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Editorial

Clinical Research in LMICs : A Luxury or a Necessity ?

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Clinical research demands time and resources. A Low and Middle Income Country (LMIC) physician's day is swamped with clinical work. Taking on more work which is often unpaid is not high on their list of priorities. The culture of these countries is such the physicians are looked upon primarily as carers of ill rather than scientists. In this background, the societal view is that any time they spend not directly caring for patients is time not well spent. This has led to the conventional wisdom of LMIC physicians should leave research to their High Income Country (HIC) colleagues who have more time and resources in their hands. It is time to challenge this perception.

There is no doubt that there are tremendous time pressures on LMIC Physicians. However, this is the very same reason they should embrace research rather than shy away from it. How else can you find out ways of best managing their workload? Doing the same thing over and over again is certainly not the answer. Maybe assigning a team member to summarize all patients before the ward round can save time, a patient information system could reduce the administrative duties of physicians, categorizing patients to diseases and assigning each group to one doctor maybe an efficient way of conducting clinics. The only way to find out if each of these interventions work is through carefully conducted research. Such research would help physicians actually save time.

The problems plaguing LMICs are unique. In LMICs the main reasons for treatment failure are non diagnosis, late presentation, treatment abandonment etc. These issues are often not investigated in HICs where treatment failure usually happens due to refractory or relapsed disease. Therefore the focus of HICs would be to better understand the biology of refractory disease and find ways to overcome this issue. LMICs can only benefit from this type of research if it first addresses the immediate causes of treatment failure in their countries. It can be done only through home grown research.

There are fundamental differences such as age compositions, nutritional status, supportive care facilities available etc in HICs and LMICs. Therefore an intervention that clearly worked in a HIC might not have the desired impact in a LMIC. Whether such an intervention can be directly employed, adapted to suit the country or completely not suitable to a LMIC can only be ascertained by carefully conducted research. Hence evidence gained by research in the HICs should not be carte blanche accepted as the gospel truth in LMICs.

Two thirds of the world's population live in LMICs and is the fastest growing population. In a rare disease like childhood cancers a key ingredient of successful research is having enough number of subjects to study. This is an inherent advantage LMICs have over HICs. This advantage can only reach the ground level only if more and more LMIC physicians get involved in research.

Another major reason research output is minimal in LMICs is that health institutions are reluctant to provide logistical support necessary to conduct research. It is often considered as an expendable luxury against other competing budgetary demands on extremely limited resources. Best way to approach this is to take a leaf out of the playbook of successful corporates who commit significant resources to understand their consumer better and how to get the biggest bang for every buck spent. Similarly, the way to maximizing the gain from the limited resources of health systems in LMICs is only through robust research focused on understanding the problems and how best to deploy the resource to address those problems.

When we come to the end of a toothpaste tube we tend to be more frugal with the toothpaste with no ill effect on the job at hand. Similarly, when you have limited resources, you become apt at getting the best out of those resources. It could be an area where HIC physicians can actually learn from their LMIC counterparts.

This is why its time for LMIC physicians to think of the long game and break out of their traditional silos. Investing their time and energies in research now, will pay back with interest manifolds in the future. Although it will look like an impossible demand on their present time it will actually be a means to save

time in the future. Although it will appear to keep them away from their patients now, research can only benefit patients in the longterm. Although research related costs looks like an unnecessary burden to healthcare institutions, it will be money well spent if it can improve the health system in the future.

This issue is dedicated to the establishment of the Sri Lanka Cancer Research Group (SLCRG) and the cover page carries it's logo. The core mission of the SLCRG is to facilitate and promote cancer. It is hoped that SLCRG will provide much needed impetus to firmly establish cancer research in Sri Lanka.

Review Article

Management of metastatic colorectal cancer

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Introduction

Colorectal cancer is one of the more common cancers, and approximately 20% of patients have metastatic disease at diagnosis and up to 50% will develop metastatic disease. The majority of patients with metastatic colorectal cancer do not have curable disease. Up to 20% of patients may have potentially curable disease with oligometastatic disease in the liver, lung or peritoneum which may be amenable to surgical resection or ablation.

Prior to commencing systemic treatment for metastatic disease, it is important to establish the goal of treatment. This will aid decision making surrounding the balance of response rate and acceptable toxicity. For patients with incurable disease, the aim of treatment is to improve symptoms, overall survival and quality of life. In patients with potentially resectable metastatic disease who require chemotherapy, response rate is more important.

In patients with metastatic colorectal cancer, median overall survival with best supportive care alone is approximately 5-6 months. This can be extended to 30 months in patients eligible for all systemic treatment options.

In the current era of molecularly targeted therapy and "personalised cancer treatment", improving outcome and minimising cost involves selecting treatments based on predictive biomarkers. Currently Ras and B-Raf mutation status are both predictive and prognostic biomarkers in Colorectal Cancer. Approximately 45% of tumours have a K-Ras mutation, 4% an N-Ras mutation and 8% a B-Raf mutation. Ras and B-Raf status predict response to EGFR inhibitors. The COIN study identified variations in overall survival based on biomarker profile. B-Raf mutant tumours have the poorest prognosis with median overall survival of 8.8 months, Ras mutant tumours have a median overall survival of 14.4 months, this increases to 20.1 months in fully wild type tumours [1]. Mismatch Repair Deficiency (dMMR) resulting in Microsatellite Instability (MSI-High) is also an important biomarker which predicts response to immune check point inhibitors.

Systemic therapeutic options for metastatic colorectal cancer can be subdivided into chemotherapy, targeted agents and immunotherapy

Chemotherapy options in the first- and second-line setting

Historically, 5-FluoroUracil (5-FU) had been the sole agent available for the management of metastatic colorectal cancer. Multiple new drugs have been developed over the last 20 years, however treatment continues to be based around a fluoropyrimidine backbone.

5-FU or Capecitabine (an oral 5-FU prodrug) can be delivered as a single agent in patients with co-morbidities or poorer performance status. When 5-FU is used, short term infusional regimens (e.g. Modified de Gramont) have been shown to improve response rates when compared with bolus regimens. They are also associated with less haematological and GI toxicity [2]. Capecitabine has comparable response rates to 5-FU at a dose of 1250mg/m^2 twice daily from day 1 to day 14 on a 21-day cycle. Capecitabine is associated with a lower incidence of grade 3 and 4 diarrhoea, stomatitis and neutropenic sepsis but a higher incidence of hand and foot syndrome and hyperbilirubinaemia. Capecitabine is often initiated at 1000mg/m^2 in the single agent setting in Europe and the USA due to apparent excessive toxicity at the full dose in Caucasians and those on a Western style (high folate) diet. Single agent treatment is generally

well tolerated but has a lower response rate than combination treatment.

The fluoropyrimidine backbone can also be used as the basis for combination treatment in 'doublets' or 'triplets' with oxaliplatin (FOLFOX, XELOX) and irinotecan (FOLFIRI). The addition of more agents increases response rates but also increases toxicity. The uses of 'triplet' chemotherapy (FOLFOXIRI) with 5-FU, oxaliplatin and irinotecan is usually reserved for patients suitable for a more aggressive approach for example fit patients with potentially operative oligometastatic disease where response rate is more important. It can also be used in patients with B-Raf mutant tumours and a good performance status due to the aggressive nature of this subset of tumours, to ensure that patients receive all active agents in the first line setting.

Targeted therapies can be used alongside single agent and doublet chemotherapy and will be discussed later. Capecitabine is not recommended alongside anti-EGFR agents.

When using doublet chemotherapy regimens either oxaliplatin or irinotecan can be used in the first line setting with equal efficacy. The decision will depend on whether the patient has received any treatment in the adjuvant setting (e.g. consider first line FOLFIRI in patients relapsing within 6 months of completion of Oxaliplatin containing adjuvant chemotherapy), the side effect profiles, and patient choice. The alternative agent can be used at the time of progression.

There is no consensus on the ideal combination or scheduling of these agents. The NCCN and ESMO guidelines advise that patients should receive all available chemotherapy and targeted agents but do not comment on optimal sequencing as this has yet to be identified. The proportion of patients receiving all active chemotherapy agents correlates strongly with median overall survival [3,4], therefore exposure to all active agents is probably more important than the specific sequence of the chemotherapy agents.

There is limited data on optimal timing of treatment. Should treatment be commenced when patients have small volume asymptomatic disease? Is there an argument for monitoring until clear progression is demonstrated? Some early studies have shown an improvement in overall survival in patients treated early with 5-FU [5,6]. There is no data available to determine if this can be extrapolated to treatment including irinotecan, oxaliplatin and biological agents, however if patients delay the initiation of treatment they may not receive all active treatments

and therefore survival outcomes may be compromised. Most clinicians would suggest commencing first line palliative chemotherapy in most patients even if asymptomatic unless there are specific mitigating factors.

If patients are not significantly symptomatic objective response rate should not be the focus of treatment as this is not always a good indicator of progression free survival and overall survival [7-9], stable disease may be a satisfactory response to treatment.

Targeted therapies

Agents targeting EGFR

Epidermal growth factor and its receptor are involved in colorectal cancer cell growth as well as the development of angiogenesis and metastases [10]. Biomarker analysis is crucial for patient selection. Cetuximab and Panitumumab are only effective in patients with wild-type (WT) tumours that do not carry mutations in N-Ras, K-Ras, B-Raf (V600E). Approximately 40% of patients have wild type tumours.

Cetuximab

Cetuximab is a mouse/human chimeric monoclonal antibody binding to EGFR on both tumour cells and normal cells.

Cetuximab is used first line in combination with irinotecan containing regimens. The CRYSTAL trial compared irinotecan with or without cetuximab in previously untreated metastatic colorectal cancer (prior to a full understanding of the role of Ras mutation in the response to EGFR inhibitors). There was a significant but modest improvement in progression free survival and response rate from the addition of cetuximab but no increase in overall survival. Later analysis amongst only 'Wild type' patients demonstrated a significant improvement in response rates (59% versus 43%), median progression free survival (9.9 versus 8.7 months) and median overall survival (24.9 versus 21.0 months) [11]. There was also an increase rate of surgery for metastatic disease (7% versus 3.7%) and higher rates of complete resection (R0) (4.8% versus 1.7%) amongst patients receiving cetuximab.

Commonest adverse effects with the addition of cetuximab are diarrhoea, skin toxicity and infusion reactions.

In contrast to irinotecan containing regimens, the benefit of adding cetuximab to first line oxaliplatin containing regimens is less clear. The OPUS trial in K-Ras wild-type patients demonstrated an increase in response rate with the addition of Cetuximab to FOLFOX (57% v 34% ($p<0.05$)). There was a statistically significant improvement in median progression free survival (8.3 versus 7.2 months) but not in median overall survival (22.8 v 18.5 months ($p=0.39$)) [12]. This trial also revealed that Ras mutant patients receiving Cetuximab have poorer outcomes than those receiving FOLFOX alone. The MRC COIN trial also demonstrated an improvement in response rate (64 vs 57%) but no significant improvement in median progression free survival (8.6 months in both groups) nor median overall survival (17 versus 17.9 months) even once Ras status was taken into account [13].

Cetuximab has also been shown to increase response rates when combined with irinotecan in patients who have progressed on previous chemotherapy. The EPIC trial demonstrated an increase in response rates (16% vs 4%) and median progression free survival (4 vs 2.6 months) when cetuximab was added to irinotecan in patients with oxaliplatin refractory disease. There was no significant difference in overall survival (10.7 vs 10months). However, half of The patients crossed over to receive cetuximab after progression in the irinotecan alone group [14]. The BOND trial compared irinotecan plus cetuximab with cetuximab alone in patients with irinotecan refractory disease. Combination therapy was associated with a significant improvement in response rates (23 versus 11%) and time to progression (4.1 versus 1.5 months). There was no significant improvement in median overall survival (8.6 versus 6.9 months) [15].

Cetuximab has been compared to Best Supportive Care following 5-FU, Irinotecan and Oxaliplatin Chemotherapy in the pre-Ras era. There was a significant increase in Response Rate (8% v 0% $p<0.001$), Disease Control Rate (39% v 11% $p<0.001$), Progression Free Survival and Overall Survival (6.1 v 4.6 months) at the expense of increased Grade 3 toxicity (78.5% v 59.1% $p<0.001$) [16].

Panitumumab

Panitumumab is a fully humanised monoclonal antibody for the extracellular domain of EGFR. There is increasing data for the use of Panitumumab in combination with chemotherapy in the first- and second-line settings.

The PRIME trial, a phase III study, assessed the addition of Panitumumab to oxaliplatin based regimens in the first line setting. Panitumumab significantly improved response rate (57% v 48%), progression free survival (10.0 versus 8.6 months $p=0.01$) and median overall survival (23.8 versus 19.4 months $p= 0.03$) [17]. Further analysis has also demonstrated poorer outcomes for patients with K-Ras mutations in exons 3 and 4 and N-Ras exons 2,3 and 4 who receive treatment with Panitumumab [18]. Therefore no patients should receive EGFR antibody therapy without full Ras mutation analysis.

In the second line setting Panitumumab has shown benefit when combined with FOLFIRI. The study 20050181 demonstrated a significant improvement in response rate (36% versus 10% $p<0.0001$) and median progression free survival (6.7 versus 4.9 months $p=0.023$) with a trend towards improved overall survival (median 14.5 versus 12.5 months $p=0.37$) [19].

In the third line setting (without Ras mutational analysis) there is also weak data to support its benefit over and above best supportive care [20].

Which EGFR agent should you use?

There is no convincing evidence that one EGFR agent is superior. The ASPECCT trial included patients who had previously had chemotherapy with 5-FU, irinotecan and oxaliplatin but no prior EGFR therapy. It was designed to assess for non-inferiority of Panitumumab versus Cetuximab. There was no significant difference in progression free survival (4.2 months versus 4.4 months) or median overall survival (10.4 versus 10.0 months). This met the pre-defined limits for non-inferiority [21].

Panitumumab is a fully humanised monoclonal antibody and therefore is less likely to cause hypersensitivity reactions than cetuximab which a human/mouse chimeric monoclonal antibody.

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The NCCN and ESMO guidelines suggest that they can be used interchangeably

Agents targeting VEGF Inhibition of vascular endothelial growth factor produces an anti-tumour response by inhibiting tumour angiogenesis.

