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Quantitative Assessment of Prognosticators for Rectal Cancer's Local Recurrence and Distant Metastases

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Abstract: Rectal cancer treatment outcome has improved considerably in the TME era often with the use neoadjuvant chemoradiotherapy. However, the risk of local recurrence/distant metastases could be as high as 10%. We have designed a retrospective cohort study to assess risk factors associated with local recurrence/distant metastasis after primary curative rectal resection. Our analysis of the colorectal database in a district general hospital involved review of 131 patients who had a curative resection between 2007 and 2013. 22 patients of the 131 had local recurrence/distant metastases. We reviewed the risk factors as gender, neoadjuvant chemoradiotherapy, type of operation, anastomotic leak, tumour differentiation, EMVI, CRM and Dukes C and performed a quantitative assessment. Looking at risk factors, the presence of EMVI was found to have a statistically significant association with recurrence and distant metastases (p=0.0006) followed by poor differentiation (p= 0.038) and Dukes C (p=0.045) while CRM involvement (p=0.054), Neoadjuvant chemoradiotherapy (p=0.657), type of resection (p=0.740), Anastomotic leak (p=0.761) and gender (p=0.901) shown no obvious statistical association with recurrence or distant metastases A larger multi-centre study may help in validating our observation.

Keywords: Distant Metastases, Local Recurrence, Rectal Cancer, Risk Factors

1. Introduction

Colorectal cancer (with the most common location being the rectum) is the third most common malignant cancer for males and females in England [1]. The same can be attributed to the rest of the United Kingdom [2, 3]. In 2016, there were 34,952 cases, with 19,581 males and 15,371 females being diagnosed with colorectal cancer in England. Similarly, colorectal cancer is the third most common cancer diagnosed in both men and women in the United States. The American Cancer Society's estimates the number of colorectal cancer cases in the United States for 2018 are 97,220 new cases of colon cancer of which 43,030 new cases are of rectal cancer [4]. The burden of this disease is immense & better understanding of the molecular biology of this cancer and its management would help in alleviating this burden which afflicts these patients.

The treatment outcome of rectal cancer has improved considerably in the era of Total Meso-rectal Excision (TME), a technique whereby the avascular plane between the meso-rectum and surrounding tissues is divided down into the pelvis, by sharp dissection under direct vision [5, 6]. Thus, the excised specimen includes the complete meso-rectum, Denonvillier's fascia and the peritoneal reflection anteriorly. Since its conception, TME has become the gold standard for curative primary rectal cancer resections. Compared to conventional surgical techniques it has been proven to reduce local recurrence (and thus increase overall survival) [6] and to lower the incidence of metastatic disease due to local failure through careful excision.

The use of appropriate neoadjuvant chemoradiotherapy has been shown to improve patient symptoms, induce substantial

tumour regression, and allow for R0 resection in rectal cancer patients [7]. Survival benefit is unproven, but appropriate neoadjuvant therapy induces tumour regression and reduces local recurrence [5, 7, 8]. Thus, primary curative rectal cancer resections are often undertaken with the use of neoadjuvant chemoradiotherapy.

However, despite these improvements a significant number of patients still go on to develop a local recurrence and/ or distant metastases. In 1986 Heald et al stated that at least half of rectal cancer recurrences occurred in the pelvis [9]. The development and implementation of TME +/- neoadjuvant therapy means that local recurrence is now far less common, but nonetheless, some studies still suggest the rate of overall recurrence could still be as high as 10% [8, 10].

Predicting the metastatic and pelvic recurrences patterns of rectal cancer is vital in the management of this debilitating cancer. Much research has gone into determining the factors which come into play with regards to local recurrence and metastatic disease. It is known now that location of tumour gives a higher propensity for metastasis to certain distant sites and this has been attributed to hematogenous spread. With this in mind, a retrospective analysis for prospectively collected cancer data from a single district general hospital was done to study patients who had a primary curative rectal cancer resection between 2007 and 2013 and to assess risk factors associated with local recurrence and distant metastasis as the primary outcome.

