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ORIGINAL ARTICLE

Outcomes of rectal cancer patients with a positive pathological circumferential resection margin

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Abstract

Purpose Evidence-based management of positive pathological circumferential resection margin (pCRM) following preoperative radiation and an adequate rectal resection for rectal cancers is lacking.

Methods Retrospective analysis of prospectively maintained single-centre institutional database was done to study the patterns of failure and management strategies after a rectal cancer surgery with a positive pCRM.

Results A total of 86 patients with rectal adenocarcinoma with a positive pCRM were identified over 8 years (2011–2018). Majority had low-lying rectal cancers (90.7%) and were operated after preoperative radiotherapy (95.3%). Operative procedures included abdomino-perineal resections, inter-sphincteric resections, low anterior resections and pelvic exenteration in 61 (70.9%), 9 (10.5%), 11(12.8%) and 5 (5.8%) patients respectively. A total of 83 (96.5%) received chemotherapy as the sole adjuvant treatment modality while 2 patients (2.3%) were given post-operative radiotherapy and 1 patient underwent revision surgery. A total of 53 patients (61.6%) had recurrence, with 16 (18.6%), 20 (23.2%), 8(9.3%) and 9 (10.5%) patients having locoregional, systemic, peritoneal and simultaneous local-systemic relapse. Systemic recurrences were more often detected either by surveillance in an asymptomatic patient (20.1%) while local (13.1%) and peritoneal (13.2%) recurrences were more often symptomatic ($p = 0.000$). The 2-year overall survival (OS) and disease-free survival (DFS) of the cohort was 82.4% and 74.0%. Median local recurrence-free survival (LRFS) was 10.3 months.

Conclusions Patients with a positive pCRM have high local and distal relapse rates. Systemic relapses are more often asymptomatic as compared to peritoneal or locoregional relapse and detected on follow-up surveillance. Hence, identification of such recurrences while still salvageable via an intensive surveillance protocol is desirable.

Keywords Circumferential resection margin · Total mesorectal excision · Mesorectal fascia · Rectal cancer

Abbreviations

APR	Abdomino-perineal resection
LAR	Low anterior resection
ISR	Inter-sphincteric resection
pCRM	Pathological circumferential resection margin
TME	Total mesorectal excision
b-TME	Beyond TME
e-TME	Extended TME
MRF	Mesorectal fascia

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Background

Outcomes of rectal cancer have improved over the last two decades with the use of MRI for better preoperative staging, use of neoadjuvant chemoradiation and the conduct of a good-quality surgery using total mesorectal excision (TME) or extended TME (e-TME) or beyond TME (b-TME) approaches [1–3]. Despite these, 5–25% patients have a positive pathological circumferential resection margin (pCRM), the rates varying between histologies, types of surgery and across institutions [4]. Patterns of relapse after margin positive resections for rectal cancer are unclear and the data is scarce on the optimal management of such patients in the adjuvant setting. While adjuvant chemotherapy remains the only option after a b-TME surgery, for patients who undergo a conservative surgery like an inter-sphincteric resection, there remains the option of doing a completion surgery in

the form of an abdomino-perineal resection (APR) or a pelvic exenteration. With this ambiguity and lack of evidence in background, current study was undertaken with an aim to audit outcomes of the rectal cancer patients undergoing curative resections for rectal cancer with a positive pCRM with respect to the pattern of relapse, timing of relapse, their methods of detection and their subsequent salvage rates.

Methods

Retrospective analysis of the prospectively maintained database of the departmental database was carried out for patients operated between January 2011 and December 2018.

Primary objective was to evaluate the patterns of failure after a positive pCRM. Secondary objectives were to analyse the methods of detection, the timing of recurrences and their subsequent salvage.

