatomegaly. CT abdomen revealed bilateral multiple focal liver lesions. The largest lesion (5.1cm x 3.9cm) was seen in segment III. Tumour

markers including Alfa fetoprotein, CEA and CA 125 were all negative.

Biopsy of the liver lesion showed infiltration by a tumour composed of clusters and sheaths of small polygonal and spindly cells with spindly hyperchromatic nuclei, favouring secondary deposits of a carcinoma. Since the biopsy tissue was inadequate for immunohistochemistry, ultrasound guided trucut biopsy of the left lung lesions was done. Lung biopsy showed linear core of tissue containing a tumour composed of nests of clear cells with plexiform growth pattern and spindling of tumour cells (Figure 2). Tumour cells were strongly positive for Pan CK and negative for chromogranin A, TTF-1, CK 7 and CK 20. Considering the past history, findings were compatible with a metastasizing ameloblastoma.

This case was discussed in the multidisciplinary meeting and awaiting resection of the lung lesions. After assessing the fitness following surgery, we are planning to start her on cisplatin based adjuvant chemotherapy as that has shown better outcome in literature¹.

Discussion

Ameloblastomas are benign rare tumours arising from odontogenic epithelium of the jaw. They usually occur in third to fourth decades of life and males and females are equally affected^{4,7}. Common clinical presentation is the painless swelling of jaw and other symptoms such as tooth mobility, pain, malocclusion, ill fitting dentures and periodontal disease.

Ameloblastoma arises from remnants of the embryonic tooth mainly the dental lamina or inner enamel epithelium¹. Five histological subtypes are

described which include more common follicular and plexiform variants and less common acanthomatous, granular, basaloid and thermoplastic variants. Based on histological architecture, these tumours are subdivided into four variants including solid, multicystic, unicystic and combination³.

These tumours are locally aggressive and rarely metastasize². Metastasizing benign Ameloblastoma lacks features of its malignant counterpart in the primary as well as in metastatic lesion as seen in this patient¹. Ameloblastic carcinoma can be differentiated from the above by its high grade malignant potential, marked cellular atypia and increased mitotic activity.

The most common metastatic site is the lung (85%) followed by regional lymph nodes, pleura, parotid gland and the liver⁵. Risk factors for metastasis include extensive initial disease, long duration of disease, mandibular focus of primary tumour and multiple surgical and radiation procedures. The routes of metastasis include hematogenous, lymphatic and by aspiration of tumour cells into lungs. Our patient had a mandibular tumour in 1973 which was reported as an inflammatory mass but in hindsight could have been an ameloblastoma. Local recurrence after 38 years requiring repeated surgical intervention contaminating the field could have contributed to metastasizing to both lung and liver. Treatment of the primary site is by radical surgery. If the resection is incomplete adjuvant radiotherapy can be considered¹. Palliative radiotherapy can be offered for unresectable tumours. Management of the metastasizing ameloblastoma is more complex and needs multidisciplinary approach. There are no definitive guidelines for treatment and only a few case reports published up-to-date discussing the management.

If removable, surgery would be the best option for treating the malignant deposits. Several chemotherapy schedules were described in case reports which need further evaluation. Cyclophosphamide, methotrexate and 5-FU based chemotherapy showed good functional outcome but no overall survival benefit⁶. Cisplatin based chemotherapy regimens including vinorelbine, cisplatin, bleomycin and adriamycin, cisplatin, cyclophosphamide have shown partial response¹.

Conclusion

Although ameloblastoma is considered as a benign tumour, rarely it can cause metastasis which can affect survival. In our case, in spite of radical

surgery, disease recurred causing lung and liver metastasis seven years later. It demonstrates the importance of continuous followup to detect metastatic lesions as early as possible. Most of the patients remain asymptomatic and surgery can be offered if the metastases could be detected at an early stage.

Oncological management of metastasizing ameloblastoma remains controversial¹. Rarity of the condition makes it impossible to conduct clinical trials to evaluate the treatment. Only through the continuous reporting of the cases it will be possible to discover the optimal strategies of management. However, EGFR expressing nature of this odontogenic tumour makes it promising that novel targeted therapies will be available in the future.