Bevacizumab

Bevacizumab is a humanised monoclonal antibody targeting VEGF. It has been shown to modestly improve outcomes when added to a variety of 1st line chemotherapy regimens. There are no predictive biomarkers for its efficacy. The greatest benefit is seen in 'weaker' chemotherapy regimens, for example single agent capecitabine. The Avex trial assessed benefit of adding bevacizumab to single agent capecitabine in elderly patients. Bevacizumab led to a 4-month improvement in progression free survival (9.1 vs 5.1 p<0.0001) and overall survival (20.7 vs 16.8months (p=0.182) [22]. There is less evidence of benefit when added to doublet chemotherapy regimens. Pooled analysis of 7 trials comparing a variety of chemotherapy regimens with and without bevacizumab demonstrated a 19% reduction in the risk of death and a modest but statistically significant improvement in median progression free (8.8 versus 6.4 months) and overall survival (18.7 versus 16.1 months) of approximately 10 weeks [23].

It is therefore worth considering the addition of bevacizumab in patients who are not fit enough for doublet chemotherapy. Bevacizumab does come with its own toxicities including bleeding, hypertension, impaired wound healing, bowel perforation, and thromboembolic events.

With the increasing use of bevacizumab in the 1st line setting, the question has been raised as to whether it should be continued beyond progression, when the chemotherapy regimen is changed. The TML trial demonstrated continuing bevacizumab was associated with a significant improvement in median progression free survival (5.7 versus 4.1 months p=0.0001) and median overall survival (11.2 versus 9.8 months p=0.0062). There was also an increase disease control rates in the bevacizumab group (68 versus 54 %), however objective response rates in both arms remained low (3.9 vs 5.4%) [24].

Should anti-EGFR or anti-VEGF therapy be used alongside chemotherapy in the first line setting?

The FIRE-3 study assigned 735 patients to FOLFIRI plus bevacizumab or cetuximab. There was no significant difference in objective response rates (58% bevacizumab versus 62% cetuximab) or median progression free survival (10.3 versus 10.0 months). There was however a significant increase in overall survival with cetuximab (25.0 versus

28.7 months) with overall survival for cetuximab increasing further to 33.1 months when data only included all Ras and B-Raf wild type tumours. The cause for an increase in overall survival with no difference in progression free survival or response rates is not clear. Toxicities varied between the groups with more nausea and vomiting, hypertension, and bleeding in the bevacizumab arm and more hypocalcaemia, hypomagnesaemia, skin toxicity and allergic reactions in the cetuximab arm [25].

The CALGB 80405 compared FOLFIRI or FOLOX plus either Bevacizumab or Cetuximab in the first line setting. There was no difference in progression free survival of (10.8 versus 10.4 months) and no difference in overall survival (29.0 versus 29.9 months) [26]. A non pre-planned analysis in patients with K-RAS wild type tumours demonstrated an improvement in overall survival and progression free survival in left sided tumours treated with cetuximab and right sided tumours treated with bevacizumab. The overall survival was poorer for patients with right sided tumours treated with cetuximab [27].

Aflibercept

Aflibercept is a recombinant fusion protein, that acts as a decoy receptor, preventing VEGF-A, VEGF-B and Placental growth factors (PIGFs) from binding to their receptors. It is a potent VEGF blocker [28]. There are no predictive biomarkers for its efficacy.

Aflibercept is licensed in addition to FOLFIRI chemotherapy in patients that have previously progressed on an oxaliplatin containing regimen. The VELOUR trial [29] included patients who had progressed during or within 6 months of an oxaliplatin containing regimen, with or without bevacizumab. It compared FOLFIRI + aflibercept vs FOLFIRI + placebo. Improvements in Median progression free survival (6.9 versus 4.7 months) and Median overall survival (13.5 versus 12.1 months) were statistically significant with the addition of Aflibercept independent of prior bevacizumab treatment.However, the clinical significance of a 6-week survival advantage is questionable. Toxicities

were increased with the addition of aflibercept and were similar to bevacizumab.

Aflibercept demonstrated no increased benefit in the 1st line setting in conjunction with FOLFOX and was associated with increased toxicity [30]. It is therefore only recommended in the 2nd line setting and can be considered as an alternative to continuing with Bevacizumab beyond progression as in the TML trial [24].

Ramucirumab

Ramucirumab is a recombinant monoclonal antibody that binds to VEGFR-2. There are no predictive biomarkers for its efficacy. It is licensed in the second line setting in combination with FOLFIRI chemotherapy, in patients who have progressed on first line treatment with oxaliplatin, 5-FU and Bevacizumab. The RAISE III trial randomised patients to receive FOLFIRI + Ramucirumab or FOLFIRI + placebo. There was a significant improvement in progression free survival (5.7 versus 4.5 months) and overall survival (13.3 versus 11.7 months). Once again although the improvement was statistically significant the improvement in survival of 6 weeks may be of dubious clinical benefit given the additional toxicity and financial cost associated with Ramucirumab treatment. Ramucirumab was associated with increased toxicity, in particular neutropenia, hypertension and fatigue [31].

Refractory disease

Regorafenib

Regorafenib is an orally administered tyrosine kinase inhibitor offered to patients with refractory metastatic colorectal cancer. It is active against angiogenic tyrosine kinases (including VEGF receptors) as well as oncogenic receptors and stromal receptors. These tyrosine kinases are implicated in tumour growth and angiogenesis.

Regorafenib is licensed for patients who have previously been treated with all available therapeutic agents including a fluoropyrimidine, oxaliplatin and irinotecan chemotherapy. They should also have received an anti-VEGF agent, and, if RAS wild type, an anti-EGFR treatment.

The CORRECT trial demonstrated a small but statistically significant improvement in median progression free (1.9 versus 1.7 months) and median overall survival (6.4 vs 5 months) when compared with placebo. Once again a 6-week survival improvement may not be considered clinically significant. Also only 1% of patients demonstrated a partial response although the disease control rate was improved (41% v 15%) [32]. Common toxicities include hand and foot syndrome, hypertension, diarrhoea, fatigue and skin rash. Patients should also be monitored for hepatic toxicity.

The approved dose is 160mg once daily for 21 days in a 28-day cycle. Due to the high rates of toxicity it is advisable not to start at the maximum dose of 160mg. Instead start at 80mg and escalate the dose in the absence of toxicity [33].

Trifluridine-tipiracil (TAS-102)

Trifluridine-tipiracil (TAS-102) is an orally administered cytotoxic agent. It consists of a nucleoside analogue (trifluridine) which is incorporated into DNA causing strand breaks, and a potent thymidine phosphorylase inhibitor which inhibits trifluridine metabolism and has antiangiogenic properties.

It has been shown to be effective in patients with refractory metastatic colorectal cancer.

The RECOURSE trial included 800 patients with metastatic disease who were refractory to or intolerant to other systemic agents. This placebo-controlled trial demonstrated a statistically significant improvement in median overall survival (7.1 vs 5.3 months) of 7 weeks. 44% of patients in the Trifluridine-tipiracil (TAS-102) group had disease control however only 2% of patients had an objective response [34].

Immunotherapy

Immunotherapy is a growing treatment strategy in many cancer sites.

Mutations in mismatch repair genes are seen in colorectal cancers associated with Lynch Syndrome (hereditary nonpolyposis colorectal cancer HNPCC) and between 15-20% of sporadic cases. These are known as tumours with deficient MMR (dMMR). This is associated with DNA microsatellite instability (MSI high or MSI-H). 3.5-6.5% of metastatic colorectal cancers are dMMR/MSI-H [35-37]. It was felt that these tumours may be more responsive to treatment with immune checkpoint inhibitors.

Pembrolizumab

Pembrolizumab is a monoclonal antibody to PD-1. The KEYNOTE-016 trial is a phase II study which

included 54 patients with MMR deficient (dMMR) and proficient (pMMR), heavily pre-treated metastatic colorectal cancer and dMMR non-colorectal cancer. The objective response rate was 40% with a disease control rate of 90% in patients with dMMR tumours. In contrast the objective response rate was 0% with a disease control rate of 11% in patients with pMMR tumours [38]. Median overall survival and progression free survival was not reached in the dMMR group. Median progression free survival was 2.2 months with a median overall survival of 5.0 months in the pMMR group.

As with checkpoint inhibitors in other studies there were a range of immune mediated toxicities. The commonest of these were rash, pancreatitis and thyroid dysfunction [39].

Ipilimumab and Nivolumab

Ipilimumab is a monoclonal antibody against cytotoxic T-Lymphocyte antigen 4 (CTLA-4). Nivolumab is a monoclonal antibody against PD-L1.

The CheckMate 142 trial included patients with dMMR heavily pre-treated metastatic colorectal cancer. They received nivolumab (3mg/kg every 2 weeks) with or without ipilimumab (1mg/kg every 3 weeks). Data presented at GI ASCO 2017 demonstrated that at a median follow up of 12 months, dMMR patients treated with nivolumab alone had an objective response rate of 31% with a median progression free survival of 9.6 months and 12-month survival of 73% [40]. Responses were seen in patients regardless of tumour PD-L1 expression level, or B-Raf or Ras mutation status.

One hundred and nineteen patients received a combination of ipilimumab and nivolumab. The objective response rate was 55% with a disease control rate >12 weeks was 80%. There was a complete response in 3.4% of patients. Median duration of response had not been reached. 12-month progression free survival was 71% and 12-month overall survival 85% [41].

Based on the above clinical trial data the NCCN guidelines 2017 have included Pembrolizumab and Nivolumab as 2nd line treatment options in MSI-H colorectal cancers and Pembrolizumab, Nivolumab and Ipilimumab have received FDA approval in 2018 for the second line treatment of MSI-H metastatic colorectal cancer. Trials in the first line setting have completed recruitment and we await results.

Continuous versus intermittent treatment

There is no clear optimal duration of initial treatment for patients with unresectable disease who respond to initial therapy. The point at which to offer treatment breaks will depend on the site and bulk of disease as well as a patient's response to treatment and symptoms. Appropriate patients may be able to have a number of months off treatment and restart treatment at the point of disease progression. This may not be appropriate for patients with bulky disease, primary disease still in-situ at risk of obstruction, or a poor performance status due to disease related symptoms.

Stepping down treatment is a reasonable alternative to chemotherapy free periods. The treatment plan will depend on the initial chemotherapy regimen used

In patients treated with Oxaliplatin, cumulative peripheral sensory neuropathy is the most common dose limiting side effect. In patients who are responding to treatment, it would be appropriate to consider stopping oxaliplatin before the development of severe neurotoxicity, usually after 3-4 months of treatment. Multiple maintenance regimens can be considered [42]. Treatment can be re-escalated or changed to an alternative regimen at the point of disease progression.

1. Infusional 5-FU or Capecitabine + Bevacizumab
   The Cairo 3 study assessed the efficacy of maintenance chemotherapy with capecitabine plus bevacizumab versus observation in patients who had received 6 cycles of XELOX plus bevacizumab. On first progression (PFS1) patients were planned to restart on XELOX plus Bevacizumab until second progression (PFS2). Maintenance treatment was associated with a significant improvement in time to second progression (11.7 versus 8.5 months $p<0.0001$) with a trend towards improved median overall survival (21.6 versus 18.1 months $p=0.156$) [43].
2. Single agent Cetuximab
   Phase II MACRO-2 trial randomised patients to receive 4 months of FOLFOX + cetuximab followed by cetuximab monotherapy or continued therapy with FOLFOX + cetuximab. Cetuximab monotherapy was found to be non-inferior based on the percentage of patients without progression at 9 months (60 versus 72 %, HR 0.60, 95% CI 0.31-1.15) [44].
3. Panitumumab +5-FU
   The phase II Valentino trial non inferiority study compared panitumumab alone vs Panitumumab +5-FU/LV following four months of induction therapy with FOLFOX plus panitumumab. Data

presented at ASCO 2018 found 10-month progression free survival was inferior with panitumumab alone (53 versus 63%) [45].

4. Infusional 5-FU or Capecitabine
   Appropriate for patients not on any targeted treatments.
5. Complete break from chemotherapy
   Can be considered in patients with small volume disease. They require close monitoring and recommencement of chemotherapy at the point of disease progression.
   The COIN trial compared continuous treatment with discontinuation after 12 weeks of treatment (until progression). The study was powered for non-inferiority. Median survival was not significantly better in the continuous arm (19.6 versus 18 months) [1] and a meta-analysis of 8 trials concluded intermittent delivery of chemotherapy did not significantly reduce overall survival vs continuous chemotherapy (HR 1.03 p=0.38). Quality of life was the same or better with intermittent therapy [46].

As irinotecan is not associated with cumulative toxicity in the same way as oxaliplat in, there is less need to offer intermittent treatment. For the majority of patients, treatment should be continued for as long as there is ongoing response and treatment is tolerable. Treatment breaks or de-escalation would still be appropriate when toxicity is impacting on quality of life.

Primary Tumour Location

A meta-analysis of more than 1.4 million patients has revealed the prognostic impact of the site of the primary tumour [47]. A left-sided (distal to the splenic flexure) primary tumour location was associated with a significantly reduced risk of death (HR 0.82 (0.79 – 0.84)). Patients with tumours of the caecum, ascending colon and hepatic flexure have almost a two-fold increased risk of dying from colorectal cancer than patients with tumours of the rectum and sigmoid.

Further, interest in primary tumour location developed with detailed analysis [48,49] of the recent FIRE-3 [25] and CALGB-80405 [26] trials and previous trials where outcomes have been analysed according to primary tumour location.

Study	Treatment	Median OS (months)	
		Left	Right
FIRE-3 [25]	FOLFIRI Cetuximab	38.3	18.3
	FOLFIRI Bevacizumab	28.0	23.0
CRYSTAL [11]	FOLFIRI Cetuximab	28.7	18.5
	FOLFIRI	21.7	15.0
CALGB-80405 [26]	FOLFOX/FOLFIRI Cetuximab	36.0	16.7
	FOLFOX/FOLFIRI Bevacizumab	31.4	24.2

As a result of these analyses the NCCN guideline 2017 changed their recommendation that EGFR Inhibitors (Cetuximab and Panitumumab) are only recommended in Left sided tumours, however the ESMO guidelines still do not include tumour sidedness in the algorithm for EGFR inhibitors. Although the survival for right sided tumours appears to be improved with Bevacizumab, the results are not statistically significant (Cetuximab v Bevacizumab in Right sided colorectal cancer: FIRE-3 HR 1.31 (0.81 – 3.11) p=0.28; CALGB-80405 HR1.27 (0.98 – 1.63) p=0.065)

These findings obviously point to biological differences between left and right sided tumours (e.g. increased rates of B-Raf mutation, Microsatellite instability and mucinous histology in right sided tumours), however they also reveal that our understanding of response to EGFR inhibitors is also lacking. It would appear that Right sided tumours with Ras and Raf wild-type do not respond as well to

EGFR inhibitors as left sided tumours. One potential explanation for this is the relative expression of the EGFR ligands epiregulin (EREG) and amphiregulin (AREG). High levels of EREG and AREG expression are known to predict for response to EGFR inhibitors [50,51], whilst low levels predict for lack of response. Epiregulin expression is usually higher in left sided tumours, and therefore may partly explain the improved response to EGFR inhibitors in left sided tumours, whilst the lower Epiregulin expression right sided tumours may explain why Ras wild-type tumours in the right colon still do not respond to EGFR inhibitors. This raises the as yet unanswered question as to whether we should avoid EGFR inhibitors in left sided tumours with low Epiregulin expression and use them in right sided tumours with high epiregulin expression. An alternative explanation may be found in the recently published Consensus Molecular Subtypes (CMS) of colorectal cancer [52].

