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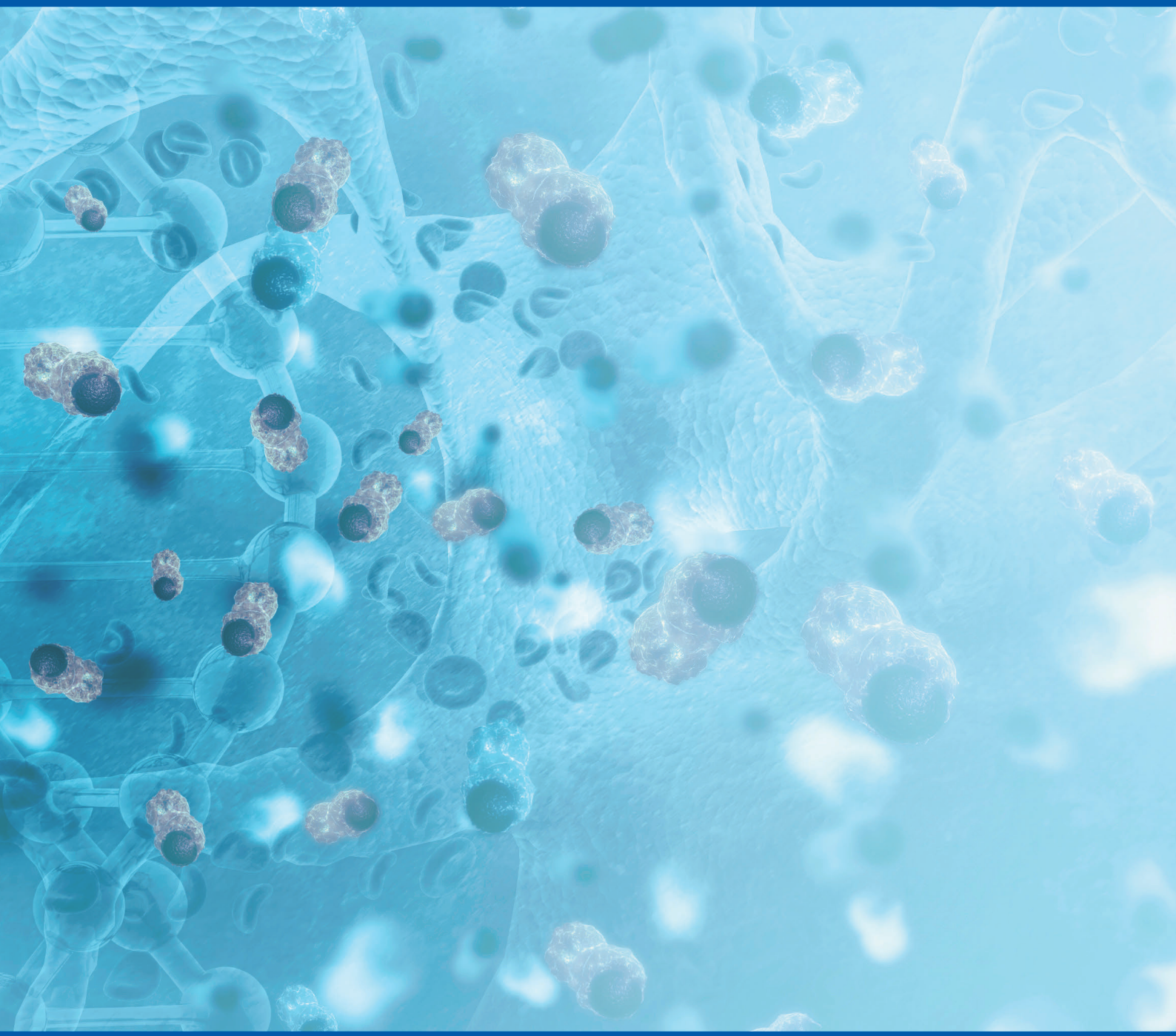

Official Journal of the Sri Lanka College of Oncologists

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The Sri Lanka Journal of Cancer is a peer reviewed medical journal published by the Sri Lanka College of Oncologists. The Sri Lanka Journal of Cancer publishes original research, review articles, brief communication etc related to the field of cancer in Sri Lanka.

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Editorial Board

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Editorial

A GOOD RESEARCH IN A GOOD WRITE UP

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The Setting up of the Sri Lanka Cancer Research Group, by the Sri Lanka College of Oncologists is a leap across the threshold. It was a real gratification to see that several scientific papers were presented and published by our young oncologists and postgraduate trainees, clearly displaying their excellent work in varying subject areas. Congratulations to all!

Placing an attractive manuscript correctly in a journal is of great value to readers and the authors as well as to their respective institutions. Globally, each year, there are millions of manuscripts prepared and submitted for publication. From them about 1/3rd gets rejected while 1/3rd gain acceptance with or without conditions. About a half of them get recommended for major or minor revisions. At the end however nearly half get accepted and another half get rejected. Less than 5% would be withdrawn. It is still early for us to assess the Sri Lankan scenario specially with regards to oncology manuscripts, but it is to be expected that a considerable number of manuscripts will get rejected during the review process.

Studies on cancer are a very diverse and complex field of research. Despite many advances in recent years, there is a lot of unexplored topics. For example most bio markers are not mutually exclusive but, do complement each other. This itself warrants major research that would need to recruit a larger number of patients. This highlights the importance of collaboration in research rather than working in isolated small groups. (Although the definition of 'small' would vary according to the main study objective.)

The majority of research studies can be categorized in to audits of patient data, observational studies, clinical trials and laboratory analyses. A small study can be conducted quickly and published within a short time-frame. In addition, obtaining ethical and institutional approval is much easier in small studies compared with large multi-centre studies. Small studies do not generally yield reliable or precise estimates. ,, Although larger studies will take longer to complete they are likely to yield more reliable results . The existing network of the few cancer centers in Sri Lanka permits our researchers to conduct 'well designed' small studies which can lead to well conducted multi-centre studies on a larger scale. There shouldn't be undue hesitancy in conducting small studies if resources dictate so, provided they are well designed, well executed and interpreted carefully. Therefore, it is important to make strong conclusions about study outcomes (whether the results are positive or not) only after analyzing the study carefully.

We have seen many editorial boards of European Journals often review very interesting studies, which have small sample size. While most boards encourage the best use of such data, editors are well aware that small studies have many limitations.

A good 'Title' is a key factor that would increase the chance of citation when publishing clinical trials in a journal. A compact title with direct relevance to its content better attract readers. Shadow titles and exaggerations end up in reader's disappointment. One of the key moments in the process of publishing your work, is by receiving comments from reviewers. Editorial 'peer review' is widely regarded as an essential component of quality assurance in academic medical papers. It often provides an indication of whether all of your hard work has paid off or not. But remember that peer reviews rarely focus upon the strengths of the paper and often that can be interpreted as unreasonably critical. However, reviewers best accompany their comments with additional narration on the paper that has been submitted. You may even be asked to respond to the reviewer's comments in return. The final verdict comes from the Editor of the publication. Understanding the reliability of the peer-review process while helping editors understand the limitations of reviewers' recommendations is a must. Still there are a few authors making obvious deviations beyond basic formational standards.

THe head of Department or a research inclined person with experience would generally determine the standards of a research. Regular research discussions between researchers in our departments would certainly help to stimulate scientific proficiency. Those who are more

experienced in each department should support those who still need guidance in research and in publishing. Such attitude would furthermore, reduce egotistical motives and create an excellent academic atmosphere, which still needs to be developed in our set up.

It is becoming a more frequent observation that in academic journals, the English Language has been used in a manner that is not suitable or proper in the circumstances. Though the scientific medical terminology is still derived from ancient Greek and Latin, English is the present lingua franca in science. Just as much a wrong prescription could give a wrong medicine, outcomes of improper use of language and terminology would be catastrophic too. There are considerable number of manuscripts still rejected by the international journals purely on improper language use rather than their scientific value.

Busy readers such as clinicians mainly focus on a limited number of journals, chosen according to the journals' clinical focus. Authors spend considerable energy preparing articles for specific journals, straightening out their presentations to meet the needs and expectations of client readership etc. Academic institutions use publications as a factor in making tenure and promotion decisions. If the work remains complicit, the author should not worry about the processes, the editors use to assess your article.

I take this opportunity to honour the contribution of Editor-in-Chief for final editing of published articles and the support rendered by our authors, reviewers, the publishers and the office bearers of SLCO for their relentless support in bringing out this 4th edition of 'The Sri Lanka Journal of Cancer' in the middle of a prevailing COVID– 19 crisis.

Management of locally advanced Cervical Cancer

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The primary treatment for Stage IB2 - IVA Cervical Cancer

Stage IB2, & IIA1

- Primary surgery and definitive radiotherapy give equivalent local control and survival benefit. Hence select cases carefully. [1]

Primary chemo-irradiation for IB2 – IVA

Definitive radiotherapy

External beam radiotherapy (EBRT) with concurrent chemotherapy followed by intra- cavitary brachytherapy boost (BT) is recommended [1,2,3].

1. External beam radiotherapy

1.1 Pelvic Radiotherapy

For tumours with or without involved nodes confined to the pelvis [4].

Planning Technique

CT simulation

- Position: Supine with knee/ankle supports and arms on the chest
- Skin tattoos: Midline and laterally over a bony point
- Bladder/ bowel protocol: Comfortably filled bladder with an empty rectum
- CT simulation (3mm slices) from L3 to 5cm below the ischial tuberosities.
- IV contrast – preferable to identify the nodes

Target delineation: A. Conventional planning: Field borders:

Antero-posterior projection:

- Superior margin – L4/L5 or L5/S1
- Inferior margin – 3cm below the inferior aspect of the vaginal disease or lower border of the obturator foramen
- Lateral margin – 2cm lateral to the deepest curvature of the pelvic brim

Lateral projection:

- Superior & inferior: Same as above
- Anterior margin – 1cm anterior to the anterior symphysis pubis.
- Posterior border – S2/S3 junction or include the entire sacrum (In stage III)

B. 3-Dimensional CT-based planning

Target volumes:

GTV_primary (GTVp)- The gross disease as per the EUA findings and imaging

GTV_nodes (GTVn) - Involved nodes in diagnostic imaging

CTV_primary (CTVp)

- GTVp + 5-10 mm margin
- Cervix and include the whole uterus.
- Parametria.
- If minimal or no extension, include the upper half of the vagina.
- If upper vaginal involvement, include upper 2/3rd vagina.
- If extensive vaginal involvement, include the entire vagina.
- If stage III and IV disease, include uterosacral ligaments.
- Ovaries

CTV_nodes (CTVn)

GTV_nodes +7mm

- obturator nodes
- external iliac lymph nodes
- internal iliac lymph nodes
- pre-sacral nodes.
- common iliac nodes.
- 7mm margin around vessels extending to the pelvic sidewall and any visible node are recommended for the pelvic

nodal regions

- If common iliac nodes are involved, include para-aortic nodes or at least 2 cm above the highest involved node [4].
- If para-aortic nodes are involved, include at least 2 cm above highest involved node [4].

PTV_primary (PTVp): CTVp + 10 -

15mm

PTV_nodes (PTVn) – CTVn + 7 –

10mm

Technique:

4-field box technique (fields are shaped to the 3D volume) Beam energy: 6 -15 MV

C. Intensity Modulated Radiotherapy (IMRT)

There are potential benefits of IMRT in the radical treatment of cervical cancer patients, both in terms of dose escalation and decrease of toxicity.

IMRT is preferred for patients receiving extended field radiotherapy and when OAR dose constraints cannot be met [5].

Organ and target motion is constant and unpredictable at the pelvis, thus posing a challenge to the safe execution of IMRT. Therefore, an internal target volume (ITV) is defined in IMRT. ITV is taken with a margin to CTV that includes the variation for organs and target movements.

To add the ITV, the patient should be simulated with an empty and full bladder.

Target volumes:

Same as 3-D CT-based planning except for ITV & PTV margins

ITV: CTVp + margin to include movement of target with bladder filling

PTV p : ITV + 7 -10 mm

PTVn:CTVn + 7-10mm

OAR dose constraints [5,6]

- Generally, target coverage takes priority over non-critical organs at risk.
- Suggested contouring atlas: https://www.nrgoncology.org/About-Us/Center-for-Innovation-in-Radiation-Oncology/Female-RTOG-Normal-Pelvis
- The dose to the rectum, bladder and sigmoid colon should be recorded for use in assessing cumulative dose with brachytherapy treatment.

Organ	Dose constraints
Small bowel	• ALARA. • V45 Gy<195 cc. • V40 Gy<30%. If extended field treatment: • V40 Gy<300 cm • V30 Gy<650 cm.
Rectum	• V40 Gy<60%
Bladder	• V45 Gy<35%.
Femoral heads	• V45 Gy<50%. • V50 Gy<10%.
Kidneys (for EFRT)	• mean dose <15 Gy • V12 Gy<55% • V20 Gy<32% • V23 Gy<30% • V28 Gy<20%.
Spinal cord (for EFRT)	• Dmax<45Gy

Dose Prescription:

- External Beam Radiotherapy (2D / 3D / IMRT)
- 45 Gy -50.4 Gy, 1.8 -2Gy per fraction (25 -28 fractions) over 5 to 6 weeks.

Timing:

- Ideally the chemo-irradiation and brachytherapy should be completed in 56 days to optimize local control [7,8,9].
- **If this timing is not met in a resource-limited setting, compensation could be made by adding 0.6Gy for every delayed day [7,8].**

NB: When intracavitary treatment is not possible, the second phase of EBRT should be delivered with a small CT planned volume.

PTV for this - GTV+ 10mm margin

1.2. Extended field radiotherapy (EFRT)

For patients with involved common iliac or para-aortic lymph nodes.

The superior border should be extended to accommodate the next echelon of uninvolved nodal regions or at least 2cm beyond the highest involved nodal level.

Radiotherapy Dose

A dose of 45-50.4Gy in 1.8 Gy/fraction in 25-28 fractions, delivered over 5 weeks.

Grossly involved unresected nodes may be evaluated for boosting with an additional 10 to 20 Gy of highly conformal (and reduced-volume) EBRT.

Weekly cisplatin 40mg/m2 (maximum 70mg) for 5 weeks is administered concurrently [1,2,3].

2. Definitive Brachytherapy boost for Cervical Cancer

Purpose: Curative intent boost radiotherapy to the residual tumour following chemo-irradiation to the whole pelvis or extended field radiotherapy. [7,8,9].

Timing: Ideally the chemo-irradiation and brachytherapy is completed with 56 days to optimize local control.

Dose: 80 -90Gy -EQD2 (α/β= 10, EBRT plus brachytherapy) [11,12] Needs to be calculated based on the whole pelvis dose. Some recommended dose regimes offer the minimum dose to point.

2.1. Conventional Brachytherapy

Dose Prescription:

- To Point A
- A minimum dose of 80Gy EQD2 (□/□ = 10, EBRT plus brachytherapy) to be delivered to point A.

Organs at risk (Figure 01)

- Bladder point – to be documented
- Rectal point – to be documented

Applicators:

Tandem: Length to be determined by the uterine sound during the procedure

Ovoids: Size to be determined during the procedure (Small, medium, large)

Vaginal cylinder: To be used for patients with vaginal extension where ovoids cannot cover the entire length of disease.

- **Procedure:**
  - Procedure under anaesthesia is recommended
  - Patient in lithotomy position
  - Do a vaginal examination to assess residual disease and the size of the vagina.
  - If the response is good, proceed with brachytherapy
  - If the response to radiation is suboptimal, either give more time for the tumour to shrink and re-schedule the appointment

EBRT prescribed dose	EBRT (EQD2)	Brachytherapy dose	Total Point A prescription dose (EQD2)
45Gy/25#	44.3Gy	24Gy/3#	79.6Gy
46Gy/23#	46Gy	24Gy/3#	81.2Gy
50.4Gy/28#	49.6Gy	22Gy/3#	80.5Gy
50Gy/25#	50Gy	22Gy/3#	80.9Gy

or abandon brachytherapy and consider further EBRT boost.

- **Bowel preparation:**
  - Laxatives to be started 2 days prior to the inter- vention,
  - Antispasmodics IV/IM before procedure to reduce bowl movement
- **Bladder preparation:**
  - Insert an indwelling catheter into the bladder and instil, 7ml of diluted gadolinium into the balloon and pull the catheter down to bring the balloon against the urethra.
  - Empty the bladder and then instill 50 ml of N/saline prior to MRI scanning
  - The urinary catheter is then left open throughout the entire treatment planning procedure and the 50 ml saline solution is then again instilled prior to the BT delivery process

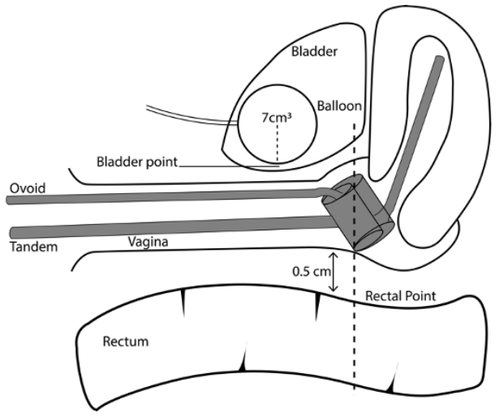

Figure 01.