Figure 1:

The chest Xray showing two coin shaped lesions in left mid and lower zones

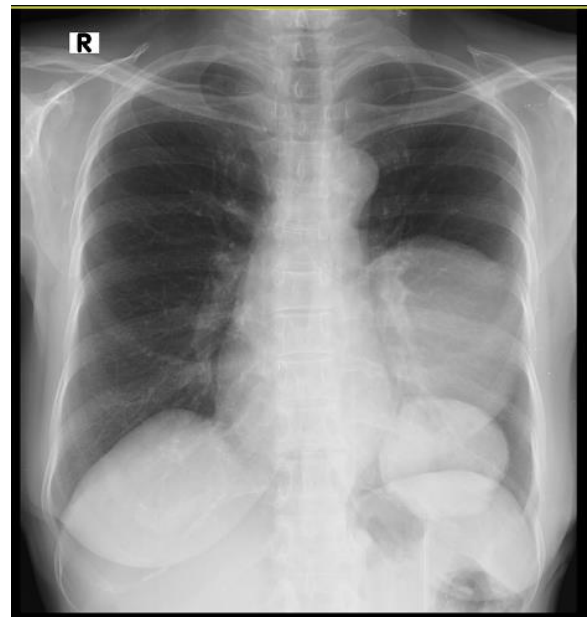
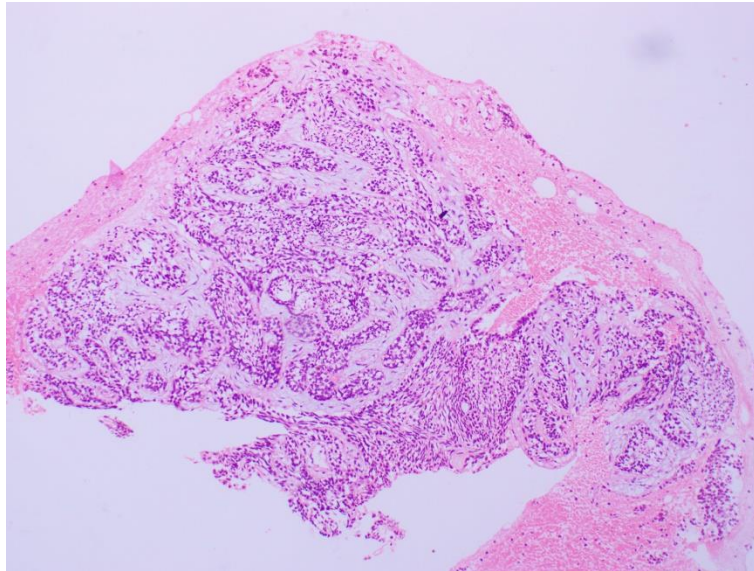


Figure 2: Lung biopsy showing nests of clear cells with plexiform growth pattern consistent with plexiform ameloblastoma



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Review Article

Management of multiple myeloma in Sri Lanka

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Keywords : Multiple Myeloma, Investigating, Treatment

INTRODUCTION

Multiple myeloma (MM) is characterized by neoplastic proliferation of plasma cells. Excessive plasma cells results in osteolytic lesions, osteopenia and subsequent pathologic fractures. MM most commonly presents with bone pain; particularly back pain (due to osteopenia, osteolytic lesions or pathologic fractures of vertebra) and high ESR. Other presentations are; end organ damage which includes unexplained anemia, acute renal failure, hypercalcaemia, spinal cord compression and constitutional symptoms. Differentiation of MM from other plasma cell dyscrasias is vital as prognosis and treatment vary among them. Any delay in diagnosis has been associated with a bad outcome.

The availability of agents such as thalidomide, lenalidomide, bortezomib and the introduction of autologous stem cell transplantation (ASCT) at 'Apeksha' Hospital, Maharagama (National Cancer Institute, Sri Lanka - NCISL) have changed the management of myeloma and extended the overall survival of MM patients in Sri Lanka.