Inclusion criteria

1. Patients with positive pCRM
2. Histopathology—rectal adenocarcinoma of upper, mid and lower third rectum
3. Extent of surgery included—TME, e-TME, b-TME
4. Non metastatic or synchronous limited metastatic disease treated with curative intent

Exclusion criteria

1. Patients with macroscopic residual disease (R2 resection)
2. Recto-sigmoid cancers
3. Positive distal resection margin
4. Patients who defaulted after rectal surgery without any follow-up

The current study conforms to the ethical principles for medical research involving human subjects, including research on identifiable human material and data, as per the Declaration of Helsinki of World Medical Association (WMA) [5].

Treatment protocol

Initial staging was done using a magnetic resonance imaging of pelvis (MRI 1) and a contrast enhanced computed tomography of the thorax and abdomen (CECT). Tumour height was measured as the distance of the inferior edge of the tumour from the anal verge. Tumours within 5 cm, 5 to 10 cm and more than 10 cm from the anal verge were classified as upper, middle and lower third rectal cancers. Patients with locally advanced rectal cancer (T3, T4 or node-positive disease) were offered neoadjuvant long-course chemoradiation (50.4 Gy with concurrent Capecitabine) or short-course radiation therapy (25 Gy in 5 fractions) after discussion in tumour board. Patients with limited burden visceral metastatic disease, chosen for a curative intent treatment, were given short-course radiation therapy with chemotherapy (5-fluoouracil or capecitabine with leucovorin and oxaliplatin). Response assessment was done using a repeat MRI (MRI 2). MRI 1 and MRI 2 were reviewed retrospectively and data was collected for the involvement of mesorectal fascia (MRF) on MRI for these high-risk patients, both at baseline and at restaging after neoadjuvant therapy. Involvement of mesorectal fascia was classified as per the quadrant of involved margin (anterior, posterior, lateral). The closest distance of the tumour from the mesorectal fascia was recorded.

After adequate neoadjuvant therapy, patients underwent surgery, either in TME or outside TME plane. Subsequently, adjuvant treatment was planned after the review of the histopathology report in the tumour board. The pathologists at the institute use a 1-mm cutoff is for a clear pCRM [6]. Any tumour or a tumour bearing lymph node lying within 1 mm of the margin is considered as involved pCRM. Patients with positive pCRM were either planned for adjuvant chemotherapy or offered additional local treatment (re-irradiation or surgery) after recovery from the surgery. Patients were then followed up at 3 monthly intervals using CEA levels, annual CT scan and a colonoscopy at 1 year and 5 years after surgery.

Statistical analysis

Statistical analyses were performed using SPSS Version 25. Overall survival (OS) was calculated from the time of surgery till the time of death or last follow-up. Disease-free survival (DFS) was calculated from the time of surgery till the time of first relapse. Survival analysis was done using Kaplan Meir curves. The local recurrence-free survival (LRFS) was calculated from the date of surgery to first evidence of local recurrence. Comparison of proportional hazards for recurrence and death was done using the log rank test. Univariate and multivariate analysis was done using the Cox regression analysis.

Results

1. Study population

   Amongst the 1800 rectal cancer resections done in the study period, 105 patients with positive pCRM were

initially identified. Only those patients with a clear distal resection margin were included. Of these, 19 were excluded in accordance with the identified criteria. 9 patients had non-adenocarcinoma histologies (4–melanoma, 2–undifferentiated carcinoma, 2–squamous cell carcinoma, 1–neuroendocrine carcinoma), 2 underwent cytoreduction surgery for peritoneal disease, 5 patients defaulted after surgery, 1 was declared unfit for any further treatment and two post-operative deaths occurred (Fig. 1).

2. The demographic, treatment and operative characteristics are as detailed below in Table 1. Most of the parameters were equitably distributed between the patient group who had recurrence and the one with no recurrence.
3. Assessment of circumferential resection margin

   a Radiological assessment:

   Of the 86 patients, MRF was involved in 55 patients (64%) on the baseline MRI 1. The MRF involvement was most commonly seen in anterior quadrant (30, 34.9%) followed by lateral (18, 20.9%) and posterior quadrant (7, 8.1%). Upon restaging, 49 (56.97%) patients had tumour within 1mm of the MRF on MRI.

   b Pathological assessment:

   The involvement of pCRM was classified with respect to involvement by node or by primary disease. Majority of patients, 75 (87.2%) had pCRM involved by the primary tumour while 11 (12.8%) had pCRM involved by a positive node.