- **Vaginal preparation:**
- 30–50 cc of the gel injected with a sterile syringe into the vagina until reflux is obtained
  - Dilate the cervix
  - Measure the length of the uterine cavity with uterine sound and select the appropriate tandem. Use ultrasound guidance to prevent perforation if available.
  - Select the most appropriate sizes of ovoids (Small, Medium or Large)
  - Insert the tandem into the uterine cavity and place the ovoids in the vaginal fornix and fix the applicators.
  - Pack vagina with gauze soaked in radio-opaque gel
  - Use rectal spatula to push the rectum away from the vagina
  - Take antero-posterior and lateral radiographs and make sure the applicators are in the**Ideal positioning of applicators:**
- Tandem bisecting the midpoint of the pelvis in both anterior and lateral projections [16]
- Get the most appropriate library plan
- Deliver treatment
- Discharge the patient home

Documentation

1. Document dose at point A

2. Bladder reference point: Draw an antero-posterior line on the lateral radiograph, from the centre of the catheter balloon to the posterior surface of the bladder wall. Document the dose at this point [17]

3. Rectal points: On the lateral radiograph, draw a line from the lower end of the intra-uterine source or the mid source of the ovoid. The rectal point is located 5mm behind the posterior vaginal wall. Document dose at this point.[17]

2.2. Three-dimensional (3D) conformal brachytherapy (GEC-ESTRO recommendation)

Dose Prescription

- Total dose of 80-90Gy (ideally >85Gy) EQD2 (α/β = 10, EBRT plus brachytherapy) to HR-CTVbrachy.
- Total dose of 60Gy EQD2 (α/β = 10, EBRT plus brachytherapy) to IR-CTVbrachy.

- **Target volumes [18] (Figure 2)**

GTVbrachy:

Macroscopic tumour extension at the time of brachytherapy as detected by clinical examination and MRI imaging

High risk CTVbrachy:

GTVbrachy+ whole cervix and presumed extra-cervical extension at the time of brachytherapy as detected by clinical examination and MRI imaging

Intermediate risk CTVbrachy:

HR CTVbrachy + safety margin of 05 -15mm

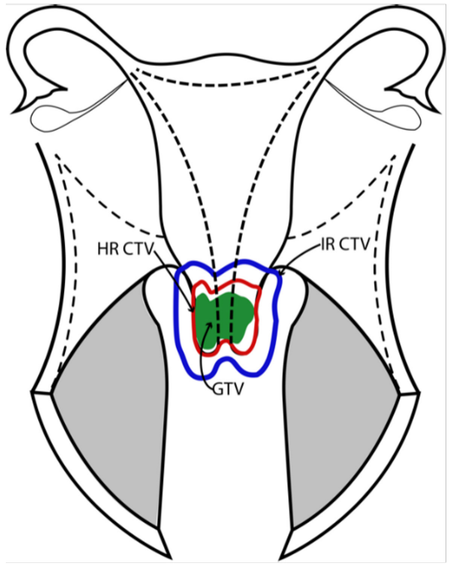

Figure 02

OAR	Dose constraints
Bladder	Maximum: D2cc < 90Gy EQD23 Planning aim: D2cc < 80Gy EQD23
Rectum	Maximum: D2cc < 75Gy EQD23 Planning aim: D2cc < 65Gy EQD23
Sigmoid	Maximum D2cc < 75Gy EQD23
Adjacent bowel	Maximum D2cc < 75Gy EQD23 Planning aim: D2cc< 70Gy EQD23

- **Applicators:**

Applicators should be MRI compatible

- **Procedure:**
  - **As above**
  - The applicators should be further stabilized with sutures as the patient needs to be wheeled to the MRI scanner
- **Documentation:**
  - Doses to High risk CTVbrachy, Intermediate risk CTVbrachyand the OAR maximum D2cc to be documented

[3] CT based 3D conformal brachytherapy

- As MRI is not freely available for brachytherapy planning in Sri Lanka, CT based conformal brachytherapy is an alternative to improve outcomes.
- Simulation: After the insertion and stabilization of the applicators, a CT scan of the pelvis, 3mm slices should be done

- **Dose prescription:**

As per GEC-ESTRO recommendation

- **Target volume**

As the tumour and extension into uterus and adjacent structures cannot be assessed clearly on the CT scan, the target can be defined using clinical information and CT findings as follows;

Target: Entire cervix and the uterus excluding a rind of fundus [20]

OR

GTV: Delineate macroscopic tumour as appropriate as possible [21]

CTV: Add a safety margin of 10mm to GTV

OR

Follow the IBS-GEC-ESTRO-ABS guidelines [22]

OAR:

Same as for GEC-ESTRO recommendations as above [18,19]

[4] Trans abdominal ultrasound scan (TAUS) based brachytherapy

Target: Entire cervix and the uterus excluding a rind of fundus [20]

Postoperative adjuvant chemoradiotherapy/ radiotherapy

Absolute Indications for adjuvant radiotherapy

i. Presence of tumour at the resection margin

ii. More than one node with metastatic infiltration or extracapsular nodal spread

iii. Inadequate surgery such as an incidental finding at simple hysterectomy

a. Post-Surgery - Positive lymph nodes

Patients who have undergone surgery for cervical carcinoma and have positive nodes should be considered for adjuvant treatment with concurrent chemoradiotherapy using platinum based chemotherapy [10].

b. Post Surgery – Negative Lymph nodes

At least two of the following risk factors [4]

i. Lympho-vascular invasion

ii. Deep stromal invasion

iii. Poorly differentiated tumour

iv. Tumour diameter of >4 cm

v. Invasive tumour less than 5mm from the resection margin

NB: Consideration should be given to the relative risks and benefits of treatment for each individual patient. Concurrent chemoradiation should be considered in preference to radiation alone.

EBRT prescribed dose	EBRT (EQD2)	Brachytherapy dose	Total Point A prescription dose (EQD2)
45Gy/25#	44.3Gy	12Gy/2#	60.3Gy
46Gy/23#	46Gy	11Gy/2#	60.2 Gy
50.4Gy/28#	49.6Gy	9Gy/2#	60.5Gy
50Gy/25#	50Gy	8.4Gy/2#	60.0Gy

Post-operative brachytherapy

Indication:

- There is a lack of robust data regarding the advantages of brachytherapy in the adjuvant radiation setting [10, 11]
- Brachytherapy may be considered in the postoperative setting in the presence of a positive or close vaginal mucosal margin.

Technique:

- Using vaginal ovoids or vaginal cylinder to deliver dose to the vault and the proximal 3-4 cm of the vagina

Prescription:

- To the surface of the applicator

Dose:

- Aim to deliver 54-60Gy EQD2 (α/β = 10)
- Brachytherapy dose needs to be calculated based on the whole pelvis dose
- Some recommended dose regimes to offer approximately 60Gy to the vagina.

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Histological Evaluation of Tumour Infiltrating Lymphocytes in DNA Mismatch Repair Deficient Colorectal Carcinoma

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Introduction

Colorectal Cancer (CRC) has been recognized as a major cause of morbidity and mortality worldwide with early detection and prompt treatment, of utmost importance in improving the rate of survival. Colorectal cancer (CRC) is the third most common cancer in the world, affecting 1.93 million people in 2020. It is the second most common cause of cancer-related deaths, causing 935173 deaths (9.4%) in 2020(1).

Currently, three different mechanisms which may occur alone or in combination leading to CRC have been identified as chromosomal instability (CIN), CpG island methylator phenotype (CIMP) and microsatellite instability (MSI). MSI occurs due to inactivating mutations of DNA mismatch repair (MMR) genes responsible for the correction of DNA replication errors. DNA mismatch repair deficiency (dMMR CRC) accounts for around 15% of sporadic CRC cases(2) and lynch syndrome (LS) accounts for 3% of all CRC and is the most common hereditary cause predisposing to CRC(3),(4).

The host immune lymphatic response against dMMR CRC is well known(5) which probably accounts for the better prognosis of such patients(6). The deficiency of the MMR proteins and the accumulation of mutations causing neoantigens is hypothesized to result in immune cell infiltration(7). The tumour infiltrating lymphocyte (TIL) count has been implicated in the prediction of dMMR tumours thus facilitating the selection of patients that require further testing using immunohistochemistry (IHC) or molecular studies. The development of newer anti-cancer medications such as immunotherapeutic agents necessitates criteria for the selection of patients for treatment for which TIL count is considered(8).

Although a well-established method of evaluating TILs has been developed for breast cancer(9), in colorectal cancer the methods of quantification and analysis of the TIL count have highly varied among different researchers. This review compares the different methods used in previous literature which could be of value in developing a universally accepted TIL assessing method for colorectal cancers.

Importance of Detecting

Prediction of prognosis

Studies of the immune response in CRC have shown that infiltration of tumours with T cells has proven to be predictive of better patient outcomes (10),(11). A systematic review and meta-analysis conducted by Idos et al.(6) suggest that TILs and specific TIL subsets serve as prognostic biomarkers for colorectal cancer. The TILs act via the mediation of recruitment, maturation and activation of immune cells which suppress tumour cell growth(6). A significantly better overall survival has been recognized in patients with CRC regardless of dMMR status which demonstrates the importance of evaluation of TILs even if the dMMR status is detected through PCR or IHC(8),(12),(13),(14),(15).

A prognostic index, the 'immunoscore' has been developed which is based on the lymphocyte populations at the tumour invasive front. Specifically, the CD3+/CD45RO+, CD3+/CD8+, or CD8+/CD45RO+ cell concentrations which are detected through IHC which however may not be freely available in many laboratories(10).

Prediction of dMMR CRC (Table 1)

Tumour-infiltrating lymphocytes (TILs) are considered important in the prediction of MSI tumours, which only requires ordinary light microscopy. Identification of dMMR CRC

is valuable in the prognostic assessment, therapeutic consideration, and screening of family members in patients affected by CRC(4). According to the clinical trial KEYNOTE-177, dMMR CRC patients had a significantly longer progression-free survival with the immunotherapeutic agent pembrolizumab rather than chemotherapy when used as a first line agent(16). TILs have been considered as a hallmark of dMMR CRC(14) with a significant association found between the two in many studies(8), (15), (17), (18), (19), (20).

Loupakis et al.(8) used 2 methods of assessing TILs by counting of 5 fields to obtain the average count per HPF and using one single field with the highest count of which both showed significant association with the MMR status.

In a study that used previous CAP guidelines for the evaluation of TILS, a significant association was found between dMMR CRC and TILs. They further assessed the TILs for the loss of each dMMR CRC protein markers, with TILs observed in 72% of the tumours with loss of expression of all markers, 81% of tumours with MLH1/PMS2 loss, 50% of tumours with MSH2/MSH6 loss, and 20% of tumours with isolated MLH1 loss(17).

Greenson et al(19) developed a model for the prediction of dMMR CRC using clinicopathological features. In multivariate analysis, it was found that the TIL count was the strongest predictor of dMMR CRC. In Smyrk et al(20), a TIL count of five as a cut point had shown a sensitivity of 93% and specificity of 62% in the prediction of MSI high tumours. It was deduced that TIL could reduce the number of CRC referred for MSI testing by greater than one-half, and still 93% of the MSI-high carcinomas would be identified. They suggest quantitation of TILs as a simple, single criterion for choosing which CRC cases to test for MSI.

However, one study which used the TIWG method did not find a significant association between the TIL count and the MMR status13. The K-M grading system for the assessment of TILs also did not show a significant association with the TIL count(12),(21),(22).

The therapeutic decision of adjuvant therapy

Knowledge of the MMR status and TIL status facilitates individualized decision-making regarding the treatment of patients(12). The development of successful immunotherapeutic agents necessitates relevant biomarkers for the decision on this type of therapy. TILs have been provided as a useful biomarker of immune checkpoint inhibitor efficacy as evidenced by a study on MSI high metastatic CRC tumours(8). The use of the immunotherapeutic agent pembrolizumab which is a PD-1 inhibitor has been recommended for untreated metastatic dMMR CRC(23).

Methods of Assessing TILs

The above factors show the importance of a standard method of TIL quantification as a method of prognostic indication, therapeutic decision-making, and standardized comparison in research. Earlier studies on the histological features of dMMR CRC have simply considered the presence or absence of TILs(24). TIL quantification could be done by assessing the infiltrating cells in H and E-stained sections or by IHC staining for specific lymphocyte subsets such as CD4+ and CD8+(25). Even newer techniques that utilize PCR assays to detect TILs have been developed for other cancers such as ovarian cancer(26).

The focus of this review is on the different methods used for the quantification of TILs using histology with simple H and E staining which still has no defined standardized method in the context of CRC.

In the determination of the TIL count in CRC various studies have used inconsistent specifications (Table 1). With no clear guidance, quantitative analysis of TILs in H & E-stained sections may be afflicted by low precision and inter-observer variability. A standard and reproducible method for the determination of the TIL count would be of convenience for the pathologists and clinicians dealing with cancer patients as well as for quality research.

Considering previous studies, the area considered for the measurement of TILs mostly were limited to the tumour tissue(8),(11),(12),(13),(15),(17). However, within the tumour, some considered only the stromal tissue13, or the epithelium only(8), (11),(12) while others did not have such specification(15),(20).

Presence or Absence

Much earlier studies(24) have only mentioned the presence or absence of TILs. They mention MSI-high tumours as Replication Errors (RER) positive, MSI-low as RER +/-, and MSS as RER negative cases. RER+ tumours had a significant difference compared to RER– and RER+/- cases with regard to the TILs (p= 0.001).

Counts per high power fields

Earlier studies(5),(15),(20) counted TILs per 10 HPFs, while later studies have used 5 HPFs(8),(11),(14),(19),(27). In Greenson et al.(19), only the cells infiltrating between tumour cells were considered with the cut-off point considered as >5 per HPF. Olevian et al.(18) used the same method for the quantification of TILs though they considered ≥3 as the cut-off point to consider positivity for TILs.

In another study, the total intra-tumoral stromal area was assessed for mononuclear inflammatory cells and expressed as a percentage in the invasive front or areas surrounding the deposits, except for tumour areas with crush artifacts, necrosis, or regressive hyalinization(27).

In two studies using the same method, tumour enriched areas of more than 60% of neoplastic cells were evaluated and average TILs less than two were defined as low-TILs and two or more as high-TILs. However, only the lymphocytes that infiltrate the epithelium were considered, excluding the stromal lymphocytes contrary to the TIWG method(8),(11).

Jimenez-Rodriguez et al.(14), assessed two metrics: the addition of 5 consecutive HPFs parallel to the invasive tumour margin and the highest TIL count in a single HPF within the advancing tumour margin. The intra-tumoral and stromal lymphocytes within the boundary of the tumour were considered, excluding apoptotic bodies. These two values were strongly correlated, and the recurrence-free survival showed a slightly stronger hazard ratio with the highest TIL count. The concordance probability estimate was also higher and the RFS Kaplan Meier curves separate more cleanly for the highest TIL count than for the sum TIL count in 5 HPFs rendering the highest count more useful. Patients with 3 or more TILs had a significantly longer RFS. Therefore, the optimal binary cut-off point was classified as TIL high (≥3) and TIL low (<3).

CAP guidelines (2016)

Previous CAP guidelines (3.4.0.0) of January 2016 recommend counting of intra-tumoral lymphocytes with a cut-off of less than 3 TILs per high power field of ×400 magnification as a mild to moderate response and 3 or more as a marked response. However, with universal recommendations for dMMR testing by many major organizations the evaluation of TILs was removed from later protocols. This method has been utilized by Hashmi et al.(17).

K-M grading

First introduced in 2005, this method assesses H and E-stained sections for lymphoid cells as well as the neutrophilic and eosinophilic granulocytes at the central areas and the invasive margin of colorectal tumours. Thus, assessing both the adaptive and innate components of the immune system. Although high-grade inflammation was observed in a higher percentage in MSI high tumours compared to MSI low or MSI stable tumours, the difference was not statistically significant. This could indicate a more organized and adaptive immune response in dMMR CRC with a more lymphocytic response. This inflammatory score has shown a significant association with the 5-year survival(22).

TILs Working Group (TIWG)

In 2014, the International Immuno-Oncology Biomarkers Working Group initially introduced a standard method for the quantification of TILs in breast cancer(9). This method is comprehensive and thorough and has led to a systematic method for describing TILs in breast cancer that facilitates comparison and standard decision-making.

The same group has further extended their intention to provide a standardized method of TIL quantification to other solid malignancies. They have published articles in two parts on the assessment of TILs in solid tumours. For colorectal carcinoma, separate mention of invasive margin and the central tumour is recommended as the former appears to have the most prognostic significance(28).

Fuchs et al.(13) have adapted the ITWG method in the characterization of TILs in CRC. According to the ITWG method, the density of TILs is assessed in a representative H&E slide, in the stromal compartment of the tumour and scored as a percentage of stromal area, rounded to the nearest 5%. Scores are based on average across the whole slide not concentrating on hot spots. Only TILs within the border of invasive tumour are assessed, and inflammation outside the tumour border is disregarded. All mononuclear cells (lymphocytes and plasma cells) are included as TILs, whereas other inflammatory cells (neutrophils/granulocytes) are excluded. Areas of necrosis and TILs within nests of epithelial cells are excluded.