EPIDEMIOLOGY

MM accounts for approximately 1-2% of all cancers and about 20% of haematological malignancies in Sri Lanka with an annual incidence of 4 to 5 per 100,000¹. Worldwide, there are approximately 154,000 cases and 101,000 deaths per year attributed to MM².

CLINICAL FEATURES

Seven percent (7%) of MM are extra-medullary plasmacytomas (EP) at the time of diagnosis. Additional 6% of patients will develop EP in the disease course. EP is best diagnosed by PET/CT scan. Presence of EP at presentation is associated with poor survival^{3,4}.

Anemia, usually, normocytic normochromic, (defined by Hb ≤ 12 g/dL) is present in 73% of patients at

diagnosis and in 97% at disease course⁵. Cause of anemia can be due to bone marrow impairment, renal damage and dilutional anemia due to M-proteins.

Bone pain, usually in back but less frequently at extremities, is as common as 60% at the time of diagnosis⁵. The pain exaggerated by body movements and the rest pain at night is uncommon. Plasmacytomas may present as expanding soft tissue masses.

Renal disease (serum creatinine >2 mg/dL or 177 μ mol/L) is present in about 50% of patients at diagnosis and is the presenting complaint in about 20%^{5,6}. Most common causes of kidney injury in MM are light chain cast nephropathy (also called myeloma kidney) and hypercalcaemia. Patients who do not secrete light chains are not at risk for myeloma kidney disease. When serum involved FLC level is <500 mg/L, other causes for renal damage must be excluded.

Approximately 30% of MM at the time of diagnosis have hypercalcaemia (serum calcium ≥ 11 mg/dL or 2.75 mmol/liter)⁵.

Radiculopathy is the most common neurological symptom. This can be due to compression of nerve roots by plasmacytoma in paravertebral area or by the collapsed bone itself. Unfortunately 5% of patients present with spinal cord compression. Severe back pain with weakness and bladder and bowel incontinence should be treated urgently to preserve ambulatory functions. Peripheral neuropathy is uncommon in the absence of amyloidosis. Generally, CNS involvement is rare in MM⁷.

Immune dysfunction due to suppression of normal plasma cells leads to frequent infections in MM.

DIAGNOSIS

Monoclonal proteins

Malignant plasma cells usually secrete monoclonal (M) protein and only 3% of MM are non-secretory. M Protein can be detected with electrophoresis in serum or urine (SPEP or UPEP)⁵ and the M-band usually rises as a single sharp peak in the gamma region. Serum immunofixation is used to determine the type of immunoglobulin, where IgG predominates followed by IgA. This can either be immunoglobulin heavy chains plus light chains or light chains alone⁵. Twenty percent (20%) of MM are light chain alone and renal damage is common in this subset. Among light chains, Kappa is the mostly affected but in IgD myeloma lambda light chain involvement is predominant, and this is commonly associated with amyloidosis⁸.

Serum protein electrophoresis (SPEP) will show M protein band in 82% of MM and immunofixation increase the sensitivity to 93%. Further, the serum free light chain (FLC) assay or urine protein electrophoresis increases the sensitivity up to 97%. Patients who fail to show any of these are confirmed as "non-secretory myeloma". Eighty five percent (85%) of non-secretory myelomas actually produces monoclonal protein which can be detected inside the cytoplasm but not secreting in to the serum. Rests of the non-secretory myelomas are considered as "non-producer myeloma". Further, presence of normal levels of uninvolved immunoglobulins is associated with better clinical outcome irrespective of the treatment⁹.

In case of oligo-secretory myeloma, FLC level can be used to monitor the disease if involved FLC level is more than 10 mg/dL¹⁰. Otherwise, the disease monitoring has to depend on bone marrow studies and imaging as with non-secretory disease.

Urinalysis

Urine dipstick is characteristically negative for protein, because Bence Jones proteinuria composed of immunoglobulin rather than albumin. Myeloma cast nephropathy can be identified by large, waxy, laminated casts lodged in the distal and collecting tubules in a renal biopsy. In contrast, amyloidosis dipstick for protein is positive due urinary albumin (nephrotic syndrome). Cast nephropathy and amyloidosis may rarely occur simultaneously.