2. Material & Method

A retrospective analysis of the prospectively collected colorectal database in a district general hospital was performed. This database is kept and updated by the colorectal nurses. All patients were staged using chest, abdomen and pelvic CT scan and MRI pelvis. Cases were discussed at a multi-disciplinary meeting (MDT) prior to surgery and this determined the curative intent of the procedure as well as the need for neoadjuvant treatment. Cases were done within the colorectal department and all were performed by 4 surgeons in TME fashion using open or laparoscopic approach. Recovery of all patients were using ERAS protocol and immediate and short-term complications were recorded and dealt with. All patients were discussed post operatively on the MDT and adjuvant chemotherapy and oncology input planned as per outcome. Post-operatively, patients were seen by a consultant within 6 weeks of discharge to discuss histopathology and further management and followed up thereafter in nurse led clinic as per colorectal cancer protocol for 5 years.

The search of this database yielded 131 patients who had a curative rectal resection between 2007 and 2013. Review of this database revealed 22 patients of the 131 had local recurrence and/ or distant metastases. Collected patients' demographics, but more specifically, investigated possible risk factors of gender, neoadjuvant chemoradiotherapy, type of operation, anastomotic leak, tumour differentiation, EMVI, CRM and Dukes C and performed a quantitative analysis with a view to identifying prognosticators of local recurrence and distal metastasis in these 22 patients. Statistical analysis was done using Chi squared test for all categorical data and P value of <0.05 was considered significant.

3. Results

All patients who were diagnosed with rectal cancer from Jan 2007 to March 2013, were reviewed from database showing 196 patients who had rectal Cancer. Patients with distant metastases were excluded leaving 158 patients and all patients which were treated with palliative intent were also excluded leaving 131 patients which were treated with curative intent (Table 1). Median age of patients was 68.6 years old (26-86) with male to female ratio 1:1.7 (83:48). 22 patients developed local recurrence or distant metastases during median follow up period of 5 years (2.75-5.00) (Figure 1 &2). Looking at risk factors (Figure 3), EMVI was found to have a statistically significant association with recurrence and distant metastases ($p=0.0006$) followed by poor differentiation ($p= 0.038$) and Dukes C ($p=0.045$) while CRM involvement ($p=0.054$), neoadjuvant chemoradiotherapy ($p=0.657$), type of resection ($p=0.740$), anastomotic leak ($p=0.761$) and gender ($p=0.901$) shown no obvious statistical association with recurrence or distant metastases (Table 2).

Table 1. *Patients number, age, follow up, treatment (chemo-radiotherapy & Operations) and Dukes classification.*

	Recurrence/Distant Metastases	**No Recurrence/Distant Metastases**
No patients	22	109
Males	13	70
Females	9	39
Median Age (Range) Years Old	65.5 (42-86)	68.6 (26-86)
Median Follow-up (Range) Years	5 yrs. (2.5-5.0)	5 yrs. (3.1-5.0)
Neoadjuvant Chemoradiotherapy	11	43
Operations:		
Anterior Resection	12	74
Abdomino-perineal Resection	8	30
Others	2	5
Dukes Classification:		
A	3	33
B	6	32
C	13	47
No Residual Disease	0	12
Not Recorded	0	7

Table 2. *Risk factors in rectal cancer local recurrence and distant metastases with statistical significance.*

Risk Factors	Of 22 Patients	Of 131 Patients	P Value
Positive EMVI	18	30	0.000554252
Poor Differentiation	6	15	0.038228712
Dukes C	13	47	0.045208399
Involved CRM	5	12	0.053703896
Neoadjuvant Treatment	11	54	0.656729392
Type of Resection (APR)	8	38	0.740421506
Anastomotic Leak	0	3	0.761150092
Gender (Male)	13	83	0.901473261