Feature	CMS 1 (MSI Immune)	CMS 2 (Canonical)	CMS 3 (Metabolic)	CMS 4 (Mesenchymal)
Prevalence in early stage CRC	15%	40%	15%	30%
Primary tumour site	Right: 35% Left: 9%	Right: 26% Left: 48%	Right: 11% Left: 13%	Right: 28% Left: 30%
Cancer cell features	MSI, hypermutated, hypermethylated, Enriched for B-Raf mutations	MSS, chromosomal instability, EGFR and ERBB2 upregulation	Mixed MSI/MSS status, chromosomal instability, metabolic deregulation, enriched for K-Ras mutations	MSS, chromosomal instability, epithelial mesenchymal transition and stemness
Microenvironment features	Immune infiltration and activation. Infiltrated with cytotoxic T, helper T and NK cells	Limited immune cell or stromal infiltration	Limited immune cell or stromal infiltration	Highly infiltrated with stromal cells, regulatory T cells, B cells and myeloid derived suppressor cells. Angiogenesis
Prognosis	Better relapse free survival but worse survival after relapse	Better relapse free and overall survival	Better relapse free and overall survival	Worse relapse free and overall survival

One could predict that CMS 2 and possibly CMS 4 would have a higher response rate to EGFR inhibitors due to their underlying molecular and microenvironment features, and these two subtypes dominate in left-sided tumours.

In summary we can be confident that EGFR inhibitors are highly likely to work in left sided tumours, whilst they are less likely to work in right sided tumours, and therefore the extra cost and toxicities must be balanced against the reduced likelihood of benefit.

Management of Oligometastatic disease

Introduction

Outcomes for patients with oligometastatic colorectal cancer have improved over the last 10 years. Surgical series in selected patients can result in 5-year survival rates of 25-40% [53-55] whilst 5-year survival rates with chemotherapy are only 10% [56]- Most of the evidence available is non-randomised and is from the management of colorectal liver metastases, due to the predisposition for colorectal cancer to spread to the liver and for a number of patients to develop liver only metastatic disease.

Hepatic metastases

Appropriate patient selection is key to ensuring appropriate treatment and the best long-term outcomes. Patient selection depends on both patient factors (e.g. age, significant medical comorbidities, obesity) and also tumour biology factors (e.g. number of metastases >3, node positive primary, poorly differentiated primary, extrahepatic disease, metastasis diameter >5cm, CEA level >60ng/ml, Ras and B-Raf mutational analysis, MSI status, Synchronous versus metachronous presentation and disease-free interval). Clinical risk scores have been developed to stratify patients on their likelihood of recurrence, unfortunately none of the scoring systems is able to predict disease-specific survival, particularly beyond five years [57].

Appropriate investigation of the patients with liver metastases is vital for treatment planning. Usually biopsy of metastatic lesions is avoided to minimise the risk of biopsy track seeding, however biopsy may be appropriate if there is clinical uncertainty. Following a CT scan of the chest abdomen and pelvis, Liver specific MRI scanning has higher sensitivity and specificity for detecting subcentimeter lesions. In patients who go on to receive neo-adjuvant chemotherapy, a Liver MRI scan should take place both before and after chemotherapy treatment to aid surgical planning. Although the NCCN guideline recommends staging PET-CT imaging particularly to exclude extra-hepatic metastatic disease, its role has not been confirmed in subsequent trials. All patients considered for liver resection should be discussed in the Multi-disciplinary meeting for surgical planning with input from a hepatobiliary radiologist.

As surgical practice has evolved the boundaries of resectability have expanded, driven by what is feasible rather than evidence based. The presence of extra hepatic disease is no longer considered an absolute contraindication, provided the patient is carefully selected and complete R0 resection of both the intra- and extra-hepatic disease is feasible. Patients may be resectable if the surgeon is able to preserve two contiguous liver segments with adequate vascular flow and biliary drainage whilst preserving a future liver remnant >20% of the original healthy liver volume (>30% after chemotherapy) [58]. For patients presenting with bi-lobar disease, it may be feasible to surgically remove the lobe of the liver bearing the bulk of disease and ablate small volume disease in the other lobe. Alternatives include a two-stage resection whereby one lobe of the liver is cleared of metastases (e.g. by non-anatomical resection) and the portal vein is embolized/ligated to the lobe bearing the residual metastases. Over a number of weeks the non-embolised portion of the liver hypertrophies until the future liver remnant is sufficient and the embolized lobe can then be removed safely.

The surgical management of synchronous liver lesions presenting with the primary tumour still in-situ is more complex. In certain situations simultaneous resection of the primary and the metastasis is feasible (e.g. right sided primary and limited liver metastases) and is dependent on the expertise of the surgical team. The advantage is that the patient only undergoes one operation and is able to proceed directly to adjuvant chemotherapy. In other patients a staged resection will take place, either the primary first or the liver resection first. There is no difference in outcomes regardless of which approach is undertaken and this should be tailored to the individual patient. In patients presenting with a symptomatic primary (e.g. bleeding, obstructing), then colonic resection should take precedent to prevent subsequent complications from the primary tumour. Subsequently neoadjuvant chemotherapy may be administered to “assess tumour biology” prior to a staged liver resection after 3 months pre-operative chemotherapy, with a further 3 months adjuvant chemotherapy following liver resection. If the patient presents with bulky liver disease with an

asymptomatic primary, liver surgery first may be warranted to reduce the risk of the patient developing inoperable liver disease whilst the primary is resected and the patient recovers for their subsequent operation. This may then be followed by resection of the primary and then subsequent adjuvant chemotherapy. In patients presenting with inoperable primary disease (more commonly with circumferential resection margin (CRM) threatened Rectal cancer), initial neoadjuvant chemotherapy +/- chemoradiotherapy may be given. The liver metastases may be resected following the chemoradiotherapy whilst the primary is still responding to the radiotherapy.

There is a lack of clear evidence for the oncological management of resectable liver metastases. Patients with resectable liver metastases and "favourable biology" (e.g. metachronous presentation) should proceed directly to resection. In the EORTC EPOC Trial, patients with resectable liver metastases were randomized between resection +/- 6 cycles of pre- and post-operative FOLFOX chemotherapy [59]. There was no difference in the resection rate (83%), however the post-operative complication rate was higher (25% v 16%), without an increase in post-operative mortality. Although there was a trend to an improvement in 5-year Progression Free Survival (38% v 30% P=0.068), the 5-year overall survival was not significantly improved (51% v 48%) [60]. The subsequent New EPOC Trial investigated the addition of Cetuximab to the peri-operative FOLFOX regime (6 cycles pre- and post-operative) in patients with K-Ras wild type resectable colorectal liver metastases. The addition of Cetuximab was associated with a worse Progression Free Survival (14.1 v 20.5 months) [61].

Patients with resectable liver metastases and "uncertain" or "poor" biology (e.g. synchronous presentation, numerous hepatic metastases, borderline resectable metastases) may benefit from an "assessment" of the tumour biology by chemotherapy. A registry analysis of over 12,000 patients found that the overall survival in patients who underwent surgery following disease progression during neoadjuvant chemotherapy was 15% compared to 40-45% in those who responded to neoadjuvant chemotherapy [62]. Neoadjuvant chemotherapy +/- biological agent can also cause progressive liver damage (e.g. sinusoidal obstruction syndrome, steatohepatitis) resulting in an increase in post-operative morbidity and mortality [63-66]. Therefore, if neoadjuvant chemotherapy is to be used the duration of chemotherapy should be limited to 3 months and at least a 4-week gap should be maintained after completion of chemotherapy and a 6-week gap if Bevacizumab was used as part of the neoadjuvant therapy.

A number of patients will present with unresectable liver metastases, however about 20% of these may become resectable following a sufficient response to "conversion chemotherapy" [67-69]. Chemotherapy combinations with the highest response [70,71] should be considered (e.g. FOLFOXIRI [72,73], FOLFIRI Cetuximab [74], FOLFOX Cetuximab [75]) and chemotherapy may be continued beyond 3 months to maximise the response, with regular re-imaging to determine if and when resection may be achieved [76]. Treatment in a large volume hepatobiliary surgical centre can increase the likelihood of resection, by combining intensive chemotherapy with aggressive surgical management.

If neoadjuvant chemotherapy is to be used, then the ESMO and NCCN guidelines recommend a doublet regimen (FOLFOX, XELOX, FOLFIRI) with or without a targeted agent (Bevacizumab, Cetuximab, Panitumumab), despite the results of the New EPOC Trial [61]. The addition of Bevacizumab to doublet chemotherapy only increases the response rate by 6% [23] with additional risks of significant complications [77] which may not be justified. For patients with metachronous metastases who have received adjuvant Oxaliplatin based chemotherapy, neoadjuvant FOLFIRI (+/- targeted agent) would be advised. There is no evidence to support the use of dual antibody therapy (i.e. VEGF Inhibitor + EGFR Inhibitor). Given the recent analysis of right versus left sided tumours EGFR inhibitors should be avoided in patients with right sided Ras and Raf wild -type primary tumours.

Following complete resection of liver metastases, the NCCN guidelines recommend a total of six months of chemotherapy (including any pre-operative chemotherapy). Adjuvant chemotherapy would comprise FOLFOX or XELOX as there is no data to support the use of adjuvant Irinotecan [78] or biological agents [61]. The evidence for adjuvant chemotherapy shows an improvement in disease free survival but not for overall survival [60,79]. It may be appropriate to offer adjuvant Oxaliplatin based chemotherapy to patients following liver resection who did not receive any adjuvant chemotherapy or only 5-FU based adjuvant chemotherapy at the time of their original colorectal resection. In patients with resectable metachronous metastases who have previously received adjuvant Oxaliplatin based chemotherapy in my practice I would rarely offer adjuvant Oxaliplatin based chemotherapy following liver resection.

Although long-term survival after resection of colorectal liver metastases is a reality for up to 50% of patients, many patients will develop recurrent metastatic disease. The liver is the principle site of recurrence in 35-40% of patients and further potentially curative surgery may be possible, therefore close surveillance is warranted [80,81]. Close surveillance should include regular CEA monitoring (every 3-6 months for two years and then every 6 months until 5 years), CT imaging (every 3-6 months for two years and then every 6-12 months until 5 years). MRI imaging of the liver can also be used for more sensitive monitoring of the liver.

Although the evidence base for surgical resection is the most extensive, there are numerous other modalities for treatment of liver metastatic disease (e.g. Stereotactic ablative body radiotherapy (SBRT), radiofrequency ablation (RFA), microwave ablation, selective internal radiotherapy (SIRT), electroporation (Nanoknife), Trans-arterial chemoembolization (TACE)) and they can be used in combinations with surgery. Usually the choice of treatment depends more on local expertise than clinical evidence for benefit.

Given the survival benefits of resection of oligometastatic liver disease, the boundaries are constantly being expanded without randomized trial evidence. Patients may now be offered lung resections, adrenal resections and lymph node resections. A recent randomized controlled trial of chemotherapy +/- lung metastasectomy for oligometastatic colorectal lung metastases (PulMiCC) in the UK closed due to lack of recruitment as clinicians were unwilling for patients to be randomized to the non-surgical arm.

Peritoneal Metastases

Approximately 5–10% of patients with colorectal cancer present with synchronous peritoneal metastases and 20–50% may present with metachronous disease [82]. 10% of these patients have isolated peritoneal carcinomatosis. The occurrence of peritoneal carcinomatosis is associated with poor prognosis, without treatment the median survival is six to nine months.

The increased effectiveness of systemic chemotherapy in combination with targeted chemotherapy has improved the survival of patients with peritoneal metastases, however selected patients with localized peritoneal spread may benefit from additional surgical cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC) [83,84] with five-year overall survival approaching 50% [85,86]. Therefore, all patients with isolated peritoneal metastases should be evaluated by specialist multidisciplinary teams to assess their suitability for a multimodality treatment strategy. The concept of complete surgical cytoreduction to remove all macroscopically visible tumour (resection of the peritoneum, omentectomy and can also involve multi-visceral resection e.g. small bowel, kidney, uterus and ovaries) has been developed over the last 20 years [87,88].

Appropriate patient selection is vital [89,90] and scoring systems have been developed to assess the extent of peritoneal metastatic disease (e.g. the Peritoneal Cancer Index which is predictive for the outcome following surgery – High PCI scores are associated with worse outcome) [91,92]. Other factors involved include Ras and B-Raf mutational analysis, synchronous versus metachronous presentation, disease free interval, node positive primary and response to any neoadjuvant chemotherapy. Patients with mucinous and signet ring cell carcinomas have a greater predisposition to the development of peritoneal metastases and are often associated with B-Raf mutation status and poor prognosis [93].

Only 25% of patients diagnosed with peritoneal carcinomatosis are suitable for a curative approach such as cytoreductive surgery [94]. Complete cytoreduction is the key to a successful outcome and an essential prognostic factor [95,96]. Complete surgical cytoreduction is a major surgical undertaking with significant post-operative morbidity and also mortality [89], and therefore patients are required to be of good performance status without significant co-morbidities and should undergo this treatment in specialist centres.

As with liver metastases patients may benefit from neoadjuvant chemotherapy to assess the tumour biology. Only patients who do not progress on chemotherapy should be considered for cytoreductive surgery [89,90].

Hyperthermic intraperitoneal chemotherapy (HIPEC) involves the instillation of heated chemotherapy (often mitomycin C or Oxaliplatin) [84] into the abdominal cavity for 30-60 minutes whilst the patient is still under anaesthesia. It has been part of cytoreductive surgery for many years however the recent results from the PRODIGE-7 Trial have questioned the role of HIPEC. The trial randomized patients to cytoreductive surgery +/- HIPEC and there was no difference in median overall survival (41.7 v 41.2 months), nor 30-day mortality rate (1.5% v 1.5%) however the 60-day

complication rate was much higher in the HIPEC group (24.1% v 13.6%) [97]. A Dutch Trial (COLOPEC) assessed the role of adjuvant chemotherapy +/- adjuvant HIPEC in patients at high risk of developing peritoneal metastases (T4 or perforated primary tumour). The results were presented at ASCO GI in 2019 and revealed that the addition of adjuvant HIPEC does not reduce peritoneal recurrence in high risk colorectal cancer patients [98].