Peripheral smear

Rouleaux formation is a common finding in MM. Less commonly leukopenia (20%) and thrombocytopenia (5%) can be noticed in peripheral blood⁵. However, detection of monoclonal plasma cells in peripheral

blood is uncommon unless plasma cell count is ≥ 100 cells/ μ L ($\geq 0.1 \times 10^9/L$) which occurs only in 10% of cases. Whenever peripheral plasma cells are detected, diagnosis of plasma cell leukemia should be strongly considered.

Bone marrow examination

Mainstay of diagnosis of MM is the percentage of plasma cells in bone marrow aspiration and trephine biopsy. Clonality of the plasma cells must be confirmed using kappa/lambda light chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Presence of $\geq 10\%$ of monoclonal plasma cells in bone marrow is required to establish the diagnosis of MM. More than 60% clonal plasma cells in bone marrow is associated with 80% chance of developing end organ damage within next two years^{11,12}.

Immunophenotype

In healthy bone marrow, kappa/lambda ratio is 2:1 and disturbance in ratio of more than 4:1 or less than 1:2 is accounted as monoclonal disease. Both normal and malignant plasma cells express CD79a, CD138, and CD38¹³, but CD19 is expressed only in normal plasma cells. Further, most myeloma cells are CD45 negative. CD56 is used to differentiate myeloma cells from normal plasma cells and plasma cell leukemia where CD56 is negative in latter two conditions. However, only 70% myeloma cells are positive for CD56. Therefore, six antigens are used to differentiate myeloma cells from normal plasma cells and to establish clonality which are; CD38, CD45, CD56, CD19, kappa, and lambda.

Free light chain assay

The normal kappa/lambda FLC ratio is 0.26 to 1.65 in serum. Ninety percent (90%) of MM has altered FLC ratio at the time of diagnosis¹⁴. Serum FLC ratio of >100 is now considered as diagnostic of MM, as it is associated with a 80% chance to develop end organ damage within next two years^{15,16}.

Imaging

Skeletal surveys are reserved for patients who are unable to undergo low-dose whole body CT, MRI, or PET scans. The skeletal survey includes lateral view of skull, postero-anterior view of chest, antero-posterior and lateral views of whole spinal segments, antero-posterior views of humeri, femora and pelvis¹⁷. Cross sectional imaging (eg; low-dose whole body CT without contrast, whole body PET/CT, MRI of the spine and pelvis) is preferred as they are more sensitive than plain radiographs. The choice of cross sectional imaging

modality depends on availability, cost, and institutional preference. MRI is the most sensitive modality to identify bone involvement, while PET/CT is more sensitive to detect extramedullary disease.

Table 1: Diagnostic Criteria of MM

Both criteria must be met: • Clonal bone marrow plasma cells $\geq 10\%$ or biopsy-proven bony or extramedullary plasmacytoma. • Any one or more of the following myeloma defining events: ○ Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically: 1. Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL) 2. Renal insufficiency: creatinine >177 mmol/L (>2 mg/dL) 3. Anemia: hemoglobin value of >2 g/dL below the lower limit of normal, or a haemoglobin value <10 g/L 4. Bone lesions: one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography-CT (PET-CT) ○ Clonal bone marrow plasma cell percentage $\geq 60\%$ ○ Involved: uninvolved serum free light chain (FLC) ratio >100 (involved FLC level must be >100 mg/L) ○ >1 Focal lesion on magnetic resonance imaging (MRI) studies (at least 5 mm in size)

FRONTLINE TREATMENT

Only the patients with symptomatic myeloma require treatment. Those with smoldering or asymptomatic myeloma should be monitored closely without therapy¹⁸.

The approach to therapy largely depends on transplant eligibility. Generally, the age 65 is considered as a therapeutic divergence point. Those below 65 years and free of significant comorbidities are considered transplant eligible. They are treated with induction chemotherapy to achieve the best possible response. A triple combination induction regimen including bortezomib and an immunomodulatory drug is the current standards. Non-transplant candidates are generally treated with melphalan-based regimens¹⁹.