Findings: TIL Prediction of dMMR CRC	Findings: Survival Data	Technique	Area	Sample	Method	Source
No significant association (p=0.641).	Overall survival was best in TIL high group (p=0.0001)	Reported as a percentage of the stromal area. The average of the stromal TIL density over the entire section, rounded to the nearest 5%.	Stromal compartment, within the borders of tumour.	1034	ITWG system	Fuchs et a.,2020
No significant association (p=0.06)	TIL high, dMMR tumours showed the best overall survival.	In addition to K-M grading, the mean TIL value per hpf was obtained. Then grouped as TIL-high (≥2 TIL/hpf) and TIL-low (<2 TIL/hpf).	Tumour-rich areas. Only the tumour epithelium, excluding the stromal lymphocytes.	83	K-M Grading	Sari et al., 2021
No significant association (P=0.398).	CD3+ T lymphocytes within the cancer cell nests was independently associated with survival (P<0.001),	Inflammatory reaction and the number of lymphoid cells, neutrophilic and eosinophilic granulocytes were assessed by using a four-degree scale.	The invasive margin	228		Park et al., 2016
No significant association (with MSS p = 0.370) and (MSI-L p = 0.206)	Inflammatory score showed a significant association with 5-year survival. (p<0.0001).		Central area and invasive margin.	386		Klintrup et al., 2005
Statistically significant (P < .00001).	Not assessed.	TIL high if ≥4 per HPF.	Tumour-rich areas. Within epithelial compartment.	499	Counted in 5 HPF	Keshinro et al., 2021
Significant association for both measures (P < .001).	Significant association. Five-year RFS was 90.2% (95% CI = 83.7–94.2) in TIL high compared to 78.9% (CI = 74.1–82.9) in TIL low (P < .0001).	TILs counted in 5 consecutive HPFs parallel to the invasive margin. The sum TIL in five HPFs and the highest TIL count in a single HPF.	Intratumoural and stromal area within the tumour.	1095		Jimenez-Rodriguez et al., 2020
Statistically significant (P < .001).	TILs-H patients had better survival (HR = 0.41; 95% CI, 0.14–0.98; p = .046)	Mean value of the count at high-power fields (40×). Grouped as low (<2.0) and high (≥2.0).	Tumour-rich areas. Only the tumour epithelium, excluding the stromal lymphocytes.	85		Loupakis et al., 2020
Significantly associated with TIL high status.	Poor DFS in both TIL-low/dMMR tumours (HR=3.48; 95% CI=1.93 to 6.27; P<0.001) and TIL-low/ pMMR tumours (HR=3.01; 95% CI=1.86 to 4.87; P<0.001).			1265		Williams et al., 2018
Not assessed.	Survival data not assessed.	Percentage of mononuclear inflammatory cells over the total stromal area within tumour.	The invasive front and areas surrounding cancer cell deposits.	163		Jakubowska et al., 2017
Statistically significant (OR, 18.0; 95% CI, 11.2-28.9)	Not assessed.	If TIL/HPF ≥3 considered as positive for TILs and <3 as negative.	The area with the most TILs. Only cells infiltrating between tumour cells, excluding apoptotic cells.	947		Olevian et al., 2017
Statistically significant: Univariate (OR:7.4423, 95% CI: 5.363-10.3278). Multivariate (OR: 3.77, 95% CI: 2.52-5.641).	Survival data not assessed.	The mean TIL/HPF for each tumour was calculated. Cut-off point: >5 per hpf.		1649		Greenson et al, 2009
Statistically significant (p=0.007).	Survival data not assessed.	Sub-grouped into mild to moderate (up to 3 intra-epithelial lymphocytes (IEL)/HPF) and marked (>3 IEL/HPF) according to the CAP guidelines.	Within neoplastic epithelium.	102	CAP guidelines (2016)	Hashmi et al., 2017
Statistically significant (p<0.001).	Univariate analysis - high TIL count and MSI-H status favor age-independent survival. Multivariate analysis – No significant association.	Average count per HPF. TIL 2/10 HPF significant.	Not specifically mentioned.	248	Counted in 10 HPF	Kakar et al., 2004
Statistically significant (P=0.0001).	Not assessed.	TILs per 10 HPF. Cut of point: 5 TILs per HPF.	Randomly selected areas (excluding intramucosal carcinoma).	138		Smyrk et al., 2001
Statistically significant (p=0.01).	Increased IEL was associated with improved overall survival (HR 0.29 (CI 0.09–0.95); p=0.04).	Classified as conspicuous if more than 30 were present per 10 HPF.	Within tumour epithelium.	302		Ward et al., 2001
Statistically significant (p= 0.001).	Not assessed.	TILs present or absent.	Not specifically mentioned.	303	Presence/ absence.	Jass et al., 1998

Pitfalls

Heterogenous pattern

The heterogenous patterns of the tumours have to be taken into consideration when assessing TILS. In a study by Loupakis et al.8, a case initially classified as low TILs was found to be of high TILs on reassessment. They emphasize the importance of careful consideration of heterogeneity of tumours especially when evaluating small biopsies or mucinous tumours.

Interobserver variability

Interpretation errors may occur during the histological assessment among pathologists or even by the same pathologists on reassessment of specimens(18).

Lack of Universally accepted cut-off value

A lack of a universally accepted cut-off to define a robust TIL response has hindered the development of a TIL measurement protocol(14).

Conclusion

Thisreviewexplorestheimportanceandcompares the different methods of evaluation of TILs in colorectal cancer. Even though well established and widely utilized in breast carcinoma, currently, there is no standardized method of assessing TILs in colorectal cancers. The K-M grading method used by few studies considers inflammatory cells other than lymphocytes and has proven to be a significant predictor of survival while having a poor association with dMMR tumours. Thirteen other studies which have used a count of TILs per high power fields with varying specifications demonstrate statistically significant association with the MMR status. Only one study has used the ITWG method which is established and universally used for the evaluation of breast carcinoma. Although the group has recommended the separate mention of the invasive margin in colorectal cancers, this study considers the average presence of lymphocytes across the whole slide. This also shows a significant association with survival although no significant association was found with MMR status. Further studies evaluating the association between the ITWG method for colorectal cancers may be suggested as it is clear and methodical.

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Clinicopathological analysis of breast cancers, in a single unit of a Sri Lankan Tertiary Care Hospital.

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Key words: *Breast Cancer, Clinico-pathological features, axillary nodal spread.*

Abstract

Introduction and objectives:

Breast cancer is the most common cancer in females in the developed world and Sri Lanka. The purpose of the study was to analyse the distribution of clinicopathological factors and their association with lymph node status.

Materials and Methods:

A retrospective analysis was carried out among 125 female patients with breast carcinoma or ductal carcinoma in situ (DCIS) presenting to University Hospital, Kotelawala Defence University (UH KDU) from May 2019 to July 2021.

Results

Most affected age group was 55-65 years (n = 30). The mean age was 60.45 years (SD=14.02). The mean tumour size was 3.59 cm (SD=2.17). Most of the cases (88%) were Infiltrating ductal carcinomas NOS, 4% DCIS, 3.2% Invasive Papillary carcinoma, 1.6% were invasive lobular and 0.8% were tubular carcinomas. Mostly, (67.22%) the histological grade was grade 2, 22.68% were grade 1 and 10.08% were grade 3. The mean lymph node harvest was 17.79 (SD 6.58) and only 43.2% of tumours had nodal spread (pN1-28.00%, pN2-8.8%, and pN3 6.40%). Hormone receptors were negative in 27.77% and 71% of patients has estrogen receptors (ER) and only 46.66% had progesterone receptors (PR). In this series, lymph nodes spread had no association with tumour size, grade, or ER/PR status ($p > 0.05$). There was an insignificant correlation of axillary nodal status with Ki67 proliferative index ($r = 0.285$)

Conclusion

In our study population most affected age group was the 55-65 age group with grade 2, IDC/NOS being the commonest histologic type. Most were >3 cm and lymph node involvement were less than 50%. We failed to demonstrate any association between lymph nodes status with tumour size, grade, or ER/PR status in this study.

Clinicopathological analysis of breast cancers, in a single unit of a Sri Lankan Tertiary Care Hospital.

Introduction and Objective

Breast cancer is the most frequent cancer in females, both in developed and developing regions including Sri Lanka [1, 2]. Breast cancer mortality rates have also increased in the past 20 years in almost every country. One of the most striking features of breast cancer is the variation in both incidence and mortality across countries [1]. The age-standardized rates of breast cancer incidence in South Asia including Sri Lanka are significantly lower compared to developed North America and European regions [1, 2]. Although multiple reasons are attributed to these variations observed globally, it is accepted that both genetic and sociocultural factors contribute to these differences [3, 4].

The triple assessment to the diagnosis of breast carcinoma, with clinical examination, imaging mammography with ultrasound and fine-needle aspiration cytology (FNAC), has an accepted place, however, FNAC is being replaced by core needle biopsy in many centres [5]. The traditional pathological factors of lymph node status, tumour size, histological type, lymphovascular space invasion and histological grade are the most useful prognostic factors in breast cancer patients [6-8].

Approximately 4% per year increase in Breast Cancer incidence is observed in Sri Lanka over the last 10 years and this was attributed to the rapid increase of breast cancers in the postmenopausal population of females [9]. Breast cancer incidence is around 70/100,000 in the patient of 60–65-year age group while the overall incidence is 20/100,000 [9].

There are many patient factors and disease factors that affect the prognosis and outcome of breast cancer. Patient characteristics like age, race, socioeconomic status, education and language barrier are also contributory factors affecting treatment and ultimately the outcome of breast cancer [10]. Moreover, tumour characteristics like high grade, large tumour size, axillary nodal involvement, and negative hormone receptors had a higher risk of recurrence or death [11, 12].

This study was conducted to describe the clinic pathological profile and associations of the patients with breast carcinoma, as well as relevant macroscopic and microscopic features, of the histology specimens with associations with axillary nodal status in patients who underwent breast surgery for breast carcinoma at a University Hospital in Sri Lanka.

Methodology

Study design

This was a cross-sectional analytical design

Study population

All biopsy-proven breast cancer patients undergoing breast surgery in the University Hospital Kotelawala Defence University (UH KDU), diagnosed with breast cancer during the period of 01 May 2019 to 31 July 2021 were included. All patients have undergone either breast conservative surgery or mastectomy with a minimum of level II axillary nodal dissection.

Study setting

This study was conducted at the Departments of Surgery, Oncology and Histopathology, at UH KDU.

Data collection

The clinical and investigational data were collected from patient's hospital records for sociodemographic data such as age, educational status, income and menopausal status.

The pathology specimens were assessed with H&E and immunohistochemistry for receptor studies of ER, PR, HeR2Neu and Ki67 LI. All patients had standard treatment according to the stage and other findings following the MDT meeting.

Data analysis

Continuous variables were expressed using mean and standard deviation while discrete variables were expressed using numbers and percentages.

The data were analysed with Stata 17 version for Windows.

A sample of 125 breast cancer patients with a 95% confidence interval and a 9% margin of error as for the national annual incidence is 3592 cases (incidence 28.1/100,000) will make the power of the study 82% [2].

Ethics

Ethical clearance for the study was obtained from the Ethical Review Committee of the Kotelawala Defence University (KDU)

Results

The average age of the study population was 60.45 years with a standard deviation of 14.04, the interquartile range from 49-72.5 and the age ranged from 31 to 94 years **(Table 1 and Figure 1)**. The age distribution showed that most patients were clustered around the 45-65 age group and a peak was observed at 55-65 years, **(Table 1 and Figure 1)**. A second small peak was also observed at the 75-85 age group (Figure 1).

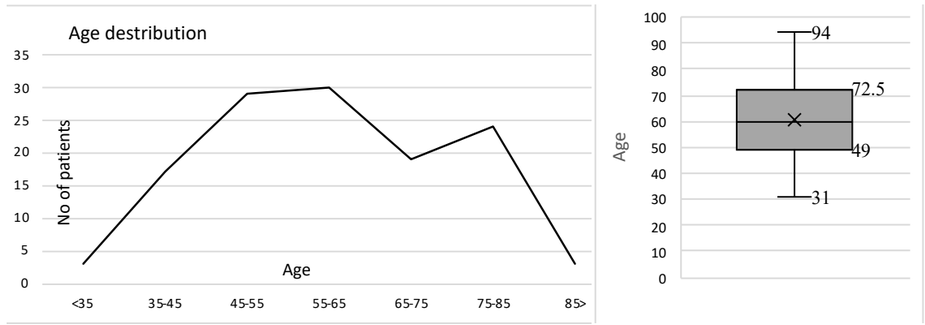


Figure 1: Age distribution charts of the study population ranged from 31 to 94 with a mean of 60.45 years and SD of 14.04.

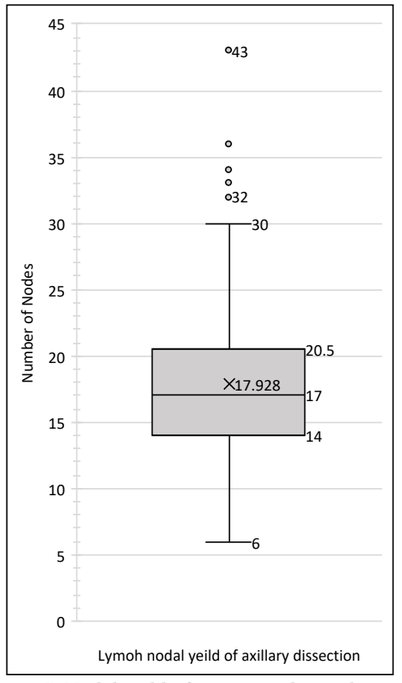


Figure 3: Nodal yield of patients who underwent axillary nodal dissection

The tumour size of the study population ranged from 0.2cm to 11cm with a mean of 3.58 cm and a standard deviation of 2.17. The majority of the cases in this study population (80 cases, 64%) had T2 tumours, 20 (16%) cases were T1 or less, 23 (18.4%) patients had T3 (Table 1 and Figure 2) and 2 patients (1.6%) were pT4.

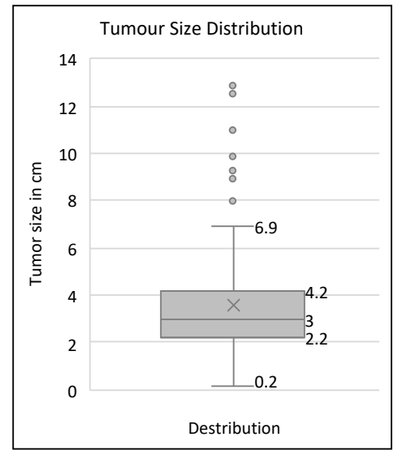


Figure 2: Tumour size of the study population. Median 3cm with an interquartile range from 2.2 to 4.2cm

Most of the cases (88%; 110 cases) were histologically diagnosed as Invasive Ductal Carcinoma NOS (Not Otherwise Specified). All the other histological types were observed only in 15 cases (12%). The most common histology was grade 2 tumours (80 cases- 67.22%). In situ carcinomas were found only in 5 cases (4%) and

all were ductal carcinoma in situ (Table 1).

The average lymph node harvest of level II axillary nodal dissection was 17.93 nodes per case with a standard deviation of 6.34 and an interquartile range of 14-20.5 (Figure-3).

Axillary lymph nodes were negative for metastasis in more than half the patients (56.80%). Among those patients with nodal involvement, 28.00% were in the pN1 stage, 8.80% were in pN2 and 6.40% were pN3 (Table 1).

Relationship between breast cancer features and axillary lymph node metastasis (Table 2)

Axillary lymph nodal status remains the main prognostic factor of breast cancer survival. We assessed the association of axillary nodal status with pathological features of tumour size, grade and hormonal status.

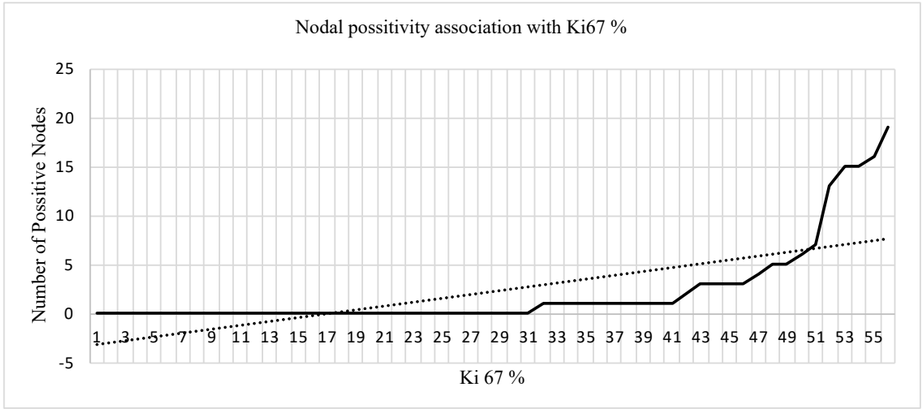
The T stage (p=0.165, Df =2) and grade (p=0.502, Df 2) of the tumour had no association with nodal status.

Among the 125 breast cancer cases, only 119 had invasive cancer which can be graded from grade 1 to 3. In this patient population, hormone receptors were traced only in 90 patients and Her2Neu were traced only in 65 patients. We could not find any significant association of axillary nodal status with hormonal receptor status or Her 2 Neu receptor overexpression (ER - p=0.111Df 1, PR - p=0.651 Df 1and Her2Neu p = 0.709).

However, the Ki 67 proliferative index had only a weak positive correlation with the number of positive nodes (correction coefficient r = 0.2855) (Figure 4).

Table 2 - Associations of lymph node status with tumour characteristics

Tumour character assessed	Nodal Status			χ^2 - p-value
T stage	**Node -ve**	**Node +ve**	**Total**	
T1	12	8	20	
T2	49	31	80	
T3	10	15	25	
Total	71	54	125	0.1649132
Tumour Grade				
G1	16	11	27	
G2	42	38	80	
G3	8	4	12	
Total	66	53	119	0.5062697
ER status				
ER+	34	30	64	
ER-	9	17	26	
Total	43	47	90	0.1110809
PR status				
PR+	19	23	42	
PR-	24	24	48	
Total	43	47	90	0.6518492
Her2 status				
Her2 +	5	5	10	
Her2 -	24	31	55	
Total	29	36	65	0.7096056



Discussion

Breast cancer is a clinically, pathologically and prognostically heterogeneous disease [3]. The tumour size, histological grade and prognostic biomarkers are different in different parts of the world [3, 4, 13 -15].

Histological grade has a significant influence over cancer-specific survival and disease-free interval of breast cancer [16]. In the Breast, cancer is uncommon before 25 and after 85, the peak incidence is between 45 and 60 studies of breast cancer survival in Sri Lanka in a large cohort of 2104 patients, J. Balawardena et.al. indicated 56% were grade 2 tumours, 30% were grade 1 tumours and 14% were grade 3 and an Iranian study with 366 patients also show similar results [6, 17]. However, in most Western World studies like the study done by Rakha E. et.al. in the UK with 2219 patients showed a higher proportion of grade 3 tumours in 45.6% patients with 35.6% of grade 2 and 18.6% of grade 1 tumours [7,16,18]. The histological tumour grade of this population was closer to the previous Asian and Sri Lankan studies with 67.22% of patients were having grade 2 tumours could be due to similar genetic or socio-cultural reasons. Similarly, tumour size at presentation also varies, in previous studies the most frequent tumour stage is T2 and T3 in most Western and Asin studies [16, 19-21]. In this study the most frequent tumour size encountered was T2. This may be due to a good education level and cancer awareness among individuals compared to other Asian countries.