Conclusion

The outcome for patients with metastatic colorectal cancer has improved significantly over the last 20 years. At that time the median overall survival was 6 months, but today we would expect patients to survive up to 30 months in the good prognostic groups. This improvement has come about through the development of new drugs (Oxaliplatin, Irinotecan and the biological agents) however the success of these agents has unfortunately lagged behind many of the developments seen in other cancers (e.g. Breast Cancer, Lung Cancer, Melanoma). The role for Immunotherapy in Colorectal cancer appears to be limited to the MSI-H category for whom the outcomes thus far mirror the exciting results seen in other Immunotherapy responsive tumours. In Colorectal cancer we do now understand some of the biomarkers that both predict outcome and response and these must be used accurately to give our patients the best treatment schedule.

The exact order of treatments is likely of lesser importance than that the patient receives all available treatment options (Oxaliplatin, Irinotecan, 5-FU, EGFR inhibitor (if appropriate) and VEGF Inhibitor). The location of the primary tumour has introduced extra complexity to the targeted agent decision, however the true biological mechanism behind “sidedness” is still to be elucidated. Many of the newer targeted agents (e.g. Aflibercept, Regorafenib, Ramucirumab and Tas-102) offer slight survival benefits (around 6 weeks) that must be balanced against the cost and toxicities of these agents in patients who have received multiple lines of previous treatment. Where clinically appropriate treatment breaks can be of great benefit for patients in allowing them time off the “treadmill” of continuous chemotherapy.

Patients with truly oligometastatic disease can be offered a “second chance” at cure with appropriate combinations of systemic and localised therapy. Most evidence has been accumulated for liver resection and Cytoreductive Surgery +/- HIPEC for peritoneal metastases, however very little of this is randomised, and we must continue to apply our understanding of the biology of the patient’s disease to the discussion on their future treatment and just because the resection is technically feasible does not mean that it is clinically appropriate. Incorporating all the localised treatment options (Surgery, SBRT, RFA, SIRT, TACE etc) into treatment algorithms is a challenge moving forward.

Trial	Line of treatment	Patient numbers	Treatment Arms	ORR (%)	PFS (Months)	HR	p-value	OS (Months)	HR	p-value
EGFR										
CRYSTAL [11]	1st	1198	FOLFIRI Cetuximab v FOLFIRI	**47 v 39**	**8.9 v 8.0**	**0.85**	**0.048**	19.9 v 8.6	0.93	0.31
CRYSTAL [11]	K-Ras WT			**59 v 43**	**9.9 v 8.7**	**0.68**	**0.02**	**24.9 v 21.0**	**0.84**	**0.0093**
OPUS [12]	1st K-Ras WT	337	FOLFOX Cetuximab v FOLFOX	**57 v 34**	**8.3 v 7.2**	**0.57**	**0.0064**	22.8 v 18.5	0.86	0.39
COIN [13]	1st K-Ras WT	1630	FOLFOX/XELOX Cetuximab v XELOX/FOLFOX	**64 v 57**	8.6 v 8.6	0.96	0.6	17.0 v 17.9	1.04	0.67
EPIC [14]	2nd	1298	Irinotecan Cetuximab v Irinotecan	**16 v 4**	**4.0 v 2.6**	**0.69**	**<0.0001**	10.7 v 10	0.98	0.71
BOND [15]	2nd	329	Cetuximab Irinotecan v Cetuximab	**23 v 11**	**4.1 v 1.5**	**0.54**	**0.001**	8.6 v 6.9	0.91	0.48
NCT00079006 [16]	3rd	572	Cetuximab v BSC	**8 v 0 DCR 39 v 11**		**0.68**	**<0.001**	**6.1 v 4.6**	**0.77**	**0.005**
PRIME [17]	1st K-Ras WT	1183	FOLFOX Panitumumab v FOLFOX	**57 v 48**	**10.0 v 8.6**	**0.8**	**0.01**	**23.8 v 19.4**	**0.83**	**0.03**
Study 20050181 [19]	2nd K-Ras WT	1186	FOLFIRI Panitumumab v FOLFIRI	**36 v 10**	**6.7 v 4.9**	**0.82**	**0.023**	14.5 v 12.5	0.92	0.37
[20]	3rd	463	Panitumumab v BSC	**10 v 0**	**2.0 v 1.8**	**0.54**	**P<0.0001**		1	0.81
ASPECCT [21]	3rd	999	Panitumumab v Cetuximab	22 v 19	4.2 v 4.4	0.98	Non-inferior	10.4 v 10.0	0.97	Non-inferior
VEGF										
Avex [22]	1st (Elderly)	280	Capecitabine Bevacizumab v Capecitabine	19 v 10	**9.1 v 5.1**	**0.53**	**<0.0001**	20.7 v 16.8	0.79	0.182
Metanalysis [23]	1st	3763	Chemo Bevacizumab v Chemo	39 v 33	**8.8 v 6.4**	**0.57**	**<0.0001**	**18.7 v 16.1**	**0.8**	**0.0003**
TML [24]	2nd (after 1st line Bevacizumab)	820	Chemo Bevacizumab v Chemo	5 v 4	**5.7 v 4.1**	**0.68**	**<0.0001**	**11.2 v 9.8**	**0.81**	**0.0062**
VELOUR [29]	2nd	1226	FOLFIRI Aflibercept v FOLFIRI	**20 v 11**	**6.9 v 4.7**	**0.76**	**<0.0001**	**13.5 v 12.1**	**0.82**	**0.0032**
RAISE III [31]	2nd	1072	FOLFIRI Ramucirumab v FOLFIRI	13 v 12	**5.7 v 4.5**	**0.79**	**0.0005**	**13.3 v 11.7**	**0.84**	**0.022**
EGFR v VEGF										
FIRE-3 [25]	1st	592	FOLFIRI Cetuximab v FOLFIRI Bevacizumab	62 v 58	10.0 v 10.3	1.06	0.55	**28.7 v 25.0**	**0.77**	**0.017**

Table 2 : Summary of evidence in treatment of metastatic colorectal carcinoma.

FIRE-3 [25]	1st K-Ras WT	592	FOLFIRI Cetuximab v FOLFIRI Bevacizumab	62 v 58	10.0 v 10.3	1.06	0.55	**28.7 v 25.0**	**0.77**	**0.017**
CALGB 80405 [26]	1st K-Ras WT	1137	FOLFOX/FOLFIRI Bevacizumab v FOLFOX/FOLFIRI Cetuximab	57 s 66	10.8 v 10.4	1.04	0.55	29.0 v 29.9	0.92	0.34
Refractory disease										
CORRECT [32]	3rd	760	Regorafenib v placebo	**DCR 41 v 15**	**1.9 v 1.7**	**0.49**	**0.000001**	**6.4 v 5.0**	**0.77**	**0.0052**
RECOURSE [34]	3rd	800	TAS102 v placebo	1.6 v 0.4 **DCR 44 v 16**	**2.0 v 1.7**	**0.48**	**<0.001**	**7.1 v 5.3**	**0.68**	**<0.001**
Maintenance treatment										
CAIRO 3 [43]	1st	558	Capecitabine Bevacizumab v Observation		**11.7 v 8.5**	**0.67**	**<0.0001**	21.6 v 18.1	0.87	0.156
MACRO 2 [44]	1st	193	Cetuximab v FOLFOX Cetuximab	47 v 39	**8.9 v 9.8**	**0.69**	**0.09**	23.6 v 22.2	1.15	0.54
VALENTINO [45]	1st	229	Panitumumab v 5-FU Panitumumab	66 v 67	10.2 v 13.0	1.55	0.011 (Inferior)			
Immunotherapy										
Keynote 016 [38]	3rd	54	Pembrolizumab dMMR v pMMR	**40 v 0 DCR 90 v 11**	**NR v 2.2**			**NR v 5.0**		
Checkmate 142 [40,41]										
dMMR	2nd/3rd	74	Nivolumab	31	1yr 44%			1yr 73%		
dMMR	2nd/3rd	119	Ipilimumab Nivolumab	55	1yr 71%			1yr 85%		

Bold Type Statistically significant result NR Not Reached DCR Disease Control Rate PFS Progression Free Survival OS Overall Survival
dMMR Deficient Mismatch Repair pMMR Proficient MMR ORR Objective Response Rate HR Hazard Ratio WT Wild Type

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Original Research Article

Impact on functional outcomes in oral cavity cancers treated with different techniques of Radiotherapy at National Cancer Hospital Maharagama, Sri Lanka.

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Abstract

Aim: Radiotherapy (RT) is the mainstay of treatment for oral cavity cancers. This procedure is known to be associated with various complications including affecting functional outcomes such as pain, appearance, dryness of the mouth, salivation, speech and swallowing. However new RT techniques are associated with better functional outcomes and were used to treat oral cancer patients in Sri Lanka. The current study was conducted to assess functional outcomes in patients with oral cavity cancers treated with different modalities of Radiotherapy at National Cancer Hospital, Maharagama, Sri Lanka.

Materials and Methods: A retrospective study including 116 patients diagnosed with histologically proven squamous cell carcinomas treated with different RT techniques at different time frames from 2001 to 2014 at National Cancer Hospital, Maharagama were included in the study. Data were collected via an interviewer-administered University of Washington Quality of Life Questionnaire (UW-QOL V4). It assessed the 6 main functional domains; pain, appearance, swallowing, speech, taste and saliva of patients. The mean functional score for the 6 domains calculated and compared against the different radiotherapy techniques.

Results: Majority of the cases were carcinoma of buccal mucosa (50.8%), tongue (32.8%) and floor of the mouth (9.5%). The pain scores with different Radiotherapy techniques were not significantly different. However, the other domain scores (Appearance, Swallowing, Speech, Taste and Saliva) were significantly different in the different radiotherapy techniques compared. It also showed that except in the pain domain, patients who underwent 2D Co 60 treatment scored the lowest quality of life score in all the domains while those who had Brachytherapy and IMRT had the highest score in all the other domains.

Conclusions: There were better functional outcomes with Brachytherapy and IMRT techniques in pain, appearance, swallowing, speech, taste and salivation, and worst outcome were with 2DCF Cobolt 60 teletherapy machines.

Key words: Oral Cavity Cancers, SCC, Different RT Techniques, functional outcomes

Introduction

Radiotherapy (RT), either external beam or brachytherapy, is the mainstay of treatment for oral cavity cancers (1). Particularly in early stage oral cavity cancers such as tongue, floor of mouth and lip, radiation alone is highly effective and produces excellent survival benefits (2). Radiothetapy is associated with complications. However, novel radiotherapy techniques such as Intensity Modulated Radiation Therapy (IMRT) and 3D CF are associated with better treatment outcomes as well as significantly reduced adverse effects (3-5). Generally, novel techniques allows delivery of lower doses of radiation to normal structures, while maintaing a significant higher dose to the tumor (6).

However, complete complication profile of some of the novel radiotherapy techniques are poorly studied. There is evidence to indicate that even the newer techniques are associated with significant negative negative sequelae such as mastication, articulation and speech , residual pain, xerostomia and dryness (7-10). Some of the late sequelae progress slowly and may be completely reversible, partially reversible or irreversible. Futher, evidence indicates that the types of complications and their resultant functional limitations vary with the diferent radiotherapy types. A Couple of authors have demonstrated the superiority of IMRT in parotid gland sparing and a better salivary toxicity profile (11, 12).

Though conventional radiotherapy techniques have been used in Sri Lanka for decades, the novel techniques such as IMRT and 3D CF have only been used for less than eight years. Thus, how these different radiotherapy techniques affect the functional outcomes among the patietns with oral cavity cancers have not been studied in Sri Lanka. Our study aimed to evaluate the different functional outcomes of oral cavity cancers with different radiotherapy techniques such as 2D Co 60, LINAC based 3DF Radiotherapy technique, conventional IMRT and definitive Brachytherapy. This evidence will give new insight into the effect of diffrerent radiotherapy techniques on the quality of life of patirents, which will help the clinicians in their decision-making.

Methods

A hospital based retrospective cross-sectional study was conducted at National Cancer Hospital Maharagama. The study population consisted of histologically proven squamous cell carcinoma (SCC), TNM- T1 or T2, N0 or M0 cases, who were treated with definitive RT, definitive chemo irradiation or surgery followed by adjunct RT or Chemo irradiation.

A sample of 116 patients treated with different Radiation therapy techniques in different time frames were selected. This was done as these techniques were available in different times from 2001 to 2014 at National Cancer Hospital, Maharagama.

Patients who underwent Micoselectron brachytherapy therapy from 2001 to 2005 and Co 60 HDR brachytherapy from 2010 to 2014 for oral cavity cancers, who were attending follow-up clinics were recruited for the study. Some patient who were unable to attend clinics were contacted over the phone and evaluated. Additional data for brachytherapy patients was also obtained from the Brachytherapy registry, theatre registry and obtaining individual files from the record room. LINAC treatments - 3DCF and IMRT cases from 2011 to 2014 were retrieved from the Varian Registry and ELEKTA Registry and patient's contact numbers were accessed from patient Manager Data base. Patients who were given Co 60 2DCF teletherapy from 2013 to 2014 were collected from the registry.

The questionnaire

Data was collected via an interviewer-administered University of Washington Quality of Life

Questionnaire (UW-QOL V4) which was translated to Sinhala and Tamil Languages. Additional data was also obtained from Brachytherapy registry, theatre registry and obtaining individual files from record room. In addition to these questions, socio demographic details and data related to patients were also collected.

Name: _____
Date: _____

University of Washington Quality of Life Questionnaire (UW-QOL)

This questionnaire asks about your health and quality of life **over the past seven days**. Please answer all of the questions by checking one box for each question.

1. **Pain**. (Check one box: ☑)

- ☐ I have no pain.
- ☐ There is mild pain not needing medication.
- ☐ I have moderate pain - requires regular medication (codeine or nonnarcotic).
- ☐ I have severe pain controlled only by narcotics.
- ☐ I have severe pain, not controlled by medication.

2. **Appearance**. (Check one box: ☑)

- ☐ There is no change in my appearance.
- ☐ The change in my appearance is minor.
- ☐ My appearance bothers me but I remain active.
- ☐ I feel significantly disfigured and limit my activities due to my appearance.
- ☐ I cannot be with people due to my appearance.

3. **Activity**. (Check one box: ☑)

- ☐ I am as active as I have ever been.
- ☐ There are times when I can't keep up my old pace, but not often.
- ☐ I am often tired and have slowed down my activities although I still get out.
- ☐ I don't go out because I don't have the strength.
- ☐ I am usually in bed or chair and don't leave home.