Transplant eligible patients (<65 years with no significant comorbidities)

For younger (<65 years) patients in good performance status, induction followed by high dose chemotherapy with autologous stem cell transplantation (ASCT) is the present-day standard practice worldwide. Since October 2016, with the initiation of National Stem Cell Transplant Programme at National Cancer Institute - 'Apeksha' Hospital, Maharagama (NCIM), patients with multiple myeloma in Sri Lanka now receive ASCT consolidation post-induction chemotherapy. However, due to resource constraints, only a limited number of patients are offered ASCT with adoption of strict selection criteria.

Table 2: Selection criteria for ASCT for Multiple myeloma at ‘Apeksha’ hospital - Maharagama (NCIM)

1. Age: < 60 (or <65 with no co-morbidities)
2. Performance Status ECOG <= 2
3. Co-morbidities – free of major physical and mental health issues (including uncontrolled infection)
4. Disease specific issues – chemotherapy responsiveness and ASCT preferably to be performed soon after induction. No prior Radiotherapy to most of bone marrow sites
5. Patient understanding of benefits and risks of the procedure and signing informed consent form.
6. Adequate family and social support.
7. Adequate HSC (haematopoietic stem cells) harvested for transplant.

The aim of induction chemotherapy in transplant eligible patients is to reduce the initial disease burden to achieve a durable response post-transplant, and to reverse the end-organ damage. Four to six cycles of induction chemotherapy cycles are administered over a period of 3-4 months prior to transplant.

Response rates to induction therapy have improved dramatically in recent years with the introduction of novel proteasome inhibitor; bortezomib based regimens. Bortezomib plus dexamethasone-based triplet combinations has become the cornerstone of induction therapy before ASCT. It is superior to traditional VAD (vincristine, doxorubicin and high-dose dexamethasone) regimen²⁰.

Triplet combination of bortezomib, thalidomide and dexamethasone (VTD) has been proved superior over thalidomide and dexamethasone (TD) or bortezomib and dexamethasone (VD) combinations by two prospective trials^{20,21}. One study reported pre-transplant complete remission (CR) rates of 35% versus 14% between VTD and TD respectively²¹.

The standard conditioning regimen before transplant is melphalan (200mg/m² intravenous)²² and the peripheral stem cells are preferred over the bone marrow stem cells as the progenitor cell source²⁰. Two recent phase III trials comparing front-line ASCT at first best remission versus ASCT at the first relapse showed that progression-free survival (PFS) was better with the front-line ASCT²³.

Treatment of non-transplant candidates

Melphalan based novel combination regimens have become the standard of care in non-transplant candidates. Three randomized trials²⁴⁻²⁶ and one meta-analysis²⁷ showed that melphalan, prednisolone and thalidomide (MPT) was superior to melphalan and prednisolone (MP) in both PFS and overall survival (OS).

A combination of bortezomib, melphalan and prednisolone (VMP) is an alternative to MPT. VMP was shown to be superior to MP with a 5-year OS of 46% versus 34% respectively in the VISTA trial^{20,28}. The most common side effect of this regimen was peripheral neuropathy, with grade 3/4 occurring in about 13% of patients in the VMP arm but resolved completely in 60% of patients by 6 months^{20,28}. On further analysis of this regimen, similar efficacy and lower rates of peripheral neuropathy were shown with weekly bortezomib dosing²⁹.

Patients with high risk of peripheral neuropathy, Rd (lenalidomide plus low-dose dexamethasone) is an attractive option, which is in fact superior to MPT in terms of PFS and OS³⁰.

In the setting where novel agents like bortezomib or lenalidomide are not accessible, cyclophosphamide, thalidomide and dexamethasone (CTD) is a reasonable option. CTD has also been compared with MP and is superior in response rates but has no survival advantage over MP³.