Adequate nodal harvest is a vital requirement for interpreting the axillary nodal status in breast cancer following axillary nodal dissection [22-24]. The mean nodal retrieval in this study was17.93 with an interquartile range of 14-20.5, which is well above the standard minimum. This above-average nodal harvest could attribute to the fact that only consultants trained in surgical oncology perform all the oncological surgical procedures in UH KDU.

It is a widely accepted fact, that the axillary nodal status is the best independent prognostic factor and it is one of the vital components in the treatment planning of breast cancer patients [25-27]. The associations of pathological features and prognostic biomarkers with axillary nodal status has been extensively studied. Tumour size has shown a positive correlation with axillary lymph nodal status in most of the previous studies [19,21,28-30]. However, a study with 819,647 patients has shown the relationship between tumour size and lymph node status is not linear and tumours smaller than 10 mm and tumours larger than 60 –90 mm has a weak correlation with metastasis [19]. Some previous studies have shown tumour grade has a significant association with the axillary nodal status [16,20,31]. Some other studies have shown there is no significant association between tumour grade with axillary nodal status [21,32-34]. We failed to observe any association with tumour size or grade with axillary nodal status in this study population. This observation is shared by another study conducted in India by Ahmad Z, Khurshid A et.al. [35].

Prognostic biomarkers such as hormone receptor status, Her2Neu overexpression and Ki67 proliferative index has also shown variability with axillary nodal status. The ER/PR hormone receptors and Her2Neu amplification status showed significant association with axillary nodal status in some studies [10,28-31].

In contrast, other studies have indicated that there is no significant association with hormone receptors or Her2Neu amplification with axillary nodal status [21, 32, 36 - 39]. This study has not shown any statistically significant association with hormone receptor status and Her2Neu amplification with axillary nodal status. Ki67 index >20% compared to <20% has not shown any significant association with nodal status [21,36,39]. This study also failed to demonstrate any statistically significant difference in Ki 67 and axillary nodal status from the Chi-square test (p = 0.434). Probably Ki index was not available in 60 patients we could only assess 65 patients. Nevertheless, the correlation coefficient has shown a weak positive association with Ki 67 percentage with the number of nodes (r = 0.283)

Table 1 - Socio-demographic and Pathological Characteristics of tumour

Socio-Demographic Features				**Pathological Features**		
Age	**No of patients**	**%**		**Pathological T stage**	**No of Patients**	**%**
<35	3	2.4		pT1a	1	0.8
35-45	17	13.6		pT1b	3	2.4
45-55	29	23.2		pT1c	16	12.8
55-65	30	24		pT2	80	64
65-75	19	15.2		pT3	23	18.4
75-85	24	19.2		pT4	2	1.6
85>	3	2.4		Histology Type	No	%
Educational Level				IDC (NOS)	110	88
Primary	4	3.2		ILC	2	1.6
GCE O/L	32	25.6		IPC	4	3.2
GCE A/L	81	64.8		Tubular Carcinoma	1	0.8
Graduate	6	4.8		Mucinous Carcinoma	3	2.4
PG	2	1.6		DCIS	5	4
Monthly Income				Tumour Grade	No	%
<20,000	16	12.8		Grade 1	27	22.69
20,000-50,000	69	55.2		Grade 2	80	67.22
50,000-100,000	30	24		Grade 3	12	10.08
>100,000	10	8		Lymph node status	No	%
Menopausal Status				pN0	71	56.8
Pre	30	24		pN1	35	28
Post	95	76		pN2	11	8.8
Side				pN3	8	6.4
B/L	10	8			No	%
Right	63	50.4		ER+	64	71.11
Left	52	41.6		ER-	26	28.89
Site of tumour				PR+	42	46.67
Central	11	8.80		PR-	48	53.33
UOQ	48	38.40		Total	90	
UIQ	22	17.60				
LOQ	17	13.60		Her2 +	10	15.38
LIQ	11	8.80		Her2 -	55	84.62
MF	3	2.40		Total	65	
Not Mentioned	13	10.40				

Conclusion

In this study population, the most affected age group with breast cancer was the 55-65 age group, most tumours were more than 3 cm and axillary lymph node involvement were less than 50% of patients. Grade 2 invasive ductal carcinoma was the commonest histologic type,

We failed to observe any association with lymph nodes status with tumour size, grade or prognostic biomarkers such as ER/PR, Her2Neu and Ki 67 index, in this series of patients.

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Descriptive analysis of demographic, clinical, and outcomes data of children admitted over a one-year period to the Paediatric Intensive Care Unit of the National Cancer Institute Sri Lanka

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Key words: *Paediatric intensive care, admissions, Paediatric cancer patients,*

Abstract

Introduction

National Cancer Institute Sri Lanka (NCISL) has the only dedicated childhood cancer unit for the whole of Sri Lanka and receives more than 750 new children a year. Improvement of supportive care including intensive care forms a major component in any initiative to improve childhood cancer outcomes in a country. This study was conducted to understand the current status of demographic, clinical, and outcomes data of children admitted to the Paediatric Intensive Care Unit (PICU) while on treatment for cancer at the NCISL.

Methods

This is a retrospective cohort study of all patients 0-19 years of age and those with a diagnosis of a malignant cancer admitted to the PICU of the NCISL from 1st January to 31st December 2020. Data were extracted from the clinical records and PICU admissions book and analysed using descriptive statistics.

Results

227 individuals were admitted to the PICU of the NCISL during the study period and 57% were males. Largest age group was 0-4 years (38%) and the commonest diagnosis was Leukaemia (68%). In univariate analysis, only the diagnosis was significantly associated with admission to the PICU. Neutropenic sepsis (50%) was the commonest reason for admission to the PICU closely followed by respiratory infections (20%). The mortality rate of patients admitted to the PICU was 28% and 34% of them died on the first day of admission. For the patients who were discharged alive from the PICU, the median stay was 4 days (IQR 1- 7).

Discussion

As seen in other countries, the majority of patients admitted to the PICU were children with leukaemia and sepsis was the leading cause of admission. The high percentage of deaths within 24 hours of admission suggests that patients may be identified too late as needing intensive care and the high rate of discharges within a day of admission suggest that many patients are admitted unnecessarily. Therefore, there is a need for establishing a mechanism to identify patients needing admission objectively and promptly to intensive care.

Introduction

Childhood cancer is highly curable group of cancers that often need intensive treatment at presentation to achieve successful outcomes (1). These successes depend on early detection, appropriate treatment, and adequate follow-up. Appropriate treatment refers not only to cancer-directed care but also to supportive care treatment that is necessitated by the disease conditions as well as treatment-related morbidity. Therefore, Paediatric Intensive Care Units (PICU) play an important role in the treatment of children with cancer.

National Cancer Institute Sri Lanka (NCISL) is a dedicated cancer hospital in Sri Lanka that receives more than 20,000 new patients a year (2). The NCISL also hosts the only childhood cancer unit for the entire country and treats around 750 new children diagnosed with cancer each year (3). The Paediatric department of NCISL consists of 125-bed inpatient unit, a 15-bed outpatient treatment unit, and a 4-bed PICU. It is staffed by 2 paediatric oncologists, 2 clinical oncologists, a paediatrician, 54 nursing officers, and 34 support staff.

World Health Organization (WHO) launched the Global Initiative for Childhood Cancer (GICC) to improve outcomes of children with cancer. Sri Lanka was selected as one of the focus countries for the South-East Asia region of the WHO in 2020. In our quest to improve outcomes of children with cancer in Sri Lanka, improvement in supportive care facilities including intensive care is identified as a key area.

However, currently, there is no published data regarding demography, disease status, and outcomes of children admitted to the PICU of NCISL. These data are essential in identifying the baseline status, against which future quality improvements may be measured against. Therefore, this study was designed and carried out to find out the current demographic, clinical, and outcomes of children admitted to the PICU of the NICSL.

Patients and Methods

Setting - At the NCISL all patient data are recorded manually in a patient clinic record and all admissions and discharges to the PICU are entered into the "Ward Admission Registry". All data pertaining to this study were extracted from these two sources using a structured case report form.

Eligibility Criteria –

All patients admitted to the PICU from 1st January 2020 to 31st December 2020 with a diagnosis of histologically proven or radiologically or clinically suspected malignancy were included in this study. When considering new admissions to the paediatric oncology wards, only patients who were on active treatment or patients who are within 6 months of completion of treatment were considered. All patients admitted for routine investigations were excluded. Patients with a benign diagnosis and who were more than 18 years of age at the time of admission to the PICU were excluded.

All data were manually collected by trained abstractors using a standardized questionnaire. Data was validated in 10% of patients by a board-certified medical consultant.

Only aggregate data are presented in this study.

Statistical analysis –

Data was analysed using SPSS statistical software version 20.0 and categorical variables are presented as counts and percentages. Chi square test was used to test the significance of differences between demographical data.

Results

Demographic and disease data –

227 individuals were admitted to the PICU of the NICSL during the period. Boys formed the majority of these admissions, and the commonest age group was 0-4 years. Children with Leukaemia dominated the admissions.

ALL – Acute Lymphoblastic Leukaemia, AML – Acute Myeloblastic Leukaemia, CNS – Central nervous System

Out of the total individual admissions during this period, 29.9% of patients were admitted to PICU at least once during the study period. However, age or sex were not significantly associated with PICU admission while a diagnosis of leukaemia was significantly associated.

	Patient count	Percentage
Sex		
Male	128	57%
Female	99	43%
Age (Years)		
0-4	78	38%
5-9	56	25%
10-14	48	21%
15-19	45	20%
Diagnosis		
ALL & AML	154	68%
Lymphoma	11	5%
Sarcoma	17	7%
CNS tumours	17	7%
Other	28	12%

Table 1- Demographic data

Table 2 – Total number of ICU admissions as a percentage of total admissions to ward.

	Total Number of admissions	ICU admissions	Percentage (%)	p
Sex				
Male	404	128	31.6	0.265
Female	354	99	27.9	
Age (Years)				
0-4	272	78	28.6	0.3211
5-9	168	56	33.3	
10-14	185	48	25.9	
15-19	133	45	36.0	
Diagnosis				
ALL & AML	290	154	53.1	< 0.00001
Lymphoma	88	11	12.5	
Sarcoma	112	17	15.1	
CNS tumours	100	17	17.0	
Other	168	28	16.6	

70% of all admissions to the PICU were due to infections. Other major reasons for admission were neurological conditions including seizures and tumour lysis syndrome. The reasons for admission were evenly distributed across all major disease groups.

Reason for admission	Patient count	Percentage
Neutropenic Sepsis/ Shock	115	50%
Respiratory infections	45	20%
Tumour lysis syndrome	9	4%
Fits/Neurological conditions	34	15%
Hypersensitive reactions	6	3%
Other	19	8%

Table 3 - Reasons for PICU admissions

Outcome	Patient count	Percentage
Discharged	164	72%
Died in ICU	63	28%

Table 04: Clinical Outcomes

Mortality rate in the PICU was 28% and out of them more than a third died on the same day of admission.

Number of days	Patient count	Percentage
1 Day	22	34%
2-4 Days	18	28%
5-7 Days	13	18%
8-10 Days	5	9%
More than 10 Weeks	5	9%

Table 5 – Number of days in ICU before death

Out of all admissions who were discharged alive more than 21% were discharge within the first 24 hours of admission. Median stay in PICU for these patients was 4 days (IQR 1- 7).

Days	Patient count	Percentage
1 Day	35	21%
2-4 Days	56	34%
5-7 Days	39	24%
8-10 Days	18	11%
More than 10 Weeks	16	10%

Table 5 – Number of days in ICU before discharge

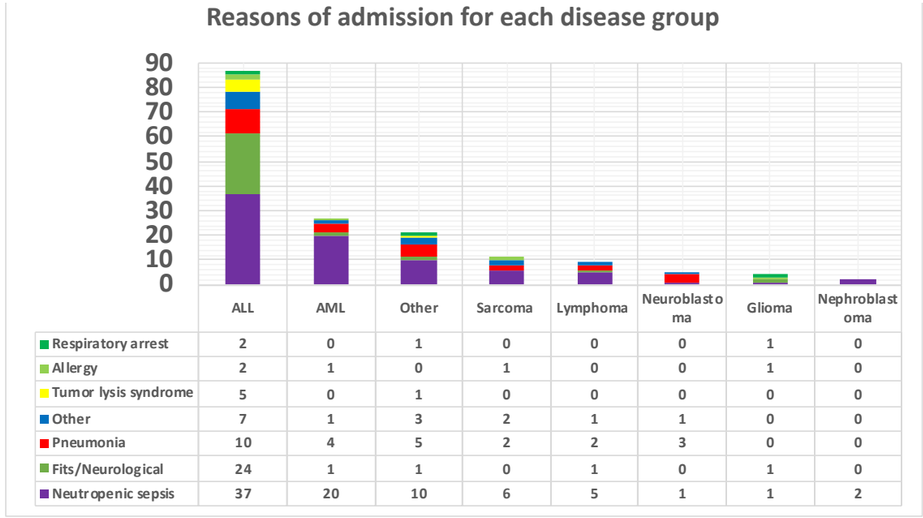

Figure 1 . Reason of admission for each disease

Discussion

This retrospective study described one of the largest cohorts of paediatric oncology patients admitted to the PICU. Patients with leukaemia (ALL and AML) were more likely to be admitted to the PICU at least once during their treatment course when compared to patients with other malignancies. Similar picture was seen in many other countries (4) and may be due to the severity of their illness at presentation, intensive treatment regimens used and relatively long duration of treatment. This is especially important considering that leukaemia is the most prevalent childhood cancer globally.

The commonest reason for admission was infective causes with respiratory infections dominating. This is expected in the Sri Lankan setting where there is severe congestion in the in-patient wards. However, a similar observations were seen in many other low- and middle-income countries (5),(6) as well as high-income countries (7). We would suggest expanding physical space in paediatric wards of the NCISL and adopting an antibiotic treatment protocol as key steps in addressing this problem.

During the period under observation PICU mortality rate was 28% at the NCISL. This is better than some of the other low- and middle-income countries including Pakistan (42%) (8) and Egypt (40%) (6). However, there may be a significant number of unnecessary admissions to the PICU and therefore, the mortality rates could be artificially diluted.

It is also observed that 34% of all deaths that occurred in the PICU happened within the first 24 hours of admission. This would suggest that these patients were too sick to be rescued when they received intensive care support. This could be due to a dearth of PICU beds for childhood cancer patients. However, we also note that 21% of patients were discharged within 24 hours of admission as well. One reason for this is that these patients did not require admission to PICU, and a better assessment process could have filtered these patients out. Therefore, in our setting, there seem to be a need for a better selection process for admission to the PICU to ensure maximum use of a scarce resource. Paediatric Early Warning System (PEWS) is used in many paediatric centres to identify clinically deteriorating patients early and escalate care. PEWS has been validated in childhood cancer settings (9) , can be implemented in the low resource setting (10),(11) and is highly cost effective (12). Therefore, we propose the implementation of PEWS in the paediatric department of the NCISL.

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Diagnostic utility of ultrasonography and fine needle aspiration cytology in the pre-operative assessment of suspicious thyroid nodules

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Key Words: *TIRADS, thyroid cytology, ultrasonography, Bethesda system*

Abstract

Introduction

The incidence of thyroid cancer in Sri Lanka has risen over the last two decades. According to current national cancer statistics, it has become the second most common cancer in females. Ultrasonography and fine needle aspiration cytology (FNAC) are pre-operative investigations that are useful to assess the nature of thyroid nodules. Although a majority of thyroid nodules are benign, it is vital to identify suspicious nodules pre-operatively to guide the most appropriate treatment.

The aim of the study was to determine the diagnostic utility of ultrasonography and FNAC in the pre-operative assessment of suspicious thyroid nodules.

This descriptive cross-sectional study conducted at the Colombo South Teaching hospital and Department of Pathology, University of Sri Jayewardenepura, enrolled 135 patients with ultrasonically suspicious thyroid nodules. Ultrasound-guided FNAC samples were collected from each patient for cytological assessment. TIRADS (Thyroid Imaging Reporting And Data System) classification was used for radiological assessment and the Bethesda system for cytological interpretation. Data were analyzed using the SPSS 23 software.

The mean age of patients was 49.8 years (range 15-76). The majority of the patients were female(81%) while 19% were male. Eleven FNAC specimens were excluded from the study due to insufficient cellularity.

Classification of the cases according to ultrasound findings showed that the majority of the patients (51.61%, n=64) belonged to TI-RADS 3 (mildly suspicious). Thirty-nine (31.45%) patients had moderately suspicious nodules (TI-RADS 4) and 21 cases (16.93%) were highly suspicious (TI-RADS 5).

Conclusion

TI-RADS 5 category had the highest sensitivity and 100% concordance between the cytology and ultrasonography results.

Introduction

Over the past few decades, the incidence of thyroid malignancy has trended upward across the world (1),(2). However, the thyroid cancer burden is largely heterogenous in different parts of the world, possibly due to variability of the genetic mutations, environmental risk factors, educational level, and availability of health care facilities (3),(4). In Sri Lanka, thyroid malignancy is the second most common cancer in females (5).

As the incidence of thyroid cancer is rising it is necessary to have minimally invasive and reliable first line investigations to decide the management plan. Ultrasound imaging technique is the most frequently used pre-operative diagnostic test (6),(7). Sonographic findings in certain cases could be non-specific, and a definitive diagnosis is most often obtained from the fine needle aspiration cytology technique (FNAC), (8).

It is important to adhere to a standardized reporting system when interpreting sonographic findings. To address this issue, several institutions have recently proposed a risk stratification system known as Thyroid Imaging And Data System (TI-RADS), following the principles of the widely accepted BI-RADS model for breast imaging (9). Over the past few years, the TIRADS recommended by the American college of radiology (ACR TI-RADS) gained popularity as this system was able to unify the language between the clinicians, radiologists and pathologists (10).