4. **Recreation**. (Check one box: ☑)

- ☐ There are no limitations to recreation at home or away from home.
- ☐ There are a few things I can't do but I still get out and enjoy life.
- ☐ There are many times when I wish I could get out more, but I'm not up to it.
- ☐ There are severe limitations to what I can do, mostly I stay at home and watch TV.
- ☐ I can't do anything enjoyable.

5. **Swallowing**. (Check one box: ☑)

- ☐ I can swallow as well as ever.
- ☐ I cannot swallow certain solid foods.
- ☐ I can only swallow liquid food.
- ☐ I cannot swallow because it "goes down the wrong way" and chokes me.

6. **Chewing**. (Check one box: ☑)

- ☐ I can chew as well as ever.
- ☐ I can eat soft solids but cannot chew some foods.
- ☐ I cannot even chew soft solids.

 v. 4

Data analysis

Data entering was done using Microsoft Excel 2010 and analysis done using SPSS version 20.0 software.

Administrative Requirements and Ethical Clearance

Ethical clearance was obtained from the ethical review committee of Postgraduate Institute of Medicine. Administrative approval to collect data was obtained from Director Cancer Institute Maharagama.

Results

The study included 116 patients with oral cavity cancers registered at National Cancer Institute Maharagama

Table 1: Distribution of the study population by socio-demographic characteristics, site of Oral Cancer, Clinical stage, Level of Lymph nodes

Characteristic	**Frequency (n = 116)**	**Percentage**
Sex		
Female	27	23.3
Male	89	76.7
Age (Years)		
Less than 40 years	03	2.6
41-50 years	12	10.3
51-60 years	24	21.6
61-70 years	35	30.2
71-80 years	36	31.0
More than 80 years	05	4.3
Site		
Tongue	38	32.8
Lip	2	1.7
Angle of Mouth	1	0.9

Buccal Mucosa	59	50.8
Floor of Mouth	11	9.5
Hard Palate	3	2.6
Right Alveolus	2	1.7
Clinical stage		
T1	30	25.9
T2	83	71.6
Not Done	03	2.6
Clinical stage		
N_0	54	46.6
N_1	49	42.3
Not done	13	11.2
Total	**116**	**100.0**

By analyzing the above table 1, the socio- demographic characteristics of the sample population of total 116 patients, there are 23.3% female and 76.7% of male.

Considering the age break down in this sample population, the highest number of patients were between the ages of 71- 80 years (31%). The next most significant number of patients is were from 61- 70 years age group (30%) and thirdly, between 51-60 years (21.6%). Others include 10.3% between 41- 50 years, and 4.3% who were more than 80 years age, and 2.6% who were less than 40 years old.

Dividing according to the sites of origin of head and neck cancers in this population, squamous cell carcinoma of the buccal mucosa was the highest number with 59 patients (50.8%) followed by the tongue with 38 (32.8%). The third most common site was the floor of the mouth with 11 patients (9.5%). The carcinomas of the hard palate accounted for 3 patients (2.6%). Lip carcinoma and alveolus had the lowest number, with 2 patents each (2% each).In table 3, analyzing the distribution of the study population by clinical stage, the highest number of the patients are T2 with 83 patients (71.6%) and followed by T1 giving a number of 30 patients (25.9%). Among them only 3 patients were unstaged (2.6%). These patients's nodal staging was done clinically and radiologically by CT imaging. Looking into the nodal staging, most patients were N0 with 54 patients constitute 46.6% and the second highest number comes from N1 with 49 patients comprising 42.3%. Nodal staging was not properly done in 13 patients who accounted for 11.2%.

Table 5: Distribution of the study population by RT technique

Clinical stage	Number	Percentage
2D Co 60	31	26.7
3D CF	24	20.7
Brachytherapy	35	30.2
IMRT	26	22.4
Total	**116**	**100.0**

None of the patients had a previous history of malignancy or history of previous chemotherapy.

Table 5 depicts the distribution of the study population by different RT techniques.

In this study, out of 116 patients, 35 patients (30%) were treated with brachytherapy, 31 patients (26.7%) with 2D conformal Cobolt 60 teletherapy machines, 26 patients (22.4%) with conventional Intensity Modulated Radiotherapy and 24 patients (20.7%) with LINAC based 3D conformal technique.

Discussion

In this study, essentially functional outcomes (e.g.: pain, appearance, swallowing, speech, taste and saliva production) were collected and analysed in early stage (T1,T2 or N0,N1) oral cavity cancers via a University of Washington Quality of Life Questionnaire (UW-QOL V4) by either direct or indirect (Telephone) interviews. Thesewere all late sequale, since this project started collecting and assessing data after six months of completion of different radiotherapy techniques.

Considering Overall functional score changes with different RT techniques, speech and swallowing were minimally affected with a mean and median of 97.6 and 100 and 94.5 and 100.

Furthermore, analyzing the functional speech scores against different RT techniques with $p<0.05$ showing a significant different, no speech problems were recorded with brachytherapy and 3DCFRT and IMRT compared to 2DCFRT with Co 60 teletherapy machines.

Speech difficulties can occur owing to post-Radiotherapy fibrosis, mouth dryness or other compounding factors such as tongue cancers, lip cancers, edentulousness and trismus, which were not assessed in this study.

Funtional scores of swallowing difficulties were also statistically significant with different RT techniques ($p<0.005$).

Most of the patents complained of acute dysphagia of varying intensity due to severe mucositis; potentially leading to Nasogastic tube feeding or enteral feeding which are transient and not addressed in my study design, giving thoughts and inspirations for a future study. Irradiation of the Pharyngeal Superior Constrictor Muscles (PSCM) seem to play a crucial role in radiation-related swallowing dysfunctions. Some centers around the world (eg; Australia) adhere to the guidelines for contouring the superior, middle and inferior constrictor musles in IMRT and tomotherapy planning to minimize the dose to these structurs and related dysphagia There are current and unpublized studies related to this. (18, 19)

In view of functional appearance, the best functional appearance is by brachytherapy, followed by IMRT,

and lastly by LINAC based 3DCRT with a highly significant difference ($p<0.001$).

Negative cosmetic effects could be due to many reasons, such as asymmetry of the face and neck as a result of surgical intervention, post-radiation and surgically induced subcutaneous and musle fibrosis, and discoloration of the skin as a consequence of increase dose to the skin by low energy X- ray treatments. (20)

Interstitial brachytherapy implants deliver optimal doses to the target volume more precisely while sparing normal structures, thus enhancing therapeutic ratio by exploiting the effect of localized therapy while concerning normal tissue tolerance including the surrounding skin with rapid dose fall-off outside the target volume. (21)

LINAC based IMRT and 3DCRT treat with high energy X- rays delivering a minimal dose to the skin and superficial tissues, giving less undesiarable cosmetic results.

Statistical calculation of taste scores with regard to different RT techniques ($p<0.001$, statistically highly significant difference) indicates that lease taste impairment was with brachytherapy, followed by IMRT, 3DCFRT and finally 2DFRT, in that order..

Literature shows that dysgeusia affects patients from the second or third week of radiotherapy onwards, and it may last for several weeks or even months and is frequently reversible. It occurs because the taste buds are radiosensitive, with the degeneration of their normal histological architecture and xerostomia itself as a contributary factor. (22)

Dysgeusia can be precipitated by doses as low as 30 Gy and the relationship of the severity of dysgeusia to radiotherapy dose is not linear. (22)

Comparison of the distribution of the pain scores with with different radiotherapy techniques with a $p > 0.05$ which showed no statistically significant difference. Pain is usually an acute symptom, possibly due to mucositis, biopsy, surgery or dental extraction. However, as a long term side effect, it may be because of surgery, post-treatment fibrosis or recurrence of the disease.

Finally, looking into functional saliva scores, different RT techniques reported highly significant differences here. there was no xerostomia caused by brachytherapy and then less with IMRT, 3DCFRT and worse by 2DCRT Cobalt 60 teletherapy.

The degree of xerostomia is largely dependent on the radiation dose and the volume of the major salivary glands within the radiation fields. Loss of function of salivary glands is usually permanent after radiation doses of 35Gy. Xerostomia is responsible for difficulty in swallowing, nutritional deficiency, compromised oral hygiene, poor dental condition, altered taste sensation, impaired speech function and poor sleep quality. It can lead to poor quality of life and poor social activity. (23)

Implementing IMRT for head and neck cancers has been reported to have a positive impact on the reduction of salivary toxicity. The goal in planning is to keep the mean dose to the parotid gland below 26Gy. (24)

Patients with xerostomia complain of oral discomfort, taste loss, speech and swallowing difficulties. Saliva also suffers qualitative alterations resulting from radiotherapy with decrease of amylase activity, buffer capacity and pH, with consequent acidification. (24)

2DCF RT is designed based on plain X-ray images (2D) and basically prescribed to the middle slice of the tumor with simple equipment, infrastructure and training. This primitive, simple technique can deliver significant doses to normal structures. Therefore, 2DCF RT by Co 60 teletherapy gives a much higher dose to salivary glands in head and neck region.

In LINAC based 3DCF RT, the beam is shaped to the outline of the target volume as demonstrated from the beam eye view. Once the beam is turned on the whole radiation dose is delivered to the shape of the target and also to the normal structures including major salivary glands. (9)

IMRT is a more advanced and a sophisticated form of 3DCF planning. In contrast to 3DCF technique, inIMRT, small leaves that move across the beam path at different patterns and speed further subdivide individual beams. This maneuver is capable of delivering a much higher dose to the tumor, while a lower dose is delivered to critical structures such as the parotid glands. (9)

National Cancer Hospital, Maharagama, Sri Lanka, in its journey of radiotherapy evolution to date, has been treating patients with 2DCF Co60 teletherapy since its inception and installed its first linear accelerator

(Variant) in 2008 and the second ELECTA machine in 2013, reaching another landmark is state-of-the-art featuring 3DCF,IMRT,VMAT, IGRT,SBRT and SRT.

These manoeuvres, such as IMRT, VMAT and Tomotherapy, are important techniques in treating head and neck cancers with excellent therapeutic and functional outcomes and more clinical and technical training must be emphasized in our setting. Though we were treating early stage oral cavity cancer with brachytherapy in the past, clinical expertise is lacking today and it is important to promote clinical, technical and dosimetry training for oncologists, radiation phycists and radiation theraphists.

According to Cancer Statistics in Sri Lanka by National Cancer Control Programme, in the year 2010, the most common cancer in males and the fifth most common cancer in females population by the site are lip, oral cavity and pharynx. However, with increased work load, long waiting list, unavailability and inaccessibility in peripheral centers to the linear accelerator treatment facilities, most of the head and neck cancer patients are treated with 2DCF Co 60 teletherapy with lot of undesirable radiation side effects such as facial and neck hyperpigmentation and severe xerostomia owing to high doses to parotid glands, which is an obslete procedure and unacceptable considering the treatment related toxicities.

Therefore, it is essentially a need to enlighten and emphasize policy makers to look for donors and allocate funds to install a few linear accelarators in peripheral centers.

There are similar studies carried out in other countries especially on nasopharynx and oropharynx. A Germen study in 2010, revieved publized data to assess whether IMRT is associated with more quality of life (QoL) benefits when compared to 2DRT and 3DCRT.(25)

English language literature published between 2005 and 2010 was analized in head and neck cancers. Study participants were nasopharyngeal carcinomas only, oropharyngeal carcinomas only and mixed populations.

The EORTC QLQ-C30 was used to assess functional outcomes and IMRT was associated with a statistically significant improvement in some QoL assessments versus 2DRT and 3DRT, exclusively those related to xerostomia, including dryness of the mouth, thick saliva and mastication. These results were similar to my study but their sample population in view of sites of head and neck region was different.(26)

Another prospective longitudinal study presented in part at the 44th Annual Meeting of the American Society for Therapeutic Radiology Oncology, New Orleans, 2002, Parotid sparing IMRT for head-and-neck cancer reduces xerostomia when compared with standard radiotherapy, which is comparable with my study.(28)

Study included head and neck cancer patients receiving multisegmental static IMRT. All patients were given a validated xerostomia questionnaire (XQ), and a head and neck cancer related QOL questionnaire consisting of four multi-item domains: Eating, Communication, Pain, and Emotion.

There was a statistically significant correlation noted between xerostomia and other domains of QOL: eating, communication, pain, and emotion. Xerostomia and QOL scores improved significantly during the first year after RT. These findings are quite similar to the results in this study.

Although there were several limitations, I believe that these results will be beneficial as an early step in continuing research in the field of Radiotherapy treatment of head and neck cancers optimizing local control, quality of life and survival.

Conclusions:

Absolute consideration of those findings in oral cavity cancers who were treated with different Radiotherapy techniques, following descriptive statistical analysis with a p value of <0.001 indicating a highly significant difference, there were better functional outcomes in pain, appearence, swallowing, speech, taste and salivation with Brachytherapy, IMRT technique and then with LINAC based 3DCFRT and worst outcomes with 2DCF Cobolt 60 teletherapy machines. In other words, best radiotherapy techniques in view of better functional outcomes and quality of life for early oral cavity cancers are brachytherapy and IMRT.

Recommendations:

When all treatment strategies are ananlysed in oral cavity cancer patients, disease effects themselves and treatment adverse effects may potentially interfere with functional outcome and the quality of life.

As a whole, our goal of treatment of oral cavity SCC is complete cure with optimal functional results with better quality of life to the patient.

According to the results of this project with descriptive statistical analysis, brachytherapy is the best Radiotherapy technique for early stage T1 and T2 oral cavity cancers, enhancing the therapeutic ratio by exploiting the effects of localized therapy while concerning normal tissue tolerance and reducing the overall treatment time. Therefore, this technique should be utilized whenever the technology, clinical experience and expertise are available and when the careful selection criteria are fulfilled.

In the present era of radiotherapy developments, there are many technically advanced treatment options such as conventional IMRT, Rotational techniques and Tomotherapy to offer to the head and neck cancer patients, which considerably increase the rate of loco regional control of the disease and remarkably reduce treatment side effects.

As an advanced development of EBRT, IMRT is capable of delivering a much higher dose to the primary tumor, while minimizing the dose to critical structures.

Likewise, in our data analysis, IMRT shows minimal late sequale with better functional outcomes than other techniques such as 3DCRT or 2DCRT. Therefore IMRT technique should be utilized for suitable candidates with oral cavity SCC whenever possible.

Late side effects are more prominent with 2DCFRT with Cobolt 60 So we must tryto avoid using thesetechniques when treating f early head and neck SCC with curative intent having a long survival. However, LINAC based 3DCFRT has better outcomes with regard to the functional aspects when compared to 2DCFRT Cobolt 60.