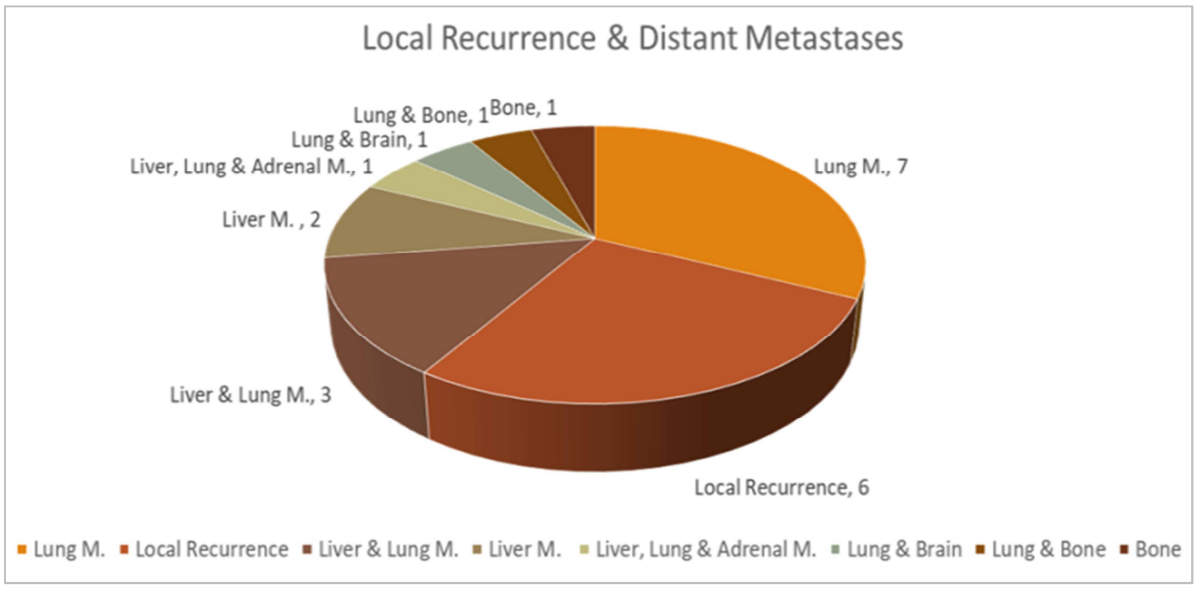

Figure 1. *Index cases with local recurrence and distant metastases.*

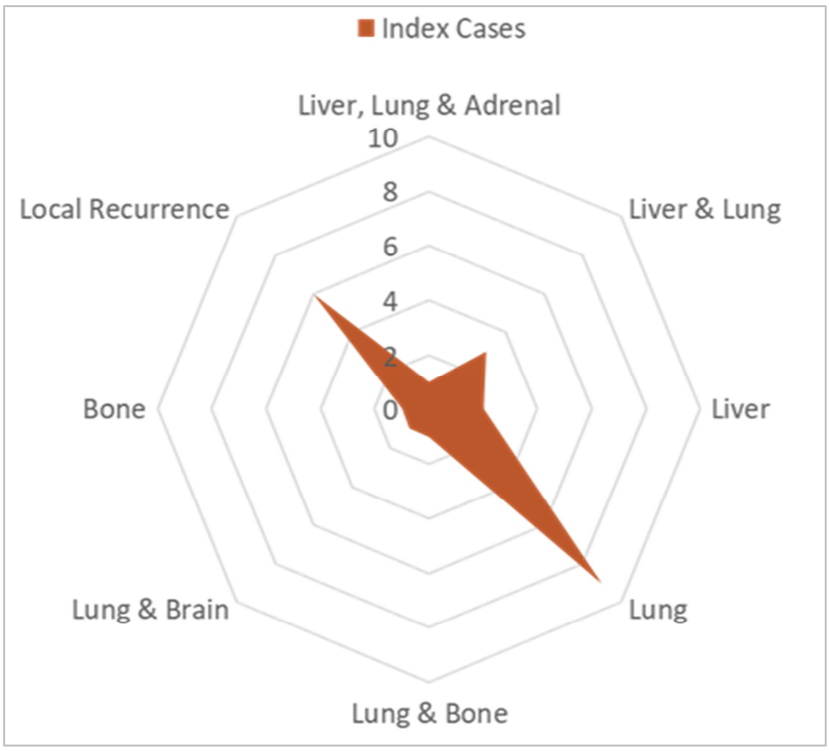

Figure 2. *Graphic representation of the local recurrences and single and multiple distant metastases from rectal cancer.*