Ultrasonography is followed by Fine Needle Aspiration Cytology (FNAC) when necessary (11). Interpretation of thyroid cytology findings is done according to the recommendations of the "Bethesda system of reporting thyroid cytology"(12). This system also helps to maintain uniformity when assessing FNAC smears and stratify patients according to the risk of malignancy (13).

The ultimate goal of these standardized diagnostic tests is to provide evidence based recommendations for the clinicians to decide the best management plan.

Objective

The aim of the study was to evaluate the diagnostic utility of ultrasound based TI-RADS findings and thyroid cytology results in the pre-operative assessment of suspicious thyroid nodules.

Methodology

A prospective study done over a period of 3 years (June 2018 to June 2021) at the department of radiology and department of pathology, Colombo South Teaching Hospital, Sri Lanka and the department of pathology, Faculty of Medical Sciences, University of Sri Jayewardenepura enrolling 135 patients with radiologically suspicious thyroid nodules.

Ethical clearance for the study was obtained from the Ethics Review Committee of the Faculty of Medical Sciences, University of Sri Jayewardenepura (65/19) and the informed written consent was obtained from all the participants prior to collecting the samples.

Ultrasonography of thyroid nodules was performed by a team of experienced radiologists and reported according to the ACR TI-RADS classification.

Fine Needle Aspiration cytology specimens were collected from the radiologically malignancy suspected thyroid nodules using 23/24 gauge needles. Thereafter, thin smears were prepared from the aspirate and immediately fixed in 95% alcohol for 20 minutes and stained with hematoxylin and eosin. Cytopathological assessment was done by two independent consultant pathologists following the guidelines of the "Bethesda system of reporting thyroid cytology". The data was analyzed using SPSS version 23 to determine the accuracy of radiological and cytological results and the concordance between the two methods.

Results

Study included patients with radiologically suspicious thyroids that were reported as TI-RADS 3 (mildly suspicious), TI-RADS 4 (moderately suspicious), or TI-RADS 5 (highly suspicious). Initial sample size was 135, however 11 cases had to be excluded from the study following guided FNAC, due to poor cellularity of the cytology smears precluding accurate assessment. Final sample size was n=124. Age range of the patients was 15-76 years with a mean age of 49 years. Majority of the patients were females (81%) while 19% were males.

In the current study, radiologically suspicious thyroid nodules were more frequently found in the 3rd to 6th decade of life. The patients in this age group were approximately 80% of the study sample. Distribution of the patients with suspicious nodules according to ultrasound findings showed that the majority of the patients 51.61% (n=64) belonged to TI-RADS 3 (mildly suspicious). Thirty nine (31.45%) patients had moderately suspicious nodules (TI-RADS 4) and 21 cases (16.93%) were highly suspicious (Figure 1).

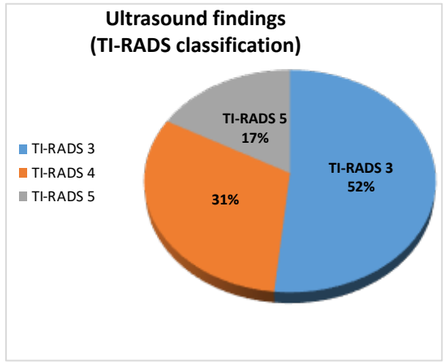

Figure 1

US guided FNAC results of the patients with suspicious nodules were categorized according to the Bethesda system of reporting (figure 2). Fifty five (44.35%) out of 124 suspicious nodules were reported as Bethesda 2 (benign). Twenty six cases (20.96 %) were reported as Bethesda 3 and 15 cases (12.09 %) as Bethesda 4.

Seventeen cases had (13.7 %) cytological features suspicious of malignancy and eleven (8.87%) were reported as malignant (Bethesda 6).

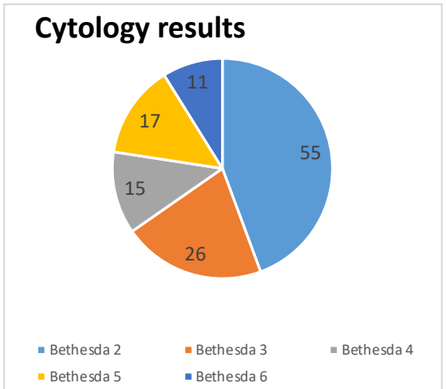

Figure 2 Thyroid cytology results (Bethesda classification)

Further to the analysis of thyroid cytology results, TI-RADS findings of the 124 patients were correlated with the FNAC results (table 1).

TIRADS system for Reporting	Bethesda System of Reporting					Total
	2	3	4	5	6	
TR 3	40	15	08	01	0	64
TR 4	15	11	07	04	02	39
TR 5	00	00	00	12	09	21
Total	55	26	15	17	11	124

Table 1 TI-RADS and thyroid cytology results

Out of 64 cases with TI-RADS 3, only one case (1.56%) was reported as Bethesda 5 (suspicious of malignancy). Remaining cases (n=40) were in Bethesda 2 (benign), Bethesda 3 (n=15) and eight in Bethesda 4 categories.

Thirty nine out of 124 had moderately suspicious nodules (TI-RADS 4), out of which 4 were in Bethesda 5 and 2 in Bethesda 6 categories. A significant number was in Bethesda 2 / benign category. The percentage of cases in Bethesda 5 and were 06 was 15.38%.

TI-RADS 5 had 21 cases, and 12 were reported as suspicious of malignancy (Bethesda 5) and 09 as malignant (Bethesda 6). None of the cases in TI-RADS 5 were cytologically reported below the level of Bethesda 5.

Risk of malignancy (Bethesda 5 & 6 cases) in TI-RADS categories are given below (figure3).

Discussion

A wide spectrum of diseases give rise to enlargement of the thyroid gland which results in the development of a diffuse or nodular goiter (14). However, in the majority of cases the cause of thyroid enlargement is due to a benign pathological entity (15). Ultrasonography of thyroid is a popular, first line investigation to identify the suspicious nodules that need further investigations. Several important criteria have been suggested by different institutions and organizations to maintain uniformity in the interpretation of ultrasound findings of thyroid.

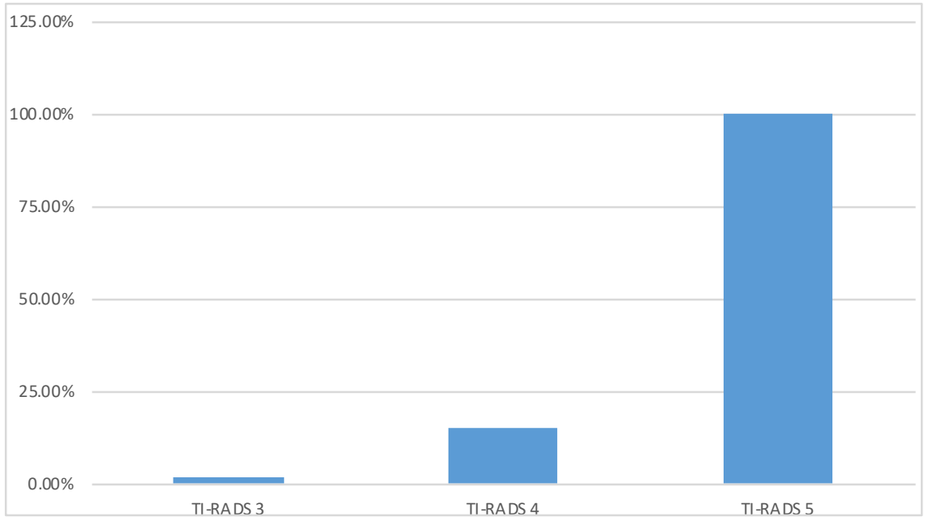

Figure 3 TI-RADS 3- 1.56%, TI-RADS 4 - 15.38%, TIRADS 5- 100%

The current study followed the ultrasonographic features recommended by the American college of radiology (ACR TI-RADS), and the key imaging features that were taken into consideration included composition of the nodule, echogenicity, shape, and margin of the nodule. Based on the ultrasound features American college of radiology classify the nodules in to TI-RADS 1 (benign), TI-RADS 2 (not suspicious), TI-RADS 3(mildly suspicious), TI-RADS 4 (moderately suspicious) and TI-RADS 5 (highly suspicious) categories. Higher the total score greater the TI-RADS group and the possibility of malignancy (16). Above classification helps to standardize the ultrasound results.

The current study was based on radiologically suspicious nodules belonging to TI-RADS 3, 4 and 5 categories. TI-RADS 1 and 2 categories include “benign” and “not suspicious” lesions and according to ACR recommendations FNAC is not recommended.TI-RADS 6 includes proven malignant nodules and was not considered in this study (17).

US guided FNAC samples of the suspicious nodules were reported according to the Bethesda guidelines. This system includes six different categories as Bethesda 1 (non diagnostic or unsatisfactory), 2 (benign), 3 (atypia of undetermined significance or follicular lesion of undetermined significance), 4 (follicular neoplasm or suspicious of follicular neoplasm), 5 (suspicious for malignancy) and 6 (malignant). (12)

In the current study there were 64 cases in TI-RADS 3, and only 01 case (1.56%) was reported cytologically as suspicious of malignancy (Bethesda 5). From the remaining 63, forty were (62.5%) were in Bethesda 2 category and reported as colloid goiter, chronic thyroiditis or hyperplastic nodule. Remaining cases were in Bethesda 3 (n=15) and Bethesda 4 (n=8).

Prospective study done in a tertiary care center in India by Periakaruppan et al (20) included a total of 184 patients. TIRADS 3 had 45 patients, and none were classified as Bethesda 5 or 6. There were 42 in Bethesda 2, and 01 case in each of Bethesda 1, 3, and 4 [table 2].

	Bethesda 1	Bethesda 2	Bethesda 3	Bethesda 4	Bethesda 5	Bethesda 6	Total
TIRADS 2	10	106	01	-	-	-	117
TIRADS 3	01	42	01	01	-	-	45
TIRADS 4	04	04	-	02	02	01	13
TIRADS 5	01	01	-	02	04	01	09
Total	16	153	02	05	06	02	184

Table 2 TIRADS & Bethesda correlation (Periakaruppan et al)

There were 39 cases out of 124 in the present study reported as TI-RADS 4. As the TI-RADS score increases the risk of malignancy rises, in keeping with this a higher number (n=6) was reported as Bethesda 5 and 6 (6/39, 15.38%).

According to the current results the malignancy risk of TI-RADS 5 was 100% as all the cases were cytologically reported as Bethesda 5 or 6.

A cross-sectional study conducted by Moifo et al, in Marne La Vallee, France (21) included 430 cases out of which 23 (5.3%) were malignant. The malignancy risks in this study were 0% for TIRADS 2, 2.2% for TIRADS 3, 5.9% - 57.9% for TIRADS 4 and 100% for TIRADS 5.

A prospective study conducted by Srinivasan MNS & Amoghl VN et al (22) including 364 patients with suspicious thyroid nodules revealed a risk of malignancy of 0.64%, 4.76% - 83.33%, 100% for TIRADS categories 3, 4 and 5 respectively. Out of the important sonographic features, irregular margins had the highest positive predictive value (95.45%).

A retrospective cross-sectional study by Grace Dy J et al (23), including 149 patients has documented that the solid nature of the suspicious nodule was the most reliable sonographic finding to predict malignancy (95% C1 1.3257 to 18.2011, p=0.017). The risk of malignancy for TIRADS categories 3,4, and 5 were 12.5%, 12.82% - 53.70% and 66.67%.

Conclusion

Diseases of thyroid gland are becoming more prevalent in Sri Lanka (24), signifying a larger burden on the national health care system. Ultrasonography and guided FNAC are effective and practical, pre-operative diagnostic tests to determine the cause of thyroid enlargement. Nodules categorized as TI-RADS 5 (highly suspicious) had a significant concordance (100%) between radiological and cytological results (p value < 0.05). It can be mentioned with a high level of confidence that TI-RADS 5 along with cytology results are sensitive in identifying malignant nodules.

Majority of the cases (62.5%) in TIRADS 3 were cytologically benign (Bethesda 2). Close collaboration between the clinician, radiologist and cytopathologist can minimize costly interventions for many of the cases which would finally follow a benign clinical course.

At the same time it is vital to have a clear understanding of the limitations and pitfalls of the pre-operative diagnostic techniques, to overcome inaccuracies that would be misleading. In such instances the pre-operative diagnostic tests can be repeated to ensure more accurate assessment.

In conclusion there is a remarkable correlaton between TI-RADS 5 and thyroid cytology but less so with TI-RADS 3 and 4. In a resource poor setting, the role and reliability of the pre-operative diagnostic tests in the assessment of suspicious thyroid nodules must be understood in order to minimize overdiagnosis of malignancy leading to inappropriate surgery.

Acknowledgement

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Conflict of interests

The authors declare that there is no conflict of interests

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Original Research Article

Impact of Timing of Adjuvant Radiation in Squamous Cell Carcinoma of Head and Neck Patients: A Retrospective Cohort Study

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Keywords: *Head and neck cancer, postoperative radiotherapy, the timing of adjuvant radiotherapy*

Introduction

Squamous cell carcinoma of Head and Neck (HNC) is the most common malignancy among males in Sri Lanka(1) and the highest cause of cancer related deaths in the population in 2010(2). Delay in administering adjuvant radiotherapy to HNC has a significant detrimental effect on overall survival(3),(4).

Objectives

1. To ascertain whether a delay in starting adjuvant radiotherapy (RT) is associated with decreased event free survival (EFS) in HNC in patients treated at the National Cancer Centre of Sri Lanka.
2. To determine the high risk pathological features of tumours that are most affected by the delay in adjuvant radiotherapy.

Method

A retrospective cohort study was carried out in National Cancer Institute of Sri Lanka (NCISL), among randomly selected patients who underwent surgery during the period 01.01.2014-31.12.2016 for HNC and received adjuvant radiotherapy. Follow up period was up to 31.09.2019 and an event was defined as recurrence/development of distant metastases/loss to follow up. Statistical analysis was done using SPSS Version 21.

Results

Out of the total of 138 patients, only 38 received RT in the recommended period of

<42 days. The median delay for adjuvant RT was 57-90 days. High-risk pathology group (HR 0.50 (CI: 0.33-0.77, p=0.001), tumour stage (HR 2.65 (CI: 1.48-4.7, p<0.001), and delayed RT (HR 1.4 (CI: 1.14-1.84, p=0.002) were independently associated with lower EFS.

Conclusion

The delay of commencement of adjuvant RT beyond 42 days has a significant detriment on EFS. Tumours with high-risk pathological features and higher tumour stage especially should be prioritized for earlier treatment.

Introduction

Squamous cell carcinoma of Head and Neck is the most common malignancy among males in Sri Lanka(1) and a staggering 72% of all HNCs in Sri Lanka present with stage III and IV disease(2) which is better managed by combined modality treatment.

In the absence of wound healing issues or medical contraindications, NCCN and ASCO guidelines recommend the start of postoperative radiotherapy (PORT) in less than six weeks(3),(4). The impact on survival by the delay on postoperative radiation for high-risk tumours is well established. In the Phase III trial carried out by Ang KK et al in M.D. Anderson Cancer Centre, USA, locoregional recurrence increased and overall survival decreased when PORT was delivered within 7 weeks as opposed to those who received PORT within 5 weeks(5). In a study done by Mantravadi et al, patients who received PORT later than 6 weeks recurred locally despite having negative margins(6).

The developed world has adopted IMRT and VMAT for the treatment of HNC due to its superior toxicity profile as a result of less xerostomia. Unfortunately, as there are only a few Linear accelerators in operation in Sri Lanka, most patients must wait a considerable time before receiving optimal treatment. Delivering 2D radiotherapy with 60Co machines result in less delay but with an increased risk of acute and late toxicity. The proportion of patients who complete the prescribed treatment course is significantly lower due to the excess acute toxicity. Treatment discontinuation itself is associated with worse overall survival. Therefore, choosing between planned IMRT/VMAT radiotherapy using Linear Accelerators which often involves treatment delays versus timely initiation of radiation therapy with 2D radiotherapy, is a dilemma faced by most oncologists in the country.

By determining the pathological high-risk features that account for the highest number of recurrences, prioritization among radiotherapy waiting lists can be carried out. Therefore, this study was carried out to ascertain whether a delay in starting adjuvant radiotherapy is associated with decreased EFS in squamous cell cancer of the head and neck region and to determine the high-risk pathological features of tumours that are most affected by the delay in adjuvant radiotherapy.

Methodology

A retrospective cohort study was carried out in National Cancer Institute of Sri Lanka. All patients who underwent definitive surgery for squamous cell carcinoma of lip, oral cavity, oropharynx, hypopharynx, and glottis and went on to receive adjuvant radiotherapy to a radical dose (dose of 54Gy or higher) during the period 01.01.2014- 31.12.2016 were selected. Time interval to radiotherapy were grouped into four categories

i. 42 days or less
ii. Between 43 to 56 days
iii. Between 57 to 90 days
iv. More than 90 days

High-risk pathological factors of tumours were grouped into two categories;

i. Presence of extracapsular nodal spread and/or positive margins
ii. Presence of one or more of- close margins less than 5mm, two or more involved lymph nodes, nodal size more than 3cm, perineural invasion vascular space invasion, poor differentiation, T3/T4 stages, tumours of oral cavity with depth of invasion more than 5mm.

Patients below 18 years, histopathological entities other than squamous cell carcinoma of above tumour sites, distant metastases at the time of diagnosis, patients who had received prior radiotherapy to the head and neck region, patients who received treatment (surgery/radiotherapy) with palliative intent and those who did not complete the prescribed radiotherapy course due to any other reason except disease relapse were excluded.

Random sampling technique was used to select the required number of patients and the relative hazard ratio was obtained through literature(7),(8). The required sample size (138) was calculated according to the formula by Schoenfeld DA. Event-free survival (EFS) was defined as the time period till local or distant relapse/ death from squamous cell carcinoma of the head and neck.