Conflict of interests

The authors declare that they have no competing interest.

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Original Research Article

A retrospective study on the outcome of childhood Germ Cell Tumours treated at National Cancer Institute, Maharagama, Sri Lanka, from 2005 to 2013

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Key words: GCT, Children, Sri Lanka, Outcome

Abstract

Introduction
Germ cell tumours (GCTs) are originated from primordial germ cells that mostly appear as midline tumours. The extracranial GCTs encompass gonadal and extragonadal types. While it is a rare malignancy in children below 15 years of age, incidence rises with the puberty. Surgical excision and chemotherapy are the mainstay of the treatment. Response assessment is evaluated by the reduction of the value of the tumour markers. GCTs in general carry a good prognosis, thus long term toxicity should be addressed at an individual level.

Objectives
was designed to evaluate the demographic data (age, stage, tumor histology, primary site ,social status) and the outcome; (5 year survival, acute and late toxicity profiles of chemotherapy regimens used, and the response to treatment by the analysis of tumour markers)

Methodology
This is a retrospective non-randomized observational study (n=54) in children with
malignant GCTs treated at National Cancer Institute, Maharagama (NCIM) between 2005 and 2013

Results
There were 33 girls and 21 boys, aged between 2 weeks to 15 years (median 3.9 years). Primary sites were ovarian (16), testicular (12), extra gonadal, (23) and intra cranial (3). Statistical analysis indicated that the completeness of the surgical excision was the most important prognostic variable. Extragonadal tumors were usually presented at an advanced stage at diagnosis, and most of them had an incomplete surgical excision. But site of the tumour did not have prognostic value and was independent of the disease stage once it was resected completely. Overall survival at 5 years was 84% in this study.
Carboplatin based UKCCSG GCT protocol showed, more feasibility and had less toxicity profile than Ifosfamide based MAKEI 96 in our clinical setting.

Conclusion
Completeness of the surgery is an important prognostic variable. Five year overall survival is 84%.

Key words : Germ cell tumours, Childhood, Sri Lanka

INTRODUCTION

Germ Cell Tumors (GCT) are benign or malignant neoplasms arising from the primordial pluripotent germ cell, that migrate from the yolk sac, through mesentery to the gonadal ridge thus occur in gonadal or extra gonadal sites close to midline. They constitute a highly heterogeneous group of tumours that significantly varies with respect to the site, clinical presentation, histology and the tumour biology.[1,2,3].

GCTs account for 3% of childhood malignancies below 15 years of age, and 14% among the adolescents from 15 to 19 years of age[4]. GCTs show a clear bimodal age distribution with peaks at 2 and 20 years of age. Biologic studies confirm this bimodal distribution, as the childhood York sac tumours (YST) are most commonly diploid or tetraploid, whereas malignant GCTs in adolescents are aneuploid.

The symptoms are generally caused by the pressure effects on adjacent organs due to rapidly growing mass or less often due to endocrinal effects including excessive production of human chorionic gonadotropin (Choriocarcinoma, dysgerminoma), carcinoid syndrome and hyperthyroidism (monodermal teratomas such as carcinoid tumor, struma ovarii)[6]. Very rarely they present as para-neoplastic limbic encephalitis[7].

Histologically this diverse group of tumours comprise of Seminomas (SE) (synonyms - germinoma and dysgerminoma), Yolk sac tumours (YST), Embryonal carcinoma (EC), Choriocarcinoma (CHC), Teratoma (TER) (including Mature, Immature, with malignant transformation and monodermal), tumours with mixed histology (MGCT), spermatocytic Seminomas and polyembryomas (POLY) according to WHO classification.

Key tumour markers of GCTs are alpha-fetoprotein (AFP), β-subunit of human chorionic gonadotropin (BHCG) and lactate dehydrogenase (LDH). Tumours with yolk sac component produce AFP and tumours derived from trophoblastic tissue produce BHCG. Mature teratoma and germinoma do not secrete AFP or BHCG. These markers are found in about 70-80% of the non seminomatous tumors. These markers can be used to monitor response, tumor progression and for recurrence.

For most sites except the liver and the retro peritoneum, tumor marker measurement in combination with imaging allows for a clinical diagnosis. In equivocal cases (i.e. non-diagnostic markers, hepatic or upper retroperitoneal tumors) a diagnostic biopsy is recommended.

Because of the diversity of the GCTs, Prognosis and appropriate treatment depend on several factors such as histology, age, stage of the disease, primary site and the completion of the primary surgery.

Prior to the era of effective chemotherapy, children with extra cranial malignant germ cell tumors (GCTs) had 3-year survival rates of 15% to 20% with surgery and radiation therapy[8]. Evolution of chemotherapy began in 1956, where Li et al demonstrated efficacy of Methotrexate for gestational Choriocarcinoma. Chemotherapeutic combinations including Cisplatin represented one of the main advances in treatment of GCTs in mid 1970s with complete response rates of 85%[9]. More recently French, Germen and North American studies with Cisplatin, Etoposide, Bleomycin (BEP) or with Cisplatin, Etoposide and Ifosfamide [,12,13,14] shows even superior results with acceptable low toxic profiles[14].

Primary surgical resection is the therapy of choice in benign tumors like Teratoma whereas in malignant lesions upfront surgical excision is indicated when possible. If the initial workup reveals infiltration into adjacent organs and/or metastases, up-front chemotherapy followed by delayed tumor resection is recommended.

Ultimate cure of GCT is compromised by the resectability of the tumour and the chemotherapy related side effects.

The Pediatric Intergroup Germ Cell studies (CCG-8891/POG-9048) were performed with Bleomycin, Etoposide and Cisplatin (BEP) schedule whereas Germen MAKEI 96 protocol used Ifosfamide, Cisplatin, Etoposide regimen (PEI). Brazilian Paediatric Oncology Society protocol, GCT-91 applied Etoposide, Cisplatin (PE) while The United Kingdom Children's Cancer Study Group's Second Germ Cell Tumour Study protocol incorporated Carboplatin, Etoposide and Bleomycin (JEB). Carboplatin based UKCCSG GCT protocol showed, more feasibility and had less toxic profile than Ifosfamide based MAKEI 96.

Commonly the electrolyte imbalance, acute renal/liver impairment, complications of bone marrow suppression, severe bacterial and other opportunistic infections are seen as acute major side

effects of chemotherapy. The hematologic toxicities were observed to be more in Carboplatin based JEB protocol than Cisplatin based BEP whereas more ototoxicity and nephrotoxicity were associated with Cisplatin containing regimes (BEP and PEI). Both protocols have observed a few treatment-related 2nd malignancies in later life in some of these patients. (20,21)

Study Design and Method

This retrospective non-randomized observational study was done using data extracted from clinical records of pediatric patients registered for treatment at NCIM, Sri Lanka from 2005 to 2013. Number of patients with clinical records containing adequate data on factors intended to analyze were 54 and all of them had been selected to the study population. Data have been compared with SPSS version 16. Survival was analyzed using Kaplan-Meier curves. Statistical significance for differences between groups was tested using Chi square test.

Staging system

Several clinical, radiographic, and surgical procedures were done for all patients at the time of diagnosis to evaluate the extent of the disease. Chest, abdominal or pelvic imaging studies were obtained for all patients. The brain was evaluated by MRI or computed tomography for patients with neurologic abnormalities. At diagnostic surgery, tumors were resected if possible, and the margins of resection were examined. Patients with testicular tumors underwent inguinal orchiectomy followed by staging abdominal CT scan to evaluate retroperitoneal lymph nodes. Tumours were classified Stage I to IV based on the resectability of the primary lesion, the extent of regional node involvement, and the presence or absence of distant metastases

Treatment protocols

During the study period we have used one of a following four standard protocols to treat our patients. (1)United Kingdom, the JEB regimen consisted of Carboplatin 600 mg/m^2 (area under the curve [AUC], 7.9 mg/ml per minute), etoposide 360 mg/m^2, and Bleomycin 15 IU/m^2, administered every 21 days for four to six cycles. (2) United States, the BEP regimen comprised Cisplatin 100 mg/m^2, Etoposide 500 mg/m^2, and Bleomycin 15 IU/m^2, administered every 21 days for three to six cycle. (3). Some selected patients were treated only with Etoposide 100mg/m^2/day and Cisplatin 20mg/m^2/day (EP) for 5 days as per Brazilian Paediatric Oncology Society protocol GCT-91. (4). The remaining were treated with Ifosfamide 1500mg/m^2/day, Cisplatin 20mg/m^2/day for five days with Etoposide 100mg/m^2/day for 3 days administered every 21 days for three to six cycle,(PEI) as per Germen MAKEI 96 protocol.

Results

Between 2005 and 2013, 54 patients with malignant GCTs were admitted to NCIM. Average of 7 cases were reported per year. There were 33(61%) girls and 21(39%) boys, with age at diagnosis ranging from 2 weeks to 15 years. A majority of the patients were in the 1 to 4 years age group (39%). The second-largest age group was less than 1 year (21%).

In about half (52%) the primary arose either from the testis or ovary. Testicular GCTs were more common within the age group of 1 to 4 years, while the ovarian GCTs were common in the age group of 4 to 8 years. The incidence of ovarian tumours increased with the age, while the extra gonadal GCT incidence gradually declines.

Characteristics		Testicular (n=12)	Ovarian (n=16)	Extra gonadal (n=23)	CNS (n=3)	Total (n=54)	%
Sex	Male	12		7	2	21	38.9
	Female		16	16	1	33	61.1
Age	<1	2	1	10		13	24.1
	1-4	8	2	11		21	38.9
	4-8	2	6	2		10	18.5
	>8	0	7	0	3	10	18.5
Histology	SE	0	0	0	0	0	0
	YST	8	7	11	1	27	50
	CHC	0	1	0	0	1	1.9
	Mature TER	0	0	0	0	0	0
	Immature	3	3	12		18	33.3
	Mixed	1	3	0	2	6	11.1
	NOS	0	2	0	0	2	3.7

Stage	I	12	0	2	0	14	25.9
	II	0	5	9	0	14	25.9
	III	0	5	10	0	15	27.8
	IV	0	6	2	0	8	14.8
	CNS				3	3	5.7
Excision	Complete	12	14	9	0	35	64.8
	Incomplete	0	2	14	3	19	35.2
CT	EP	3	1	5	0	9	16.7
	BEP	0	0	0	1	1	1.9
	JEB	8	3	1	0	12	22.2
	PEI	1	12	19	0	32	59.3

The most common histology was YST (50%), followed by immature teratoma GCTs (33%).

All testicular tumors presented as stage 1 disease and had complete resection as primary treatment modality. There were 2 patients with stage IV disease at the diagnosis, with metastasis in liver and lungs. None of them achieved complete resection even after chemotherapy.

In this population there were 45 patients who had elevated Alpha Feto protein (AFP) levels at diagnosis. Before each cycle AFP levels have been evaluated and the median has been calculated. At the 3rd cycle AFP levels have reached the normal base line value (10 ng/dl) and at the 4th cycle onwards it has come below 10 ng/dl. (Figure 6)

A total of 223 cycles were given to this cohort. Majority (n=138) had PEI.

There was a statistically significant increased incidence of febrile neutropenia (p= 0.003) with PEI chemotherapy regime than with JEB or EP regimes. Abscess formation, renal impairments and ICU admissions reported with PEI regimen were absent with either JEB or EP regimes. Patients treated with both JEB and PEI regimes had fungal infections during their treatments, but it was not statistically significant (p = 0.94)

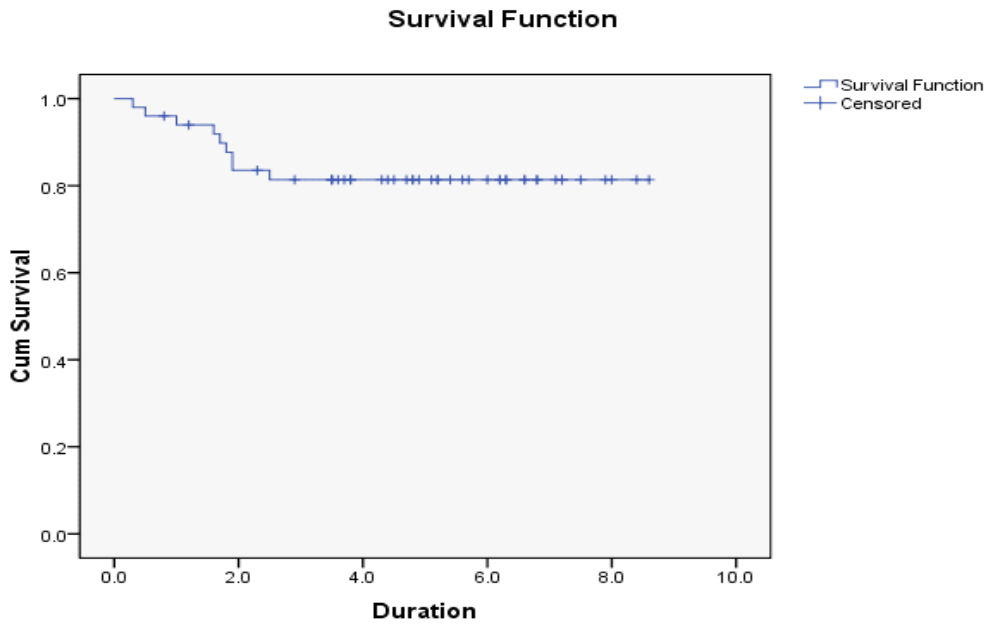
When considering the long-term side effects, there were 6 patients, with mildly elevated serum creatinine levels, which remained in stable values. All above 6 patients were treated with PEI schedule. There was another patient with hydronephrosis which was not related to treatment. Three patients treated with PEI had hearing impairment

Only 14 patients were eligible for analysis of their growth with CHDR after the completion of 5 years. Out of them, only 2 children had their growth below the -2SD line. Patients who were diagnosed at or after the age of 5 years were not analyzed.

All patients who have survived more than 3 years, had been analyzed for their social and educational interactions and performances. All of them had excellent outcome at the end of three years and beyond.

Overall survival at 5 years was calculated with Kaplan-Meier method. For this calculation, patients with intra cranial disease were excluded. Life-table analysis based on the survival for 51 patients with malignant GCTs indicates that 92.1% survived at least 12 months, and 84% are projected to survive 24 months. Overall 5 year survival was 81.3%. No disease related deaths were reported after 2.3 years from the diagnosis.