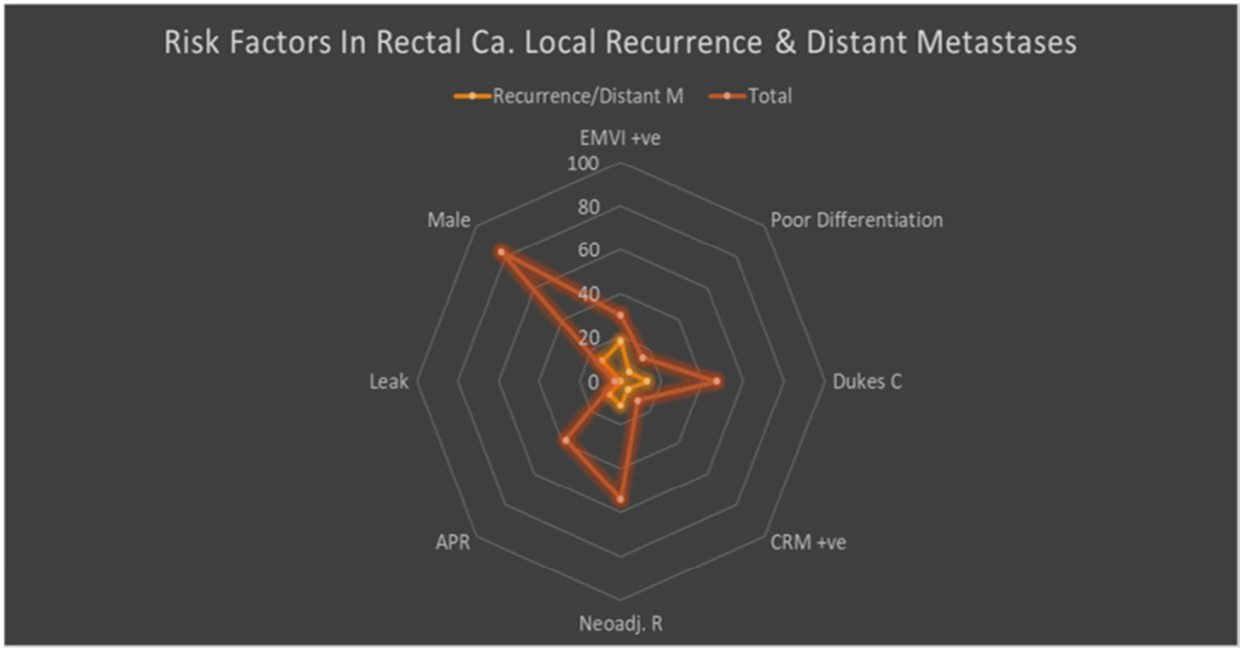

Figure 3. *Risk factors in rectal cancer for local recurrence and distant metastases.*

22 (16.8%) patients developed local recurrence or distant metastases during follow-up period which included 13 males and 9 females. 6 (22.7%) patients out of 22 patients developed local recurrence, 10 (45.4%) developed a single organ distant metastasis (7 lung, 2 liver, 1 bone) while 6 (22.7%) patients developed multiple organs metastases (1 lung+liver+adrenal, 3 lung+liver, 1 lung+Bone, 1 Lung+Brain) with obvious predominance in lung metastases (Figure 1 &2).

4. Discussion

Much has been published with regards to the prognostic significance of extra mural vascular invasion (EMVI). MRI detected EMVI (mriEMVI) has been demonstrated to be a poor prognostic factor as evidenced by the five-fold increased rate of synchronous metastases, and almost four-fold ongoing risk of developing metastases in follow-up after surgery [11]. Furthermore, regression of mriEMVI following neoadjuvant chemotherapy has resulted in improved disease-free survival (DFS) [12, 13]. This study demonstrated that the most statistically significant risk factor for metastatic disease from rectal cancer was EMVI (p=0.0006). 12 (54.5%) of the 22 patients who developed recurrence or distant metastases had pathological evidence of EMVI of which 9 developed distant metastases (2 liver+lung, 5 lung and 2 liver) and 2 had local recurrence known that within this study group of 131 patients only 30 patients shown EMVI suggesting that EMVI is indeed important as an independent prognostic indicator in rectal cancer. This could well be interpreted as a surrogate marker for the extent or lack thereof distant metastasis and pelvic recurrence and now DNA hypermethylation has been studied as a predictor of EMVI which could potentially play an important role in personalising patients' cancer care [14].