Ethical approval was obtained from the Ethical Review Committee of the Postgraduate Institute of Medicine, Colombo, and permission to access patient medical records was obtained from the Director of NCISL. No individually identifiable

information was collected/stored or published, and all patient data were de-identified.

Statistical analysis: Measures of dispersion and central tendency were analysed using SPSS software (version 21.0). Fisher's exact test and Chi Square test was used to evaluate the inter-group differences of categorical data. Survival data was estimated using Kaplan-Meir survival curves. Cox Proportional Hazards model and log rank test were used to calculate the independent effect of the time interval to radiotherapy had on EFS.

Results

The final study population consisted of 138 patients who underwent surgery from the period from 01.01.2014 to 31.12.2016 for HNC. The mean follow-up duration was 23.5 months.

Age of the study population ranged from 31-84 with a median age of 57. Most number of patients (58) belonged to the 51-60 years' age category. Majority of the study population were males -110 (80%). 69% of patients (95) had squamous cell cancer of the lip and oral cavity. From the rest, oropharngeal CA was the commonest. Pathological stages 3 and 4, accounted for 67% of patients with most frequent pathological stage being 4a/4b. Majority (70%) of patients had moderately differentiated SCC.

Summary of the high-risk pathological features are shown below. Clear margins were defined as a margin ≥5mm in the absence of an anatomical barrier.

	Recorded Present		Recorded Absent
Lymphovascular Invasion	64		74
Perineural Invasion	45		86
Margins	Involved 34	Close 63	Clear 41
Lymph node involvement	Single LN **37**	Multiple LN **45**	No LN 56

Table 1 Number of Patients by Histological High risk Features for Recurrence

Mode of radiation received (2D or 3DCRT/IMRT) was nearly equally divided with 72 and 66 patients treated with 2D RT or 3DCRT/IMRT respectively. Out of the 138 study subjects, approximately one third (48) received concurrent chemotherapy with Cisplatin. None received concurrent biologic therapy.

The time interval from last surgery to the start of radiotherapy was divided into 4 categories for ease of analysis and the median delay period was 57-90 days from the date of last surgery till the day of commencement of radiotherapy.

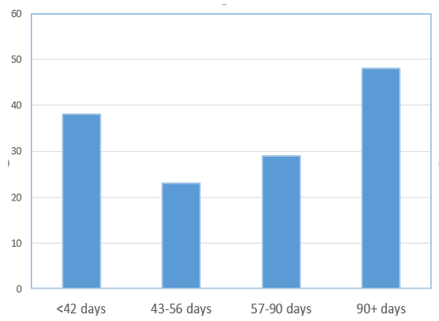

Figure 1. Time interval between surgery and the start of radiotherapy

Patient age and gender did not have a significant impact on EFS and log rank test p values were 0.64 and 0.21 respectively. Of the histopathologic characteristics, tumour site and perineural invasion (PNI) did not have a statistically significant effect on EFS. Although tumours with a higher grade and the presence of LVI had lower EFS, the difference was not statistically significant with p values of 0.27 and 0.21 respectively.

Tumour stage had a statistically significant effect on EFS with a p value of 0.006 and the presence of involved or close tumour margin on resection had detrimental effect on EFS with a statistically significant p value of <0.001.

2D RT had significantly better EFS over 3DCRT/IMRT with a p-value of 0.02.

The time interval between the date of the last surgery and the commencement of radiotherapy had a very significant impact on EFS with a p-value, of 0.002, with greater delay associated with a lower EFS. The median EFS of the group who commenced RT in < 42 days was 36 months while the group whose radiotherapy commenced after 90 days from surgery had a median survival of 24 months.

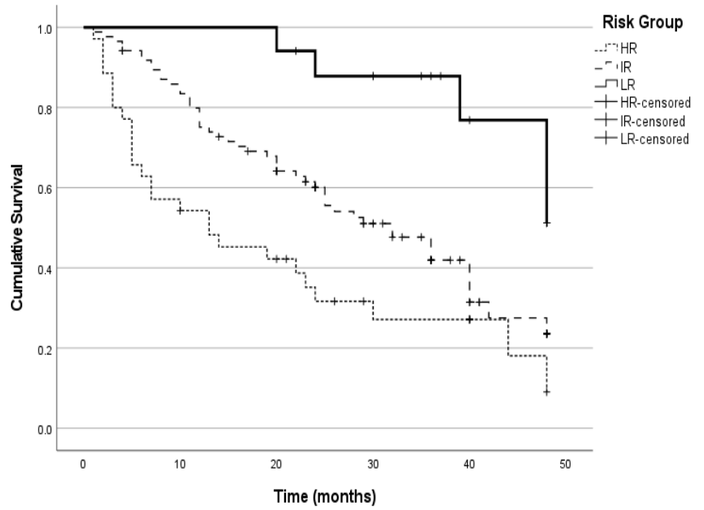

Figure 2. Kaplan-Meier Curve for histologic risk category on EFS

Delay	Median			
	Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
<42 days	36.131	2.692	30.854	41.407
43-56 days	33.760	3.445	27.008	40.512
57-90 days	23.542	2.800	18.054	29.031
90+ days	24.715	2.814	19.199	30.231
Overall	29.025	1.533	26.021	32.029

Table 2. Medians for Survival Time for RT delay

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	14.881	3	.002

Table 3. Log Rank Test for RT delay on EFS

The variables which demonstrated a p value of 0.25 or less on univariate analysis (gender, tumour margin, stage, LVI, histologic high risk groups for recurrence (HR), technique of RT and delay for RT) were selected for multivariate analysis using Cox Regression Hazard Ratio.

Out of those 7 variables: tumour stage, histologic high risk groups for recurrence (HR) and delay for RT had significant hazard ratios of 2.6, 1.4 and 0.5 respectively with p values of <0.001, 0.001 and 0.002.

Although technique of radiotherapy and tumour margin was statistically significant for EFS on univariate analysis, it was not significant in the multivariate analysis with p values of 0.54 and 0.253 (hazard ratios of 0.84 and 1.18 which crossed the null value of 1.0).

- Type of RT – denotes technique of RT used with value 1 assigned to 3DCRT and 2 to 2DRT in SPSS spreadsheet.
- StGRP – denotes the histopathologic tumour stage with value 1 assigned to early stage (1 and 2) and 2 to late stage (3 and 4) tumours in SPSS spreadsheet.
- RiskGrp- denotes the high-risk histologic features for recurrence Highest risk features (involved margins and extracapsular extension) were categorized as group 1. Group 2 was defined as presence of one or more intermediate risk features (close margins, Grade2/3, more than 01 LN involved, T3/T4 LVI+, PNI+) and group 3 as the absence of all features described above.

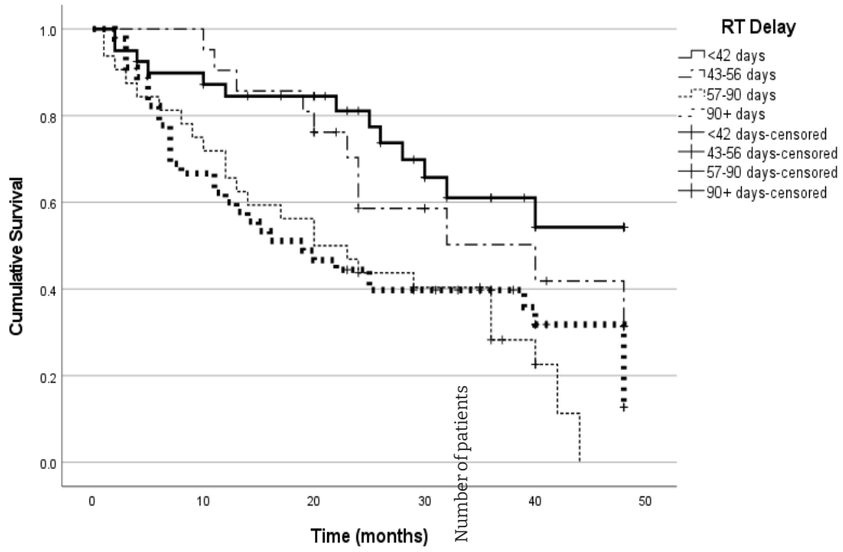

Figure 3. Kaplan-Meier Curve for RT delay on EFS

						95.0% CI for Exp(B) Upper	
Type_of_RT	-.170	.274	.383	1	.536	.844	.493	1.445
Delay	**.374**	**.122**	**9.383**	**1**	**.002**	1.454	1.144	1.847
StGRP	**.978**	**.297**	**10.862**	**1**	**<.001**	2.659	1.487	4.758
LVI	.649	.264	6.027	1	.014	1.913	1.140	3.212
RiskGrp	-.683	.215	10.091	1	.001	.505	.332	.770
sex	.478	.303	2.498	1	.114	1.613	.892	2.918
MGN	.168	.147	1.307	1	.253	1.183	.887	1.578

Table 4. Variable in the Equation of Cox Regression Hazard Ratio

Discussion

Adjuvant radiotherapy following surgery for HNC, an essential treatment for locally advanced cancers with high-risk features for recurrence7. It is well established that combined modality treatment has a survival advantage compared to single modality treatment in approximately 60% of locally advanced HNC. HNC is a category one rapidly proliferating tumour that needs prioritized treatment avoiding treatment delays and interruptions(3),(4).

The majority of patients diagnosed with HNC are males (77.8%)(1) in Sri Lanka and this is similar to the present study with 79.7% of the study population being males. The median age of the study population was 57 which is also compatible with the most recent data available which reported a median age of 60-64(2).

Most patients in the present study (67%) belonged to TNM Stages 3 and 4, and this is compatible with the inclusion criteria of the study as it targeted only patients receiving combined modality treatment which is commonly used for locally advanced disease. This also reflects the advanced stage of diagnosis at presentation in Sri Lanka with 67.3% of patients presenting with Stage III-IVB disease in 2010(2) which is similar to the findings of this study.

Details of treatment received

The mode of radiation received (2D or 3DCRT/IMRT) was nearly equally divided with 72 and 66 patients treated with 2D-RT or 3DCRT/IMRT respectively. To our knowledge, there is no data published to comment on whether this

represents the population receiving adjuvant radiotherapy for HNC in NCISL. The usage of both 60Co machines, as well as Linear Accelerators for treatmen is infrequent globally, and in a study done by A.S.Chauhan et al in Punjab, India the situation was different with most (87%) of the HNC patients receiving 60Co teletherapy(9).

Out of the 138 study subjects, 35% (n=48) received concurrent chemotherapy with Cisplatin, while none received concurrent biologic therapy with Cetuximab. Out of the 48 patients receiving concurrent chemotherapy with cisplatin, 22 patients had involved tumour margin/s at resection and 04 patients had extracapsular extension. The other 22 patients who received concurrent chemotherapy had one or more intermediate risk pathology features: close margins, poor differentiation, LVI, PNI, presence of one or more positive LN, T3/T4, and oral subsite.

For adjuvant RT of HNC, the use of concurrent chemotherapy with Cisplatin is recommended if the risk features of positive histological margin or extracapsular extension is present(4), according to the two landmark trials RTOG 9501 and EORTC 22931(10),(11). An updated 10-year analysis of the RTOG trial has reported only DFS advantage (no statistically significant OS benefit) with the use of concurrent chemotherapy with cisplatin(12). In the present study, there was no significant impact on EFS with the use of concurrent cisplatin. Therefore, more judicious use of concurrent cisplatin can be considered for cases with positive margins/extracapsular spread as recommended by international guidelines.

The present recommendation from the Royal College of Radiologists regarding the timing of radiotherapy, HNC is regarded as a Category 01 tumour and NCCN guidelines recommend commencement of adjuvant RT for HNC within 6 weeks of the last surgery(3). According to the study done by Ghanem et al. a Total Treatment Package Time (time interval from the date of last surgery to the end of RT) of more than 100 days was associated with inferior OS(13). In the present study, only 38 patients out of 138 (27.5%) commenced adjuvant RT within the time period recommended by the international guidelines. In a significant proportion (34.7%) of patients, the commencement of adjuvant RT occurred after 90 days.

It is interesting to note that use of 2D RT was associated with less delay with 34 out of 38 patients treated in less than 42 days with 2D RT, while use of Linear Accelerator was associated with more delay. (40 out of the 48 patients who received RT after 90days of surgery). Of these 40 patients, 16 started RT after 150 days of last surgery. To establish the reasons for this delay in starting RT (whether due to long waiting lists, long planning time, postoperative complications or awaiting pathology/other reports prior to decision-making) was beyond the scope of this study.

Several studies have determined that extra nodal extension and positive margins were the factors associated with worst outcome with regard to DFS and OS(6),(8). Other risk factors for recurrence identified were tumour stage of T3/T4, close/positive margin, two or more pathologically positive lymph nodes, PNI and LVI(8),(13),(14). Of the patient/tumour and treatment characteristics analyzed in the present study with univariate analysis: tumour stage, HR (high-risk histopathologic features for recurrence), margin status, the technique of RT used and the delay period prior to RT had a significant effect on EFS with p values obtained <0.05. Patient age, gender, tumour site, histology-grade, LVI, PNI, and concurrent chemotherapy did not have any significant effect on EFS.

The histopathologic characteristics were categorized into three groups in the present study according to the risk of recurrence according to the literature. The highest risk features (involved margins and extracapsular extension) categorized as group 1 had a median EFS of 20.2 months. Group 2 was defined as the presence of one or more intermediate risk features (close margins, Grade2/3, more than 01 LN involved, T3/T4 LVI+, PNI+) and had a median EFS of 29.3 months and group 3 as the absence of all features described above had the best median EFS of 43.8 months. This is compatible with the DFS, and OS periods mentioned in the literature from developed countries and ranged from 17.9 months to 33.8 months for the high-risk groups(5),(9).

Delay of adjuvant RT was associated highly significantly with EFS with a p-value obtained of 0.002, with greater delay associated with lower event-free survival. When adjuvant RT was commenced within 42 days of surgery, the median survival was 36 months which dropped to 24 months when the delay exceeded 90 days. This is consistent with literature where Mantravadi et al reported inferior overall survival when RT was initiated 6 weeks after surgery (OS 71% vs 43%) (6).

Although, many developed countries meet the target of commencement of PORT within 6 weeks(14),(15), the situation in Sri Lanka is similar to developing countries such as Nigeria and India, which reported RT waiting times ranging from 60 to 130 days(16),(17). Even though Sri Lanka has the highest MV units per million population in South Asia(17), this study indicates that RT facilities need to increase considerably in order to meet the target waiting times.

In the multivariate analysis, tumour stage, HR pathological features of tumours, RT delay were independently associated with EFS. This is in keeping with the findings of the combined analysis of the RTOG 9501 and EORTC 22931(10),(11), which demonstrated that higher T/N stage, extracapsular nodal spread, and positive margins were the high-risk features that most benefitted from postoperative radiotherapy.

The time interval between surgery and the commencement of RT was also independently associated with EFS. However, it is interesting to note that although the delay period significantly affected the EFS, the technique of RT was not significant in the multivariate analysis.

Conclusions

Only a minority of patients who receive adjuvant RT for HNC in NCISL commence RT within the recommended period of time of <42 days. The time interval between the date of the last surgery and the commencement of radiotherapy was independently associated with EFS, with greater delay associated with a lower event-free survival. Patients with high-risk pathologic features should be prioritized for earlier treatment to avoid detriment in survival and RT facilities, local treatment guidelines and protocols should be developed to reduce delays of RT.

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A Right Atrial Mass as the Initial Presentation of Invasive Hepatocellular Carcinoma Complicated with Pulmonary Embolism: A Case Report

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Key Words: *Hepatocellular carcinoma, right atrial metastasis, pulmonary embolism, vascular invasion, echocardiography*

Introduction

Intracardiac masses are rare entities that are often diagnosed by trans-thoracic echocardiography, broadly categorized into neoplastic and non-neoplastic masses. Tumors of the heart occur more commonly in the setting of metastatic disease, generally detected in patients with advanced disease. Malignancies that have a tendency for cardiac involvement include lymphoma, lung cancer, breast cancer, sarcoma, malignant melanoma, and less commonly, renal cell carcinoma and hepatocellular carcinoma (HCC) [1, 2]. HCC accounts for more than 80% of primary liver malignancies, with a rising incidence worldwide [3]. Those with chronic liver disease or cirrhosis are predominantly predisposed to HCC, and major risk factors include chronic hepatitis B and C infection, alcoholic liver disease, non-alcoholic steatohepatitis, exposure to dietary toxins, and smoking [3]. About 20-25% of HCC cases are attributed to alcoholic liver disease, which suggests cirrhosis related to alcoholic liver disease as an important risk factor for developing HCC [4].

HCC is known to be an aggressive tumor, with a marked propensity for vascular invasion. Even though the heart lies in close proximity, intracardiac metastasis are a rare manifestation of the disease, occurring in only 2% of cases, usually detected on oncologic follow-up in advanced stages or at autopsy [5]. Thus, cardiac involvement as the first presentation of HCC is unusual. We present a case of a 62-year-old man with a right atrial mass found on echocardiography as the initial presentation of invasive hepatocellular carcinoma. This case was further complicated with a pulmonary embolism, which is a rare complication of HCC.

Case Presentation

A 62-year-old man diagnosed with hypertension and chronic pancreatitis, presented with one week history of burning-type abdominal pain, associated with nausea and vomiting. Upon further questioning, he complained of grade 2 shortness of breath (New York Heart Association classification), bilateral ankle edema, low-grade fever, and loss of weight for the past two weeks. He was alcohol dependent and had consumed on average, 86 units of alcohol per week, for 30 years. He was also an ex-smoker with a 20-pack-year history. On the second in-hospital day, he developed chest pain. Electrocardiogram revealed mild dynamic changes including T wave inversions in leads III and aVF. The patient was hemodynamically stable with no features of heart failure, however his troponin I was found to be elevated up to 2.8 ng/mL. He was managed as non-ST elevation myocardial infarction with subcutaneous enoxaparin. A 2-dimensional echocardiogram was arranged which revealed a large intra-atrial mass measuring 3.06 x 3.56 cm with associated tricuspid regurgitation (Figure 1). Left ventricular function was preserved with an ejection fraction of 55%. A contrast enhanced computerized tomography (CECT) of the chest and abdomen was planned to delineate the origin of the mass.