Figure 1: Kaplan-Meier plot of the survival of all 51 patients with malignant



Patients with gonadal tumors had a significantly higher rate of survival than patients with extra-gonadal tumors ($P < 0.01$). No deaths have been reported with primary testicular GCT. However, patients with extra gonadal tumours were more likely to have advanced disease at diagnosis ($P < 0.01$). When these data were corrected for stage, primary site no longer had a prognostic significance.

Patient's with stage I disease had a 5 year overall survival (OS) of 89.5 %.

Figure 2: 5 years OS according to primary site

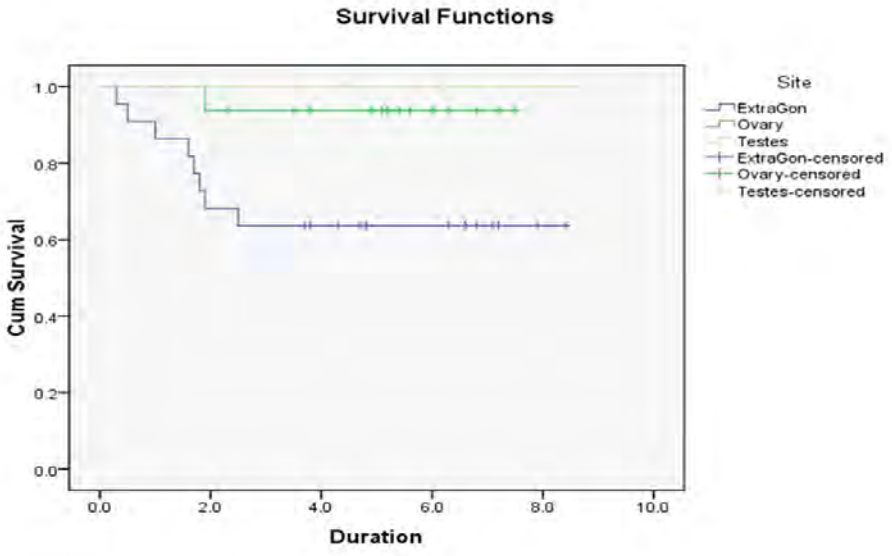
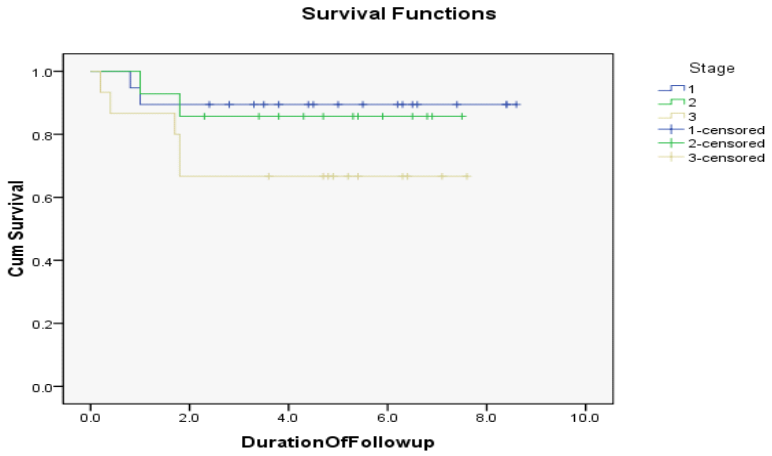


FIG. Kaplan-Meier plot of the survival for patients with malignant germ cell tumors according to primary site: gonadal (ovarian. testicular) vs. extragonadal (sacrococcygeal, retroperitoneal, mediastinal. and other) f X L = 8.8. P < 0.01. log rank test).

For stage II and III, 5 year OS was 85.6% and 66.5% respectively. None of the stage IV patients were alive at 5years. Statistically, survival does not depend on the stage

Figure 3: Kaplan-Meier plot of the survival of patients with malignant GCTs according to stage



When we consider the social back ground most of the parents were educated up to ordinary level (O/L) only. There was no statistical correlation between the level of parental education and the disease outcome ($P > 0.05$).

There was a wide variation of the distances from NCIM to patient's hometown. Only 46% of patients were within 50 km from the NCIM. However, the population density had to be considered. Loss to follow up, overall survival and deaths had been evaluated in relation to the distance from NCIM.

Statistical analysis confirmed that the distance from NCIM to patient's home town neither influenced the patient's survival, nor loss to regular clinic follow up.

Discussion

In our study of 54 children with malignant GCTs, all major tumour sites and histological types are represented. However, in this cohort, there were no patients with mature teratoma as they would have had complete excision and needed no further chemotherapy or radiotherapy. Therefore, those patients would have not been registered under our care at NCIM.

This data highlights the characteristics and age-specific trend of development of a GCT in a child. In our study the incidence rate of GCTs was slightly higher in girls. A bimodal age distribution was seen. In children aged less than 1 year, the highest age-specific incidence rates were seen for girls are the pelvic tumours. Testicular tumours were the most common among males in this age group. For 10to 14-year-old boys, the tumours occurred most often in the central nervous system while in girls, the most common site was the ovaries and the tendency increased with the age. These figures are comparable with other international studies[22,23].

The leading prognostic variable was the stage of the disease. In general, Overall 5-year survival rates reached 84% for all GCTs combined which is about 9% inferior to national UK analysis[24]. In this study all testicular GCTs were detected at stage I, therefore, they were successfully managed with complete excision. Their survival was 89.5% at 5 years, which was similar to multi centric studies. The groups with stage II and III tumours have survived 85.5% and 65.5% respectively. Even though the stage II survival figures (93.8%) were compatible with other international studies, the survival of patients with stage III and extra gonadal tumours was much inferior at just 72%[20, 27,28,29] .

Ovarian GCTs showed a 97% 5 years OS rate, while extra gonadal GCTs shows only 67% survival at 5 years. Gonadal (both testis and ovarian) GCT survival figures are compatible with international GCT studies. The German MAKEI 96 Study and the CCG-8891/POG-9048 study showed similar results[25]. However British UKCCG GCI and GC II protocols demonstrated the high therapeutic efficacy of platinum-based regimens such as BEP or JEB that resulted in a five year EFS of 57% and 87% respectively in non-gonadal GCTs[26]. The recent analysis of the UKCCG GC II study underscores the high efficacy of the JEB regimen, that resulted in a 5-year EFS of 88% with a favorable toxicity profile[20] .

The British patients with extra gonadal GCTs have shown much superior survival than ours. This difference was mainly attributed to a higher rate of incomplete tumour resections in non-gonadal tumors in our population. Factors such as primary tumour site and completion of surgical excision also played a major role in overall survival.

However, after accounting for stage, tumor site did not have an independent prognostic significance in our study. Forty four (44%) of stage III patients had incomplete resection, presuming the reason for such an inferior survival.

Toxic profiles

Considering acute side effects, PEI chemotherapy showed more toxic profile than others. In our population, those who had PEI developed the same toxic profile as the MAKEI 96 study, whereas, patients receiving JEB showed lesser and more acceptable side effects, same as the UKCCG study [20].

In our setting we encountered more septic episodes with Ifosfamide based (PEI) protocols than Carboplatin based (JEB) chemotherapy ($P = 0.003$). Moreover, 6 patients developed renal impairment and another 4 patients needed ICU care during PEI chemotherapy. During the follow up period there were 7 patients with renal impairment and only one with ototoxicity.

Socio economical back ground

The multi variant analysis did not show any relationship between 5 year overall survival and the parental education level or distance from NCIM to their hometown. Moreover, above factors did not influence the loss to follow up either.

Conclusions and Recommendations

Our study population had a wide heterogeneity. Demographic figures were comparable with other international cohorts. It was clearly evident that the ultimate survival correlated with the extent of surgical excision. Higher the stage, lesser the chance of having a complete excision and hence an adverse survival. Therefore, primary surgical excision could be delayed if proper surgical clearance cannot be achieved.

Ifosfamide based (PEI) chemotherapy had more acute adverse effects than Carboplatin based (JEB) chemotherapy. In our setting JEB was more convenient due to lesser side effects and the convenience of a administration, which does not need prolonged pre and post intravenous hydration for consecutive 5 days needed for PEI protocol. Efficacy wise both protocols had equal outcomes[17,20].

All patients, who had relapse or death were documented within first 2 years. There were no events after 3 years from diagnosis. Therefore, its quite safe to review our patients annually rather than 6 monthly intervals after 3 years.

Limitations

We had a limited number of patients and the mature GCTs were not included in this study.

Data was collected retrospectively and some events were not documented clearly and appropriately. Especially with septic events, the blood/other specimen culture reports were missing from the notes. Therefore, true incidences of septic events would have been more than our figures suggest.

Long term side effects such as ototoxicity were not routinely assessed in many patients. Only the clinical assessments were done.

Only 14 patients, who were below 5 years at the end of follow up, were eligible to be assessed for their

growth. This number was not sufficient to come to a conclusion.

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Case Report

The First Case of Castleman Disease with POEMS Syndrome Successfully Treated with Autologous Stem Cell Transplantation, Complicated by Engraftment syndrome at The National Bone Marrow Transplantation Unit of Sri Lanka - A Case Report

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Keywords: Castleman, POEM, ASCT

Abstract

Castleman disease (CD), also known as angiofollicular lymph node hyperplasia, collectively describes a group of rare lymphoproliferative disorders first described by Dr. Benjamin Castleman (1). We report the first case of multicentric castleman disease complicated with POEMS syndrome to undergo successful autologous stem cell transplantation (ASCT) from the First National Bone Marrow Transplantation Unit of Sri Lanka. This case report brings out the spectrum of clinical manifestations of castleman disease and associated POEMS syndrome along with the importance of contemplating early ASCT in such complicated patients and adds to the prevailing limited evidence on this subject. We also attempt to provide a comprehensive evidence-based insight in to the clinical features, diagnostic platforms, variety of treatment modalities and detection and management of engraftment syndrome with response assessment criteria for this rare clinical entity.

Keywords: Castleman Disease, POEMS syndrome, Engraftment syndrome, *Autologous Stem cell transplantation* (ASCT)

Background

Castleman disease (CD), also known as angiofollicular lymph node hyperplasia, collectively describes a group of rare lymphoproliferative disorders first described by Dr. Benjamin Castleman (1). Based on the number of regions of enlarged lymph nodes and the presence or absence of human herpesvirus 8, CD is categorized in to three subtypes as unicentric CD (UCD), Human Herpes Virus 8 (HHV-8)–associated multicentric Castleman disease (HHV-8-associated MCD), or HHV-8–negative/idiopathic multicentric Castleman disease (iMCD) . CD is frequently associated with POEMS (**P**olyneuropathy, **O**rganomegaly, **E**ndocrinopathy, **M**onoclonal protein, **S**kin changes) syndrome (2). It consists of a monoclonal plasma cell disorder, peripheral neuropathy, and one or more of osteosclerotic myeloma, Castleman disease, increased levels of serum vascular endothelial growth factor (VEGF), organomegaly, endocrinopathy, edema, typical skin changes, and papilledema(3). In the case of multicentric castleman disease, treatment protocols significantly vary depending on the HHV 8 status, concurrent presence of Kaposi Sarcoma (4-6), number of sclerotic bone lesions, severity of the disease and the presence of associated POEMS syndrome(7,8). Recently, there has been increase evidence on the success of ASCT to treat multicentric castleman disease associated with POEMS syndrome (8-13).

Case presentation

A 39-year-old Sri Lankan female presented with lower limb edema, numbness, difficulty in walking, loss of weight and fatigue for one and half years. There were no significant cardio -pulmonary symptoms, B symptoms nor a contact history of tuberculosis. Examination revealed generalized lymphadenopathy (cervical, axillary and inguinal regions), hepatosplenomegaly, bilateral pitting lower

limb edema and proximal predominant lower limb weakness with associated hyporeflexia and glove and stocking type of sensory impairment in lower and upper extremities. Fundoscopy revealed bilateral chronic papilledema. Furthermore, she was noted to have scleroderma like skin thickening and pigmentation in the face and limbs. System examination was unremarkable and her bladder and bowel functions were intact. Preliminary investigations revealed a normal Full Blood Count, Erythrocyte Sedimentation Rate (ESR) and CRP. (WBC 6.01 10^3U/L, Hb 12.5g/dl, Platelets 317 10^3 U/L, ESR 8mm1st hour, CRP 2 mg/L). Renal functions, serum electrolytes, liver enzymes, Lactate Dehydrogenase Level (LDH 239 U/L) and coagulation studies were normal. Total serum protein level was elevated (82.71g/l) and serum protein electrophoresis (SPE) revealed a small monoclonal band in the gamma region with a paraprotein level of 5.5g/l, subsequently identified as IgA lambda type on immunofixation. Nerve conduction study confirmed the presence of sensory-motor demyelinating polyneuropathy and abdominal ultrasonography revealed hepatosplenomegaly. Lymph node biopsy with immunohistochemistry was compatible with hyaline vascular type of castleman disease. Spiral Computed Tomography Scan (CT) of the abdomen showed hepatosplenomegaly with para- aortic lymph node thickening. Peripheral blood smear showed mild roulex formation but no evidence of plasma cells. Bone marrow trephine biopsy revealed normocellular active marrow without evidence of malignant infiltration. Following the initial work up at National Hospital Colombo, the patient was referred to the National Cancer Institute for further investigation and management. Non-contrast CT of whole spine, pelvis and rib cage identified sclerotic lesions in L1 vertebral body, bilateral iliac bones and right 9th rib. The patient was negative for HIV, but HHV8 PCR on biopsy tissues could not be carried out due to technical and financial constraints. Screening for underlying endocrinopathy with HBA1C, TSH, 9am cortisol, FSH and LH were unremarkable. At this point, a diagnosis of multicentric castleman disease complicated with POEMS syndrome was made. By this time, the disabling neuropathy was progressing, and the patient could not mobilize herself unaided. A multidisciplinary decision was made to commence her on high dose steroids along with chemotherapy. Accordingly, she was commenced on a dose of 1 mg/kg prednisolone tapered over a period of eight weeks and Rituximab 375mg/m^2 weekly (four doses). Subsequently, she received six cycles of intravenous cyclophosphamide 40mg/Kg. Supportive care with physiotherapy was also provided. Following chemotherapy, the patient's constitutional symptoms and lower limb edema improved and paraprotein levels decreased to 1.6g/l, but the lower limb weakness and paresthesia along with the dermal changes remained static. At this point, opinion from foreign experts was sought and a combined decision to perform autologous stem cell transplantation was made. Following pre-transplantation work up as per protocol, stem cells were mobilized using cyclophosphamide 2 g/m^2 intravenously for one dose, and G-CSF (Filgastrim) 10mg/kg subcutaneously for 10 days and underwent stem cell Apheresis and cryopreservation. A month later, she received high-dose Melphalan (200 mg/m2) as conditioning chemotherapy. Following day, the patient was infused 3.06×10^6/kg of CD34 stem cell dose during her transplantation. Following transplantation, she received irradiated red cell concentrates and platelet transfusions. 140g of immunoglobulin(IVIG) was given on day six. The post transplantation period was complicated with features of engraftment syndrome, where the patient developed fever of 103^0F and evidence of extravascular capillary leakage as suggested by hypotension and lung base crepitations. She also had diarrhea preceding above symptoms. Although the CRP elevated, rest of the septic screen including blood and urine cultures remained persistently negative as were the renal and liver functions. She was commenced on steroids with prophylactic broad-spectrum antibiotic coverage leading to a recovery on the 20th day. She engrafted neutrophils on day 14 and was discharged home on day 22. Two months following post transplantation, her serum protein electrophoresis completely normalized and the neuropathy and paresthesia remarkably improved. Fifteen months post-transplant, the patient is currently self-ambulatory. She is awaiting repeat evaluation with nerve conduction studies to objectively assess. the neurological improvement. Furthermore, her skin thickening remarkably improved and repeat Fundoscopy showed resolution of papilledema.