Role of Maintenance

Maintenance therapy is defined as any treatment after completion of induction, with or without ASCT. The maintenance treatment has been evaluated in both the post-transplant³² and the non-transplant³³ setting. Although it improves PFS, the data for OS were inconsistent. Several randomized trials have shown that lenalidomide maintenance was beneficial in post-transplant setting which resulted in improvement in PFS. Some of these trials have also shown a survival benefit at 3 years, though the advantage was largely confined to good risk patient population³⁴. An important point to note is that some of these studies also reported a higher risk of secondary malignancies in the lenalidomide maintenance arm with an incidence in the range of 7-8% at 3 years³⁴.

TREATMENT OF RELAPSED DISEASE

The choice of therapy in relapsed setting depends on several factors such as age, performance status, comorbidities, tolerance and side effects of previous treatments, number of prior treatment lines, interval since last therapy and whether the patient is symptomatic or not with current relapse.

Widely accepted options at relapsed setting are lenalidomide with dexamethasone or bortezomib as a single agent or in combination with dexamethasone³⁵. Newer agents like panabinoastat; a panHDAC inhibitor, carfilzomib; a newer proteasome inhibitor, daratumumab; an anti-CD38 monoclonal antibody and ixazomib; an oral proteasome inhibitor have shown promising and encouraging results in relapsed setting. However, it may take several more years before they are affordable and widely available in Sri Lankan set-up.

THE USE OF BISPHOSPHONATES

All patients with symptomatic myeloma should receive long-term bisphosphonate therapy regardless of having skeletal lesions. Bisphosphonates prevent, reduce, and delay skeletal complications in MM patients suffering from lytic bone disease or severe osteoporosis. Intravenous pamidronate and zoledronic acid are preferable and should be given for 2 years, but this may be extended if there is evidence of active myeloma bone disease. Dental

assessment must be carried out before initiating bisphosphonates and preventive steps should be taken to avoid renal impairment and osteonecrosis of the jaw.

ROLE OF RADIOTHERAPY

One-third of MM patients require palliative radiotherapy, commonly at initial diagnosis and at

progression. Most common indications for radiotherapy are pain palliation, pathological fractures and neurologic complications such as spinal cord compression. Radiotherapy, if indicated, should not be denied based solely on fears of compromising the feasibility to ASCT³⁶.

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Review Article

High tech radiotherapy: Beguiled and mesmerised whilst staying grounded

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Radiotherapy is the most effective non-surgical treatment for cancer accounting for 40% of cures and able to achieve palliation from the symptoms of pain, obstruction and haemorrhage in around 70% of those treated. Despite this the healthcare spend on radiotherapy is disproportionately low representing in the UK only 5% of GDP compared to over 20% for chemotherapy which achieves far less¹. Despite offering a highly cost-effective cancer treatment, investment in radiotherapy is often difficult to achieve because it requires expensive capital equipment housed in purpose-built bunkers run by a highly specialised workforce. We are on the verge of a technical revolution with artificial intelligence, CBCT-guided protons and MR-guided radiotherapy and although we may think that the advent of immunotherapy will see the demise of radiotherapy, history has taught us that systemic treatment alone rarely cures cancer and that medical science progresses when multi-disciplinary multi-modality treatment is delivered.

In both developed and developing healthcare economies there is increasing pressure to adopt 'high tech solutions', inflating the cost of treatment but with limited evidence of tangible benefit². Thus a modern linear accelerator will have on-board kV imaging to produce cone beam images of treatment volumes, multi-leaf collimators with rotational and stereotactic IMRT capability as standard, a far cry from the basic cobalt machine of a decade or two ago with no more than a single radiation source, a shutter, manual wedges and lead blocks to shape the beam beyond the primary collimator. Developments abound with the new generation of linear accelerators having MR imaging and adaptive planning solutions. Ever more accurate planning software gaining more precise dose estimates by just a few percentage points using Monte Carlo modelling or bespoke solutions for inhomogeneity are thrust upon us. Vendors ensure

that regular upgrades of their planning, record and verification systems are released providing a continued flow of revenue for their installation and maintenance, a familiar ploy which we encounter every time we switch on a computer to find an update of Windows or purchase a car tied into a 'necessary' servicing agreement.