Initial laboratory investigations (Table 1) revealed moderate anemia, thrombocytopenia with liver derangement. The AST/ALT ratio was 2.8 which was suggestive of alcoholic liver disease. His albumin/globulin ratio was found to be reversed and alpha-fetoprotein was repeated and confirmed to be elevated by more than 2000ng/mL. Screening for Hepatitis B and C was negative.

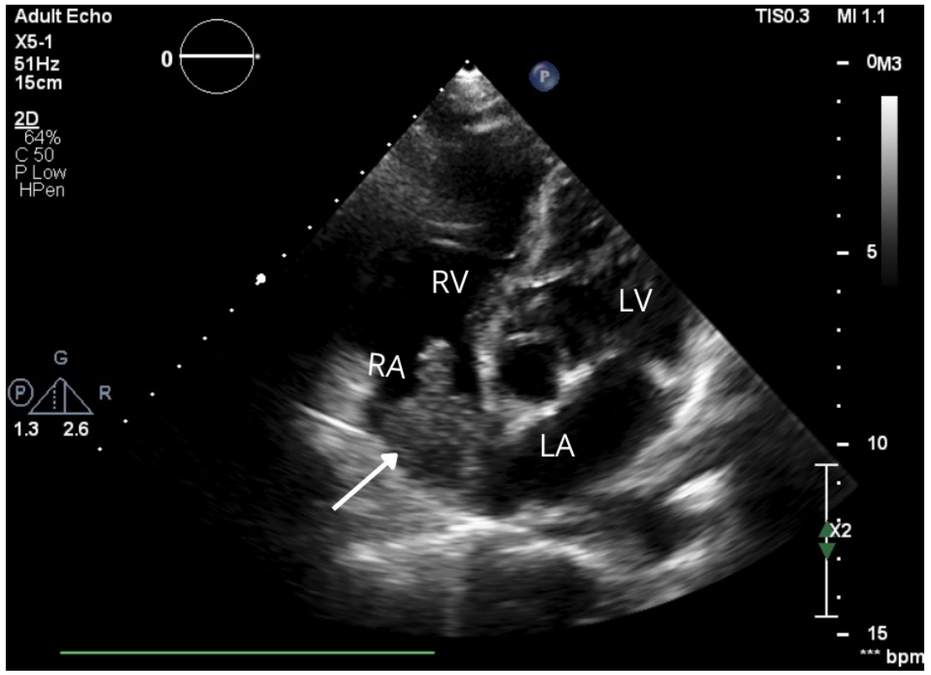

Figure 1. 4- Chamber view on transthoracic echocardiography revealing the large mass measuring 3.05 x 3.56 cm occupying 80% of the right atrium. (white arrow)

Investigation	Result	Reference Range
Hemoglobin (g/dL)	8.9	13.5 – 17.5
White blood cells (x10^9/L)	6.5	4.0 – 11.0
Platelets (x10^3/µL)	87	150 – 450
Albumin (g/dL)	1.8	3.4 – 5.4
Globulin (g/dL)	2	2.0 – 3.9
Serum Amylase (U/L)	38	40 – 140
Serum Creatinine (µmol/L)	79	60 – 110
Aspartate aminotransferase (AST) (U/L)	121	8 – 33
Alanine aminotransferase (ALT) (U/L)	44	7 – 55
International Normalized Ratio (INR)	1.4	0.8 – 1.1

Table 1. Laboratory investigation results of the patient.

The next day, patient developed worsening of shortness of breath. On examination, his lungs were clear with no evidence of consolidation or effusion. However, his oxygen saturation was found to be 92% and he was tachycardic. Urgent arterial blood gas analysis revealed a PaO2 of 57mmHg, PaCo2 of 34mmHg, and pH of 7.47 indicating type 1 respiratory failure. Considering the mass found on echocardiography, pulmonary embolism was suspected and he was sent for an urgent CECT of chest and abdomen. An ill-defined, irregular mass of 7.7 cm (AP) x 10.0 cm (T) x 10.0 cm (CC) involving segments IVa, V, VI, VII and VIII was visualized in a cirrhotic liver that heterogeneously enhanced in arterial phase, with washout in portal venous phase. (Figure 2) This enhancement pattern is known to be characteristic of HCC on multi-phase computerized tomography (CT). The detected mass was seen infiltrating into inferior vena cava (IVC) and extending to the right atrium (RA). An adjacent right atrial tumour-thrombus complex was found, with regional lymph node and possible pulmonary metastases. A pulmonary embolism involving bilateral lower lobe segmental and subsegmental pulmonary arteries with evidence of pulmonary infarction was also noted.

Sodium (mmol/L)	138	135 – 145
Potassium (mmol/L)	4.1	3.5 – 5.0
Chloride (mmol/L)	101	98 – 107
Alpha-fetoprotein (ng/mL)	>2000	<8.5
Hepatitis B	negative	-
Hepatitis C	negative	-

Based on the aforementioned imaging findings, his elevated alpha-fetoprotein level and long history of alcohol abuse, a radiological diagnosis was made, and further biopsy confirmation was deemed unnecessary. He was diagnosed with HCC in the background of chronic liver parenchymal disease, with IVC and RA extension, complicated with pulmonary embolism. For further management he was referred to the oncology team. Due to financial constraints, further management could not be continued at our hospital and the patient was transferred to an oncology center elsewhere. Unfortunately, the patient succumbed to his illness two weeks later, before treatment could be commenced, as informed by his family.

Discussion

HCC is estimated to be the fourth most common cause of cancer-related mortality worldwide, with a 5-year survival of less than 5% in non-transplant candidates [3, 6]. It is known to be asymptomatic or present with vague symptoms such as pain, lethargy, ascites, and weight loss which results in late presentation [7]. Delayed diagnosis due to the lack of surveillance programs for high-risk populations and the lack of availability of effective therapies are also thought to contribute to the poor prognosis associated with HCC. Our patient had a significant 30-year history of excessive alcohol consumption of 86 units per week, presumed to be the cause of chronic liver cell disease, and later HCC. Although he was a known patient of alcoholism, he had not presented for routine check-up due to financial constraints and lack of awareness. He was also asymptomatic until late and his symptoms started only two weeks before presentation to our hospital, which suggested, there was little opportunity to diagnose his condition at an early stage.

With the progressive understanding of HCC and its radiological features, this disease is one of the few solid organ malignancies for which diagnosis can be established using non-invasive imaging methods such as multiphase CT or magnetic resonance imaging [8]. The typical "arterial hyper-enhancement and delayed washout" feature is the diagnostic hallmark for HCC, which was seen in our patient on the quadruple phase CT scan. Biopsy confirmation is only considered when a liver mass is found whose appearance is not typical for HCC on contrast-enhanced imaging [4].

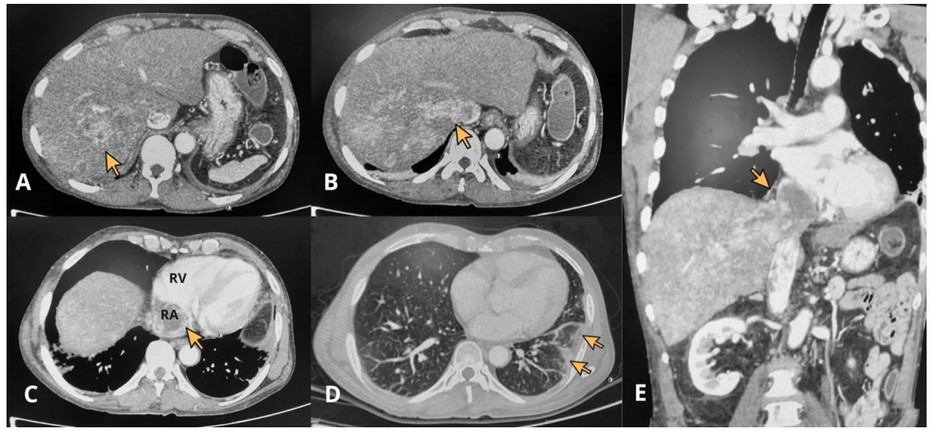

Figure 2. CECT chest and abdomen of the patient. (A) an ill-defined, irregular, heterogeneously enhancing mass involving segment VII of the liver indicated by the yellow arrow with a satellite nodule. (B) heterogeneously enhancing, infiltrative mass with satellite nodules in segments VII and VIII of the liver invading the right hepatic vein and IVC as indicated by the yellow arrow. (C) non-enhancing bland thrombus measuring 3.2 x 2.7 x 3.4 cm within the RA. (D) Hypodense wedge-shaped sub-pleural pulmonary infarctions. (E) Tumour-thrombus complex seen to invade the RA on CT in coronal view.

HCC is known to metastasize to bone, lungs, lymph nodes, and adrenal glands through hematogenous, lymphatic channels or direct extension [5, 9]. Involvement of the superior or inferior vena cava can be a prelude to cardiac metastasis, particularly seen in HCC. The proposed mechanisms of intracardiac metastases are isolated metastasis as a result of haematogenous spread or through transvenous extension of the tumour-thrombus complex through hepatic vein and inferior vena cava, as seen in our patient [5, 8, 9].Cardiac metastases may be clinically silent or present with symptoms such as dyspnea, chest pain and lower extremity oedema [9, 10]. Two-dimensional transthoracic echocardiography can detect both intra-cavitary and pericardial lesions with high sensitivity and also non-invasive, making it the investigation of choice to detect cardiac metastases [5].

Pulmonary embolism in the setting of HCC, is an infrequent manifestation thought to occur due to tumour thrombi in IVC, RA, and right ventricle [11]. Although primary cardiac thrombi are fixed to the atrial wall, secondary thrombi are known to be mobile. A mobile tumor-thrombus complex was seen in our patient which had the potential to travel to the pulmonary artery via blood flow. CECT in our patient was suggestive of pulmonary embolism along with pulmonary infarctions and metastatic deposits. The origin of the pulmonary embolism was attributed to the cardiac tumour-thrombus complex, and his lower limb venous duplex scan did not show evidence of deep vein thrombosis. They may present with vague symptoms such as shortness of breath, chest pain, syncope, cough, and haemoptysis, which should alert the physician to the possibility of a pulmonary embolism.

Unfortunately, by the time the tumour reaches the heart, the prognosis is very poor [12], and mean survival in HCC patients with IVC or RA extension is 1 to 4 months regardless of treatment [10, 13]. Currently, there are no treatment guidelines for HCC with RA involvement and management is mostly symptomatic. 1 to 8% of patients with cirrhosis develop HCC every year, and it has been proposed that at-risk populations should be screened with abdominal ultrasound and alpha-fetoprotein to detect HCC at early stages as early detection may dramatically improve prognosis [3, 4]. Early detection of HCC is pivotal in therapeutic intervention which could be curative in some patients.

Conclusions

We described a case of invasive HCC complicated with pulmonary embolism, who first presented with a right atrial mass. HCC patients usually present in advanced stages due to the asymptomatic nature at early stages, and cardiac involvement usually occurs late in the disease. Due to the dismal prognosis associated with cardiac extension in HCC, establishing a surveillance program for high-risk populations is of utmost importance to prevent cancer-related detrimental outcomes like in our patient. In addition, when HCC patients present with chest pain or shortness of breath without any underlying cardiopulmonary disease, it is necessary for clinicians to be aware of the potential complications of intracavitary cardiac involvement such as pulmonary embolism.

Consent for publication

Informed written consent was obtained by the patient prior to his transfer into specialized care. A copy is available for review by the editor-in-chief of the journal if requested.

Acknowledgements

We are grateful to Consultant Radiologist, Dr. Vijayakumar Ganesh (MD, FRCR, EDipNR) for his contribution in interpreting the CT images, and Dr. Li Xiao of Tianjin Medical University for his valuable comments.

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Moderately Differentiated Squamous Cell Carcinoma of the oesophagus in a 19-year-old girl

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Key Words: *Esophageal Carcinoma, Squamous cell carcinoma, Adenocarcinoma.*

Introduction

Malignant disease is a major burden to the Sri Lankan economy. According to the latest national cancer registry oral cavity, breast, thyroid, lung, uterus, colorectal, and esophageal cancers are the most common malignant diseases in Sri Lanka, of which carcinoma of the esophagus is 4th common among men and 7th common among women in Sri Lanka. The continuously rising incidence warrants a need for well-designed improved national primary prevention activities and effective screening programs.

This case describes a squamous cell carcinoma of the esophagus in a 19-year-old girl which mimicked gastroesophageal reflux disease (GORD).

Case History

A 19-year-old recently married nulliparous teenage girl presented with progressive symptoms of GORD for a couple of months which was resistant to standard treatment. She had progressive dysphagia for solids of 2 months duration and progressed to liquid also. She later developed haematemesis.

Her past medical and surgical histories were unremarkable. She denied long-standing dyspeptic symptoms and there was no history of corrosive ingestion. She was not on regular non-steroidal anti-inflammatory drugs (NSAID) or steroids. She was a teetotaler. She had a healthy dietary habit.

She is 2nd born child of a family with 4 children and all the developmental milestones were normal and had been immunized according to the expanded programme of immunization. There was no known malignancy or genetic disorder in her family.

The general & systemic examinations were unremarkable except for her thin build. She had no signs of Howel-Evans syndrome, scleroderma, or other genetic abnormalities.

Other blood investigations were within normal limits with a haemoglobin of 10.4 g/dl.

An endoscopic assessment of the upper gastrointestinal tract (UGIE) revealed a circumferential, ulcerated fragile growth of the esophageal wall starting at 20 cm with significant narrowing of the lumen, extending up to 29 cm.

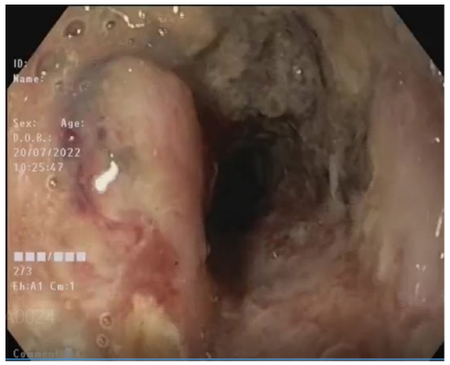

Figure 01 Endoscopic image of the tumour

Histology confirmed a moderately-differentiated Squamous cell Carcinoma of the esophagus.

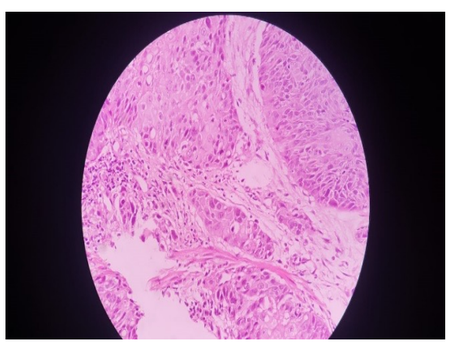

Figure 02. Characteristic microscopic appearance of keratinocyte-like cells with the intercellular bridge in Squamous cell Carcinoma of the esophagus.

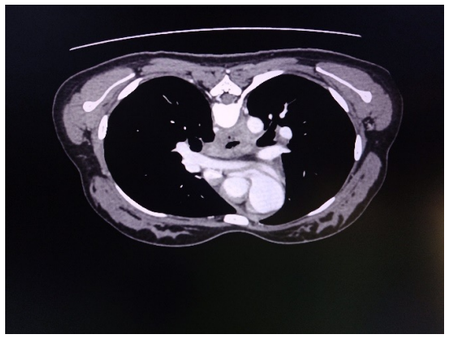

Figure 3. CECT showing mass lesion obstructing the esophageal lumen, > 90-degree arc of contact with aortic adventitia, and regional lymph node enlargement.

Contrast Enhanced Computed Tomogram (CECT) confirmed upper oesophageal tumour with infiltration of the aorta and involved regional lymph node (T4bN1M0).

As she was unable to take oral feeds, Ryle's tube was inserted and nutritional care was established. This case was discussed in the Multi-Disciplinary Team meeting (MDT) and decided to offer definitive radical chemo-radiation.

The patient and family were counseled regarding the locally advanced nature of the disease, available treatment options, side effects, and the benefits of chemoradiotherapy.

Discussion

An esophageal neoplasm can be benign or malignant. Benign esophageal tumors are relatively rare and usually asymptomatic.

Primary malignant tumor of the esophagus is exceedingly rare before 3rd decade of life. The process of carcinogenesis induced by chronic irritation or environmental factors takes around 15-20 years to become malignant.

More than 40 cases of esophageal malignancies among adolescents have been reported in the literature and the common presentation was dysphagia of short duration with rapid clinical deterioration [1].

Malignant esophageal tumour at an early age has been more frequently reported in India and the youngest of them is 8-years old girl [2]. Common entities of reported cases consist of Adeno Carcinoma (AC) and SCC. Secondary malignancies rarely involve esophagus except for bronchial carcinoma which directly invades the esophagus.

The malignant esophageal disease is multi-factorial. Non-modifiable risk factors include geographic location, male sex, advancing age, and genetic predisposition. Modifiable risk factors include physical inactivity, use of tobacco & alcohol [3], and unhealthy dietary habits.

Further, GORD, Barrett's esophagus, drinking water source, food preparation method, betel chewing with areca nut, and aspirin usage [4] significantly contributes to causing cancer of the esophagus. However, the NSAID seems to be protective [5].

Other risk factors for the carcinoma of the esophagus include achalasia cardia, tylosis, caustic injury and Plummer-Vinson Syndrome.

The case which is reported here is a 19-year-old girl belonging to a low socio-economic class and had none of the above-mentioned risk factors. There were no identifiable familial risk factors.