Discussion

This case brings out several important phenomena in relation CD with POEMS Syndrome and treatment modalities. Diagnosis of hyaline vascular variant of multicentric Castleman disease was based on the presentation of generalized lymphadenopathy,

supported with the histological features of mantle zone expansion, vascular proliferation with vessel wall hyalinization and with negative immunohistochemistry for aberrant cells (14, 15). Though our patient was not tested due to stated constraints, HHV-8 infection occurs only in up to 50% of patients with MCD who are HIV-negative in contrast to nearly all HIV positive patients (16). The patient also had almost all the features of POEMS syndrome including demyelinating polyneuropathy, hepatosplenomegaly, monoclonal gammopathy of IgA lambda, osteosclerotic bone lesions, dermal changes of skin thickening, pigmentation and papilledema except for evidence of endocrinopathy which is present in only about 67 % (3) . She fulfills both the mandatory criteria fulfilling the diagnosis of POEMS syndrome (17,18) in the form of polyneuropathy and lambda light gammopathy, in addition to several other major and minor criteria mentioned above.

There are no randomized clinical trial data to direct best therapy. Such that, optimal treatment strategy for multicentric castleman disease associated with POEMS is controversial and treatment decision is dependent upon number of factors including HHV8 status, bone marrow involvement, number of sclerotic bone lesions and overall disease severity (7, 8). Our patient had four documented sclerotic bone lesions and a progressing disabling demyelinating polyneuropathy. Her HHV8 status was unknown and there was no evidence of bone marrow plasma cell infiltration. Based on these factors, the patient was commenced on a combination of high dose steroids and rituximab followed by cyclophosphamide. There is a response rate of 60–70% to high-dose steroids with only 15–20% of the patients having a complete response (19) but this response is not durable(20) as it was with our patient. With regard to chemotherapy, clinical trial data on efficacy are limited and many of were included in to the 2016 systematic review (21). According to prevailing evidence, if the patient is an ASCT candidate, chemotherapy in the form of alkylating agent-based therapy or two cycles of lenalodimide and dexamethasone each followed by ASCT is effective(22). Both cyclophosphamide(21) and rituximab have a role as single agents, with the ,latter, having strong evidence for effectiveness in HHV8 associated MCD (23-25),but evidence is scarce in HHV negative cases (26). Response in our patient to both these agents were minimal.

ASCT is gaining popularity as the primary therapy, especially in cases of Castleman disease associated with POEMS syndrome with widespread sclerotic bony lesions. This is supported in number of case reports and studies showing durable response rates (8-13) and according to this evidence, there is no need for cytoreductive chemotherapy prior to ASCT unless the patient is too ill for such procedure or there is an anticipated delay in proceeding to ASCT. Considering both these approaches with and without preceding chemotherapy before ASCT in relation to our patient, initial high dose steroids and cytoreductive chemotherapy can be justified since patient had progressive disabling neuropathy and ASCT was being contemplated for the first time in a national scale.

Universal response criteria has not been validated to assess response and modified criteria from the universal response criteria for multiple myeloma are often used (27). Our patient achieved a complete response as per this criteria where her paraproteinemia completely disappeared two months following transplantation where the general window is of six months. Neurological response is often assessed using the Overall Neuropathy Limitation Scale (ONLS) score(28).After definitive therapy, typically, it takes three months for the neuropathy to stabilize and six months to begin to improve and two to three years for the maximal improvement to occur. Following one year and four months post ASCT, our patient has improved in to a self-ambulatory state with minimal residual paraesthesia and weakness. Another intriguing phenomenon is that our patient developed features suggestive of engraftment syndrome (ES) post ASCT. This syndrome encompasses complications after hematopoietic stem cell transplantation and characterized by non-infectious fever; skin rash; diarrhea; hepatic dysfunction; renal dysfunction; transient encephalopathy; and evidence of capillary leak features like non-cardiogenic pulmonary infiltrates, hypoxia, and hypotension. There is well documented evidence to support the occurrence of engraftment syndrome post ASCT (29-32) and patients with POEMS syndrome undergoing ASCT in particular have shown high rates of engraftment syndrome (33). The clinical features of ES have been defined according to Spitzer and Maiolino diagnostic criteria (34, 35). Our patient fulfilled major criterion of Maiolino diagnostic criteria with the occurrence of

noninfectious fever within the period of engraftment but the development of diarrhea as the minor criterion preceded this period. Delayed neutrophil engraftment was noted in the subset of POEMS patients undergoing ASCT where the symptoms preceded the engraftment (33) and this might well have been the case in our patient. This has led to liberties with the definition of ES by loosening the time restriction of peripheral blood neutrophil reconstitution (33) and in this context, our patients falls in to the diagnostic perimeter of engraftment syndrome. There was also evidence of extravascular capillary leakage as suggested by hypotension and lung base crepitations as additional supportive features. It is important to highlight that her CRP level remained elevated despite negative blood and urine cultures and absence of identifiable septic focus. Elevated CRP levels has been associated with ES (36,37) and this brings out the importance of being vigilant towards detection of ES, which might otherwise well be mistaken for neutropenic sepsis because ES has different therapeutic implications. It is usually self-limiting but treatment is warranted if symptoms persists. Early intervention with corticosteroids is shown to prevent progression to more severe manifestations (32). Early recognition, exclusion of alternative diagnosis including sepsis and prophylactic treatment with antibiotics are the other management priorities (32) all of which were addressed timely in our patient leading to an uneventful recovery post ASCT.

Conclusion.

Castleman disease often co exists with POEMS syndrome and ASCT is emerging as the primary treatment modality with durable response rates. ASCT as the primary treatment modality for patients meeting eligibility criteria must be encouraged on a national and global scale. Engraftment Syndrome is commonly observed in POEMS syndrome patients' undergoing ASCT and it is important for clinicians to detect it and initiate timely treatment in order to ensure a successful outcome.

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Case Report

A very rare case of hepatocellular carcinoma prsented with laryngeal metastasis

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INTRODUCTION

According to the WHO, Hepatocellular carcinoma (HCC) is the 4th commonest cause of cancer deaths[1] worldwide. It's thrice as common in males compared to females[2] and has a higher incidence in countries of East Asia and Sub-Saharan Africa. As per American Cancer Society Hepatitis B and C, alcoholic cirrhosis, Aflatoxin of fungi and chemicals like nitrites and Polyvinylchloride are few known causative agents. Metastasis in HCC is a rarity and we are going to present such a rare case of HCC which presented with Laryngeal metastasis

CASE PRESENTATION

A 54 year old man presented with a history of progressive hoarseness of voice, for 6 weeks duration without any other symptoms. On examination there was a firm, non tender, ovoid mass (5cm x 4cm) in the left anterior triangle of the neck, over the thyroid cartilage.

Ultra Sound Scan (USS) of the neck showed a well-defined hypoechoic mass in relation to left sided thyroid lamina causing destruction of the same. Endoscopy could not visualize his left sided vocal cord with minimal movement of the right sided cord. Contrast enhanced CT (CECT) scan of the neck confirmed a poorly demarcated heterogeneously enhancing mass lesion (3X2.9x4.2 cm) in the sub glottic area of left sided Larynx. This lesion protruded into the lumen of the Larynx and seemed to extend to the left sided vocal cord and the left thyroid cartilage causing erosion. There were few enlarged left supraclavicular lymph nodes (largest SAD 9.2 mm). Impression of CT scan was locally advanced Laryngeal Carcinoma (T2N2bMx). A FNAC of the anterior neck lump showed a low-grade neoplastic lesion.

Excision biopsy was done from the lesion at the anterior Triangle of the neck. Histology of the biopsy revealed a poorly differentiated carcinoma, most likely HCC. The tumor has infiltrated through the skeletal muscles of the neck. Subsequently USS abdomen was done which revealed a large focal vascular lesion (6x7.9 cm) in the right lobe of the liver. He was referred to Oncology at this stage.

A CECT scan abdomen- Liver series showed a hypodense lesion (6.3x7.3 cm) in segment VIII and IVa with heterogenous enhancement in the arterial phase. Lesion showed contrast wash out in delayed and venous phases and the lesion had an enhancing capsule in equilibrium phase. There were few sub-centimeter contrast enhancing para aortic nodes from renal hilar level up to Aortic bifurcation. USS guided liver biopsy confirmed it as a poorly differentiated HCC. Immunohistochemistry done on wax blocks of the excision biopsy from the neck lesion showed positivity to Hepar I and negativity to CK 7 and CK 20, which confirmed its hepatic origin. His Alfa Feto Protein level, liver enzymes and liver functions were normal with a Child-Pugh score of 6: Grade A.

Possibility of liver resection was discussed with the Hepato-biliary surgeon. It was decided to defer the surgery until metastatic laryngeal lesion is treated with radiotherapy. He was referred for a Trans Arterial Chemo Embolization (TACE) for the primary HCC. Satisfactory TACE was carried out by administering Doxorubicin.

After Radiotherapy, 55Gy in 20 fractions in 2 phases from Co^{60}machine was delivered to the neck. With a view of assessing the treatment response, a PET CT scan was done after about 10 weeks.

It showed a metabolically active lesion in the left laryngeal wall with an erosion of the left Thyroid cartilage. A large focal lesion (7.4cmx 8.3cm) was

seen in the right lobe of the liver. Irregular rim of FDG avid area in the periphery was likely due to residual disease. There were multiple lytic lesions with FDG avidity in D_7, D_{11} and in both iliac bones which was compatible with bone metastasis.

Because of the residual primary and progressive metastatic disease, it was decided to start a Tyrosine kinase inhibitor, Sorafenib and deliver palliative radiotherapy to the painful iliac bone metastasis. Currently he is getting radiotherapy but Sorafenib is not yet available for him.

DISCUSSION

HCC metastasizes rarely to Lungs, Adrenals and Bones. In literature there are case reports of HCC metastasizing to Cricoid Cartilage [3] ,Thyroid gland [4] and Oral cavity[5] but none reported with laryngeal metastasis.

Hepar1 is a characteristic immunohistochemical marker for hepatic tissue which doesn't differentiate benign from malignant. Both CK 7 & CK 20 negativity confirms liver tissue. CK 19 positive HCC have been found to have poorer prognosis (which was negative in this patient) with higher incidence of early recurrence and extrahepatic disease.[6]

Detailed histological investigation including IHC helped us correctly diagnose this disease even with a very unusual presentation.

In well differentiated HCC, role of PET CT scan is limited. It is because of retaining of dephosphorylating enzyme activity which allows FDG to be excreted from cancer cells and due to weaker activity of glucose transporter in malignant liver cells leading to weaker FDG uptake. But in poorly differentiated HCC, with poor enzyme activity, with more likely metastasis and recurrence it is a useful tool in detecting recurrence and metastasis.[7]

In this patient at first presentation the patient was treated with curative intent, hence radical

treatment options were employed. However, with progressive disease, treatment intent was changed and palliation became the main focus. This guided our subsequent choices of treatment.

TACE is used for large or multifocal tumors as a bridge therapy for liver transplant in HCCand has been shown to achieve nearly 20% complete pathologic responses when used .[8]

Major limiting factor for Radiotherapy (RT) to the liver is the toxicity. Mainly it can be delivered as 3D Conformal RT (3D CRT) or Stereotactic Body RT (SBRT), which was not possible in this case due to the larger size of the lesion. In early stage disease, 3D CRT has shown complete response in 80% of patients receiving 66Gy in 33 fractions with Grade IV toxicities in 22% of patients .[9] SBRT which allows ablative doses of radiotherapy to a highly specified area uses 30 to 50 Gy in 3-10 fractions. A sequential phase I and II study of SBRT for locally advanced HCC patients with Child-Pugh A has shown 1-year control rate of 87% with a median OS of 17 months.[10]

Sorafenib, multi- target Tyrosine Kinase inhibitor of RAF, VEGE, PDGF and C-KIT has shown survival advantage in advanced HCC. A multi-center randomized double blind placebo-controlled trial in advanced HCC has shown an overall survival of 10.7 months in the Sorafenib group, whereas in placebo group it was 7.9 months.[11]

CONCLUSION

HCC can rarely metastasize to very unusual sites like larynx. Therefore, when investigating a lesion in head and neck, secondary deposits should always be considered even though primary tumors are the commonest. Hepar 1 should be considered in secondary deposit evaluation. Use of PET/CT in differentiated HCC could also be considered when evaluating patients with HCC.

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Figure 1: Biopsy from the Anterior Triangle of neck under H & E staining and immunohistochemical staining ; hepar 1 positivity , CK 7 & CK 20 negativity

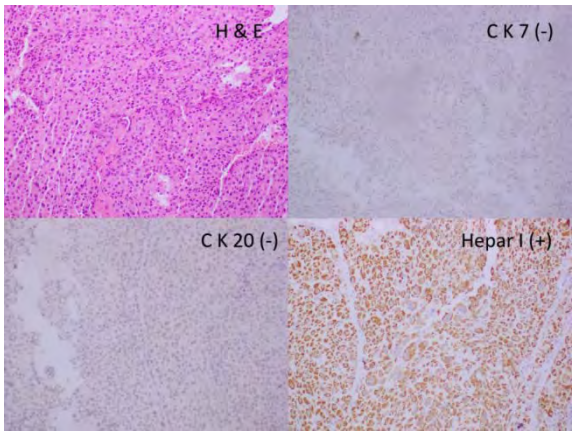

Figure 2: PET CT Scan showing increased FDG avidity of A-Larynx, B- D_7 Vertebrae, C- Primary HCC, and D- D_{11} Vertebrae