Similarly, poor tumour differentiation and Dukes C, have shown association with recurrence and distant metastases in this study but with less statistical significance (p=0.038 and 0.045 respectively). Poor differentiation has been showing as independent risk factor for local recurrence/distant metastases in literature and known as prognosticator for rectal cancer [15]. Total of 15 patients out of 131 patients in this study were noted to have poor tumour differentiation of which 6 (27.3%) out of 22 developed either local recurrence or distant metastases (3 local recurrence and 3 distant metastases) with 3 of these showing no other risk factors. 13 patients' post-operative histopathology shown Dukes C in comparison to 9 patients with dukes A&B in the 22 patients. Dukes C has long been associated with poor survival and increased rate of recurrence [16, 17] and this finding was no different in this study.

Other risk factors included in this study have not shown a statistically significant association with recurrence or distant metastases including gender, operative resection, CRM involvement, neoadjuvant chemoradiotherapy and anastomotic leak. Interestingly, CRM involvement has shown only slight association with recurrence/distant metastases but not with statistical significance (p= 0.054), contrary to current evidence [15, 18-20]. CRM has consistently been shown to be one of the most important predictors for local recurrence and a positive CRM is strongly associated with increased local recurrence, decreased overall survival, and is also predictive of distant metastasis. A strong association was not established in this study but in the MRC CLASSIC trial, the first laparoscopic RCT to include rectal cancer patients, the rate of positive circumferential margins (CRM), was non-significantly higher in patients undergoing laparoscopic anterior resection when compared to open resection (12 % vs 6%, respectively, P = 0.19) [21] yet this higher CRM positivity rate did not translate to an increase in the 3 year follow-up local recurrence rate [22].

Operative procedures ranged from predominately anterior resections followed by abdominoperineal resections (APR), Hartmann's procedures and few subtotal colectomies and pan proctocolectomies. APR is theoretically associated with high recurrence rate [23], which is due to nature of the disease rather than the operation, as patients who needs APR would have low rectal cancers which are technically more difficult to resect, have higher CRM involvement with high risk of perforation. This association was not evident in this study, but better surgical techniques with extralevator APR (ELAPR) as well as appropriate use of chemoradiotherapy, both were observed within this series, could explain the improved oncological outcome. Similarly, neoadjuvant chemoradiotherapy has shown no association with local recurrence or distant metastases, but with the observed complete pathological response with long course chemoradiotherapy of up to 35% [24] it is of no surprise that neoadjuvant chemoradiotherapy has no association with recurrence or distant metastases specially that it was the normal practice in the department during the study period that no short courses used and all patients had surgery regardless of the response.

No association was expected from gender, but interestingly the female gender was associated with high recurrence rates with 5 out of 6 patients are females and only one male patient developed local recurrence. This can be due to the female pelvic anatomy but closer look at this group shows the multifactorial association as all 5 female patients had neoadjuvant chemoradiotherapy, 3 patients had positive EMVI, 3 patients had Dukes C and 2 patients had CRM involvement.

There are limitations to this study. It is a retrospective analysis and therefore certain information was not available and case notes review were included to fulfil certain criteria leading to observational bias. Limited number of cases also restricted the statistical significance and larger study group from more than one hospital would help validate the findings. Although statistical analysis has been performed, the multifactorial association of the risk factors necessitates multivariant analysis which was not possible due to lack of certain variables and information as well as the limited number of patients possibly rendering the findings inaccurate. Also, as mentioned, short course of radiotherapy was not used during the study period and the concept of complete pathological response and surveillance was not yet established, mostly likely leading to overtreatment of certain cases.

5. Conclusion

Certain risk factors association with recurrence and distant metastases in rectal cancer are well established. Most importantly extramural vascular invasion which along with Poor tumour differentiation and Dukes C staging which were evident in this study. A large systematic review with meta-analysis, which should include this series, would still be required to identify with greater statistical significance, all possible risk factors as this could well revolutionise patient's care in rectal cancer treatment.

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