The single red flag symptom in carcinoma of the esophagus is progressive dysphagia, which in this case was ignored due to the age of the patient. Other clinical signs and symptoms of esophageal malignancy are non-specific and can be regurgitation, weight loss, chest pain, interscapular pain haematemesis, and pseudo-vomiting. These non-specific symptoms can also occur in GORD.

Treatment of esophageal cancer depends on the location of the disease, staging, performance status, and comorbidities of the patient.

As she had a locally advanced disease in the upper oesophagus, definitive chemo-radiation was considered appropriate.

Conclusion

For patients of any age presenting with red flag symptoms of the upper gastrointestinal tract such as dysphagia, an index of suspicion and early endoscopic examination is mandatory.

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Pure mucinous carcinoma of breast with neuroendocrine differentiation: a case report

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Key Words: *Breast, Mucinous breast carcinoma, Neuroendocrine differentiation*

Introduction

An 88-year-old woman with no family history of breast cancer, presented with a small right breast mass with skin tethering. On clinical examination, the lump was attached to the overlying skin and was firm in consistency with irregular margins. No evidence of axillary lymph node enlargement was detected. A Fine Needle Aspiration (FNA) was done and jelly-like mucoid material aspirated. The cytology smears were cellular and revealed scattered three-dimensional cell clusters and singly dispersed atypical cells in an abundant extracellular mucin pool. These tumor cells showed abundant eosinophilic cytoplasm, round to oval mildly pleomorphic eccentrically placed nuclei with fine granular chromatin. The mucin was deep purple material with Leishman staining. There were numerous traversing thin-walled capillaries with chicken-wire appearance (fig.1). Intracytoplasmic mucin or signet ring cells were not detected. A cytological diagnosis of mucinous carcinoma of the breast was made.

Wide local excision revealed a circumscribed tumour measuring 1.2x1.0x0.8cm with focal haemorrhages. Histopathological examination showed clusters of tumour cells floating in extracellular pools of mucin with focal neuroendocrine differentiation (NED) (fig.2). The tumour constituted of more than 90% of mucinous areas, with no component of ordinary invasive ductal cancer seen. This confirmed the diagnosis of a pure mucinous carcinoma of the breast. Tubule formation was less than 10% (score 3/3) The tumor cells were large, with a moderate amount of eosinophilic cytoplasm and mildly pleomorphic vesicular nuclei with fine chromatin (score 1/3). Mitoses were increased, (7/10 high power field (score2/3).

The tumour cells showed strong focal cytoplasmic staining for synaptophysin confirming neuroendocrine differentiation (type B) (fig. 3) in keeping with pure mucinous carcinoma of breast with focal NED, (type B mucinous carcinoma).

The tumour cells were positive for ER, PR and negative for HER 2 neu expression (figure)

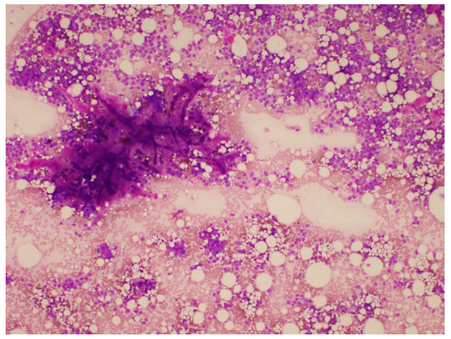

Figure 01 - Fine-needle aspiration smear showed clusters of tumor cells in a background of rich mucinous materials with traversing thin-walled capillaries. X100

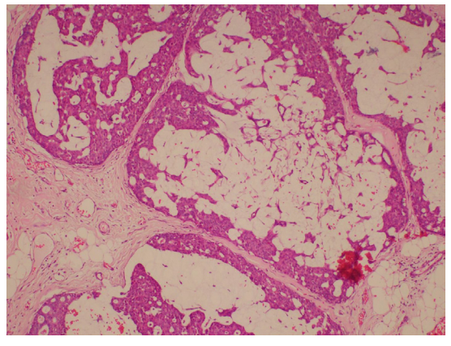

Figure 02 Sheets and clusters of tumour cells separated by mucinous pools H & E X100

Discussion

Mucinous carcinoma of the breast is a well-differentiated tumour and is categorized into pure mucinous breast carcinoma (PMBC) and mixed mucinous breast carcinoma (MMBC) (1). PMBC is rare and accounts for 2% to 5% of all breast cancers (2). PMBC is characterized by mucine-producing tumour cell clusters floating in large amounts of extracellular mucin pools

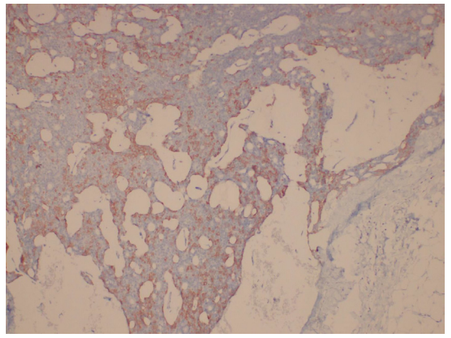

Figure 02 Tumour cells with focal strong cytoplasmic positivity for Synaptophysin (x100)

which constitute 90% or more of the tumour area (3). PMBC usually occurs in elderly females with a median age of 69 years (4).

The mixed type is defined as a combination of both mucinous and invasive ductal carcinoma components. PMBC is generally less aggressive with a lower incidence of nodal metastasis and a higher survival rate compared to MMBC which is more aggressive in nature (4).

Mucinous carcinomas usually show mild cytological atypia and may be misdiagnosed as benign lesions, especially in cell-poor samples. Mucinous carcinomas should be distinguished from benign mucinous lesions like mucocele, mucinous cysts, and mucinous spherulosis. Therefore, a histological diagnosis is needed to exclude other possibilities.

Breast lesions with mucin are encountered in various benign histological subtypes such as fibrocystic change with intra luminal mucin, mucocele-like lesion, pure or mixed type of mucinous carcinoma, and mucinous cyst adenocarcinoma. Mixed mucinous carcinoma is a tumour with 50-90% of the mucinous component admixed with invasive duct carcinoma.

The pure mucinous carcinomas (>90% mucin) are further subdivided into hypocellular(type A) and hypercellular with neuroendocrine differentiation (type B) variants.

Aspirates with cell-abundant extracellular mucin pools can arise from other breast lesions rather than breast malignancy. Those with increased cellularity are a diagnostic challenge of fine needle aspiration. Cytological features such as cellularity, the shape of the epithelial cell nests, nuclear features, and stromal components are helpful in the differential diagnosis.

The absence of cytological atypia, the presence of bare oval nuclei, and intimately associated myoepithelial cells on duct epithelial cell clusters favour benign mucinous lesions over mucinous carcinoma. The presence of only mucin does not warrant a diagnosis of mucinous carcinoma as other breast lesions such as mucinous cyst, mucinous spherulosis and mucocele-like lesions also show extracellular mucin.

Smears of fibrocystic change usually show macrophages admixed with other inflammatory cells, confirming the cystic nature of the lesion. Ductal epithelial and myoepithelial cells are also commonly seen in cyst aspirate, mostly as small balls and clusters mixed with the cyst macrophages. Fibrocystic change associated proliferative lesions such as usual ductal hyperplasia and fibroadenoma with mucinous and cystic change shows hypercellular smears with extracellular mucin pools

Cytological diagnostic clues for mixed mucinous carcinoma are high cellularity, nuclear atypia with prominent nucleoli and tumour necrosis. It is important to distinguish pure mucinous carcinomas from “mixed” mucinous carcinomas, as the prognosis of pure mucinous carcinoma is much better than that of the mixed one. PMBC is less likely to spread to the axillary lymph nodes than other types of invasive carcinomas. In this situation FNAC only concludes the diagnosis of the breast malignancy with mucinous component.

The paucicellular lesions such as fibrocystic change or mucocele-like lesion which lack cytological atypia, need to be differentiated from mucinous carcinoma of the breast and is recommended to do conservative surgical excision for the assessment of definitive histological malignant features.

Mucinous spherulosis is a variant of collagenous spherulosis of the breast characterized by cribriform structures containing basophilic material embedded in a loosely mucinous acellular background. This lesion is associated with Sclerosing adenosis and atypical ductal hyperplasia

Therefore, FNA diagnosis of mucinous carcinoma needs to be further subcategorized by histopathological examination as it is prognostically valuable.

Pure mucinous carcinoma is usually positive for estrogen and progesterone receptors, while androgen receptors are expressed at low levels and HER2-neu is not usually amplified.

Mucin production is an important indicator of low biological aggressiveness. Estrogen and progesterone expression are also correlated with a better prognosis. Our case revealed similar expression of receptors with better outcomes.

Conclusion:

Pure mucinous carcinoma of the breast with neuroendocrine differentiation is a rare histological variant reported in postmenopausal women. Fine needle aspiration cytology plays an important role in pre-operative diagnosis. it is essential distinguish between the pure and mixed mucinous carcinomas as they differ in management.

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Surgical clips as a tissue marker in breast cancers treated with neoadjuvant chemotherapy: a Sri Lank-an case series

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Key Words:

Introduction

Intra-mammary marker clips are important as they accurately identify the margins of the tumours and help to mark the tumour bed in patients who get a complete pathological response after neoadjuvant chemotherapy.

Accurate tumour marking at the time of core biopsy is helpful specially in small tumours, as the tumour can get distorted after the core biopsy and might be difficult to identify in subsequent imaging. It also acts as radiological proof of correct accession of the suspicious lesion.

Neo-adjuvant chemotherapy is used in the management of breast cancer for various indications. One such indication is to downstage a breast tumour to conserve the breast. Chemo-responsive malignancies can be clinically and radiologically non detectable after successful neo-adjuvant therapy. Hence, marking the tumour is crucial in the subsequent management.

Cancers which are sensitive to neo-adjuvant chemotherapy can radiologically dissappear after initial treatment and marker clip acts as a navigation tool to the tumour bed. Therefore, it is particularly important in breast conservative surgery.

Commercially available biopsy marker clips are non-allergenic and MRI compatible. All the marker clips are radio-opaque and some of the marker clips can be identified ultrasonically. They are inserted into the breast tissue via a needle under ultrasound guidance or mammographic guidance. After the placement, its position is confirmed by two field mammography.

Biological breast marker clips are widely used in developing countries. However, their utilization is limited in developing countries like Sri Lanka due to the high cost.

We consider surgical clips as a cheaper alternative to these biological marker clips as they are readily available, non-allergenic, radio-opaque and MRI compatible. They are available in various sizes. Under sterile and aseptic conditions we bent these clips using an artery forcep to bring both arms together to make an “U” shaped clip. Afterwards, using a 14G co-axial needle and a stylet, the “U” shaped clip is introduced into the breast tumour under ultrasound guidance.

In this study, we report successful utilization of this surgical clips in six patients who presented to National Cancer Institute Sri Lanka for neo-adjuvant chemotherapy.

In the literature survey, we found a similar study which had been carried out in South Korea1.

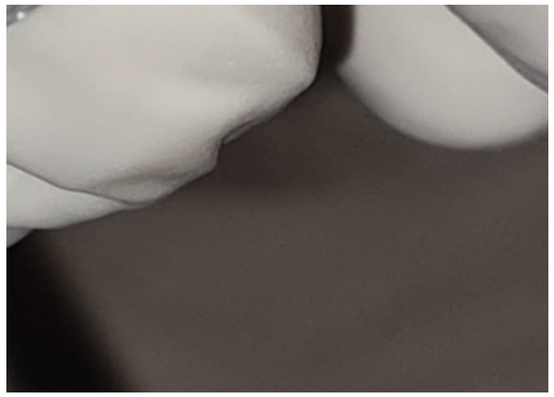
Methadology

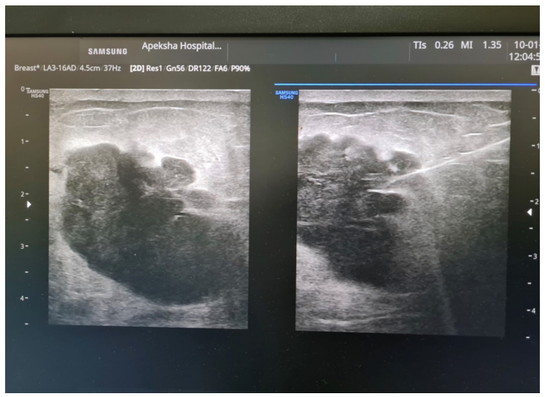
Patient data was collected both retrospectively (demographic) and prospectively from January 2020 to 10th of January 2022. Demographic data were collected in all the patients who underwent marker clip insertion before the commencement of neo-adjuvant chemotherapy. This was performed as an out-patient procedure. All the procedures were performed by the Consultant Radiologist.

Informed written consent was taken from the patients before the procedure. Pre-procedure ultrasound scan was performed to localize the malignancy and to plan the placement of the needle.

Under aseptic conditions, a sterile Ligaclip was bent using an arterial forcep to make a narrow mouthed “U” shaped clip. Afterwards, the clip was inserted into a 14G co-axial needle to examine its free movement within the needle.

The puncture site skin was cleaned using the





Betadine solution. Under ultrasound guidance, skin and the breast tissue were infiltrated with local anaesthesia. After satisfactory ultrasound localization, the tip of the 14G co-axial needle was placed in to the center of the tumour. The stylet was removed and the "U" shaped surgical clip was introduced into the co-axial needle with its' arms facing the tumour.

Post procedure two field mammogram was performed to confirm the localization.

Patients were educated to come to hospital if they develop any acute pain, fever or redness in the breast.

After completion of neo-adjuvant chemotherapy the tumour size is revaluated by USS and mammography.

On the day of the surgery, pre-operative wire localization of the marker clip or the residual tumour was done by the Consultant Radiologist under ultrasound guidance.

We didn't mark the positive axillary lymph nodes, as the wire localization of the axilla is not comfortable to the patient. Radio-active seed is not available in our country at the moment due to financial constraints.

Results

We inserted clips into six patients after obtaining their consent. All had biopsy proven invasive duct carcinoma. They were between 36 – 47 yrs. All patients were given neo-adjuvant chemotherapy and the clips were inserted before the commencement of the neo-adjuvant chemotherapy. Out of these, one had triple negative breast carcinoma.

None of them developed any complications due to the insertion of clips such as excessive pain or infections.

Two of them underwent wide local excision (WLE) and pre-operative wire localization of the residual tumour was performed by the Consultant Radiologist. Successful removal of the malignancy and reconstruction done on the two patients who underwent WLE. Other four patients are still undergoing neo-adjuvant chemotherapy.

Discussion

Successful treatment of the breast cancer requires early identification, staging, surgery and chemotherapy with or without radiotherapy.

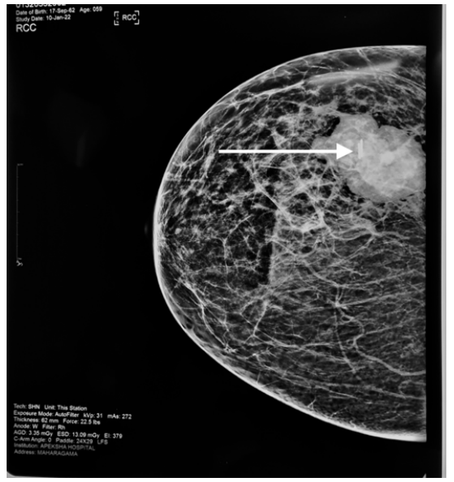
Radiologist play a crucial role in the management by radiological detection, biopsy and fine needle aspiration of axillary nodes, staging, pre-operative localization and follow up imaging.

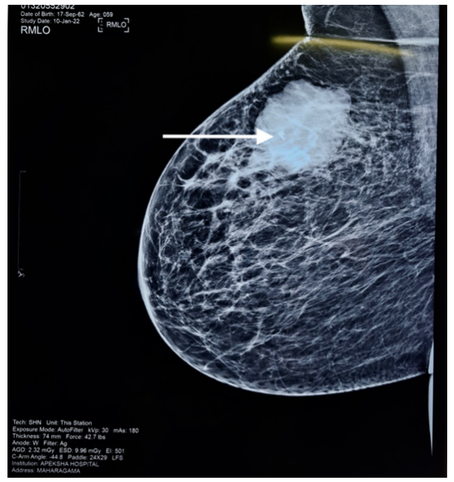
In the patients who expect breast preservation, down grading of the tumour can be done with neo-adjuvant chemotherapy.

Some tumours, respond to the neo-adjuvant chemotherapy favourably and they might be radiologically occult at the time of surgery. Hence, marking the tumour is essential in the further management.

Breast biopsy marker clips are commercially available worldwide. However, their utilization is limited in developing countries like Sri Lanka due

to the cost. Under continuous ultrasound monitoring it was pushed into the malignancy using the stylet.





We propose to use metallic surgical clips as an alternative to the biopsy marker clips in the setting of breast conservative surgery due its wide availability and low cost.

A marker clip should be radio-opaque, non-allogenic and MRI compatible. Metallic surgical clips have all these characteristics and are easy to place under ultrasound guidance. We used the widely available Ligaclips.

Usually these are wide mouthed and "U" shaped. To place it through a co-axial needle we bent it using an arterial forcep under aseptic conditions in to a narrow mouthed "U" shaped clip. After bending they are of 5 mm to 10 mm in size. We used 10mm ones for larger tumours and 5 mm ones for smaller tumours.

These clips can be clearly visualized ultrasonically.

We found this method is more convenient and can be performed with a 100% accuracy as described by the Youn I et al, a South Korean study.

Drawbacks of this method are, relative high chance of infection if sterility is not maintained throughout the procedure and limited usage compared to dedicated breast biopsy marker clips, due to their size. In addition, we found it's difficult to convince the patients to undergo this procedure due to their fear of a new procedure and requested for total mastectomy.

Conclusion

The early evidence of this study suggest use of surgical clips to mark the breast malignancies as an alternative to biological tissue marker clips in the setting of breast conservative surgery is effective and safe.

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