It may then be useful to stand back from this technology drive and reconsider what we are trying to achieve. Our aim is simple, to deliver photon energy to malignant cells causing sufficient DNA damage to render them non-viable whilst avoiding such effects in surrounding normal tissue. The impact of the 'high tech solution' over more basic approaches has rarely been objectively tested and the most effective means of delivering localised high dose radiation treatment using brachytherapy, far more cost effective than external beam solutions, is in decline.

Although as technophiles, innovations excite us, technological developments contribute to the rising cost of healthcare. The evaluation of complex new technology is often inadequate and challenging leading to excessive use at unnecessary cost^{3,4}. The integration of health economics in to healthcare is becoming increasingly important. Delivering value-based healthcare is a priority in all countries regardless of the underlying funding strategy. Different countries spend different proportions of national income on health⁵. Every day the media is full of reports of underfunding and inadequate resourcing within healthcare. There is a dilemma when it comes to innovative radiotherapy technology; with new drugs, pharma acquires the evidence and then the health service pays for the drugs, however, when it comes to technology, the health service must invest in equipment before the evidence is obtained.

For example the introduction of IMRT pre-dates the justification by some years. The first trial to justify IMRT is based primarily on toxicity reduction, with reduced dry mouth in the PARSPORT trial in head and neck radiotherapy, but no improvement in tumour control demonstrated⁶. There is only now an ongoing randomised trial comparing protons with photons for prostate cancer (NCT01617161)⁷ despite the routine use of proton therapy for this indication in the US for many years. It remains a challenge to ensure that the evidence base for implementation of advanced technology is robust. There is a need for innovative, novel methodologies to ensure that appropriate clinical questions are answered in a timely fashion as traditional randomised control trials take many years to deliver. One suggestion is to use the IDEAL framework⁸ combining phases for innovation, development, exploration, assessment and long-term studies. By adding a preclinical stage with *in silico* predicate studies for radiotherapy, the framework has been adapted and termed R-IDEAL^{9,10}.

This question of implementing costly technological advances in radiotherapy is particularly important in the current climate where excessive healthcare spending is being scrutinised. We have a responsibility to our patients to continue to improve clinical outcomes without being shackled by political whimsy. The Global Task Force on Radiotherapy for Cancer Control has shown that over 50% of people in the world do not have access to basic radiotherapy¹¹ and this should be a priority for us all. The challenge is to discard our parochial concerns in the developed world and adopt a more global perspective supported by industry and politicians. There are inexpensive ways of improving radiotherapy outcomes for patients. Organisation of health care provision, early diagnosis and timely access to radiotherapy will achieve far more than replacing cobalt machines by state of the art linear accelerators. A reduction in waiting time for radiotherapy from 8 weeks to 4 weeks would have a substantial impact on cure rates. Ensuring efficient use of the available resources will maximise opportunities for all. This may mean cultural changes with adoption of hypofractionated schedules in place of conventional 2 Gy per day prolonged treatment. The use of 40 Gy in 15 fractions for breast cancer, 60 Gy in 20 fractions for prostate cancer and single doses of 8 Gy for many palliative indications can double machine capacity overnight. Robust quality control and quality assurance is a further essential component to ensure the safe and accurate process which our patients deserve. We should avoid being dazzled by the bright lights of expensive high tech

and keep our sights on our ultimate aim which is universally to provide the best

treatment possible for all those in our societies who require it within the limitations of our healthcare system. This will often involve simple organisational solutions rather than shiny new machinery. There are ways of delivering radiosensitisation that do not involve invasive procedures, prolonged visits to hospital or systemic therapy expertise. One simple intervention is to ensure that patients have adequate haemoglobin levels¹². Hypoxia modification with carbogen and nicotinamide either within the ARCON¹³ or BCON¹⁴ protocol can be delivered with minimal additional infrastructure, but with proven benefit to patients.

We live in interesting times – there is so much that we can do, so many shiny new toys to beguile and mesmerise. Whatever we do, it is important that we keep sight of our ultimate goal, to improve the clinical outcomes for our patients. It is a great honour to be part of the first edition of the Sri Lankan College of Oncology journal as we all journey together.

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