4. Adjuvant treatment

   Majority of these patients, 83 (96.5%) received chemotherapy as the sole adjuvant treatment modality. Two patients (2.3%) were given post-operative radiotherapy (one received radiation boost after prior preoperative radiotherapy) and one patient underwent revision surgery (initial inter-sphincteric resection was converted to a completion abdomino-perineal excision, APR).

   Nine patients had undergone an index inter-sphincteric resection with a positive pCRM on final histopathology report. In the adjuvant setting, 7 of these were offered a choice between a revision surgery (to an APR) and chemotherapy and 2 patients were offered chemotherapy alone in view of delayed recovery from the

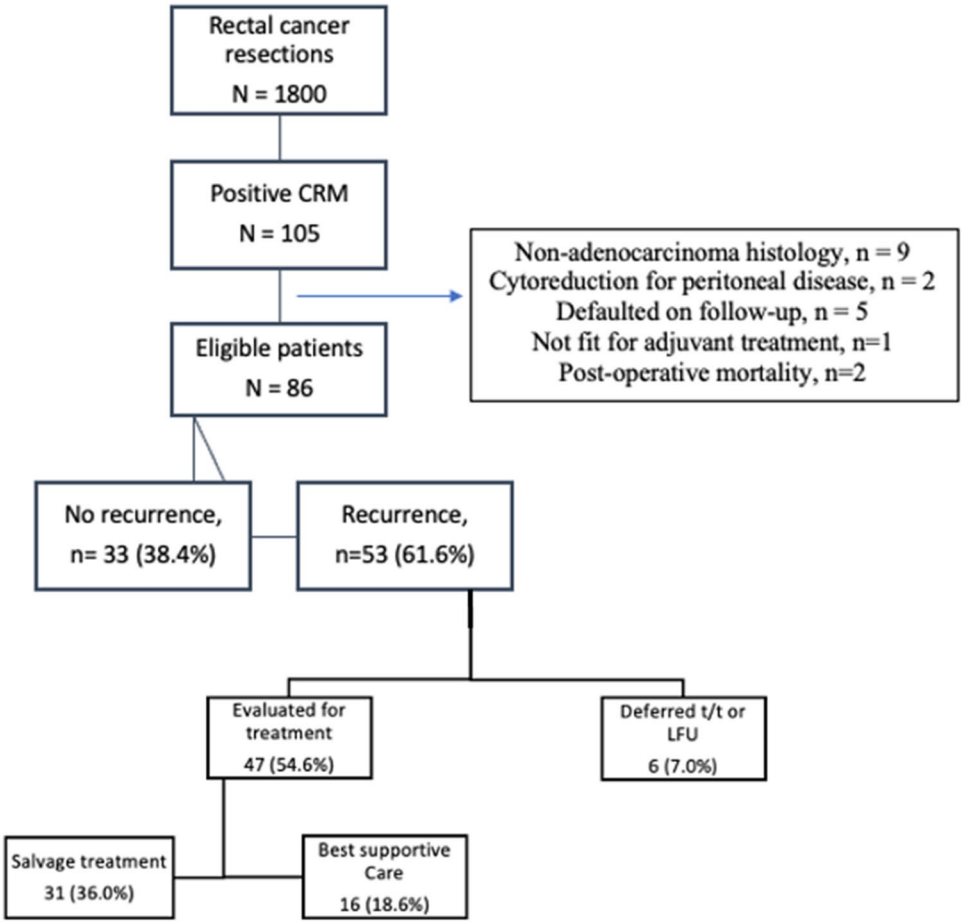

Fig. 1 Cohort diagram

Table 1 Demographic, treatment and histopathology characteristics amongst the patients with recurrence and no recurrence

Variable	No recurrence $N=33$	Recurrence $N=53$	P value
Age			
< 50 years	15 (17.4%)	36 (41.9%)	0.039
> 50 years	18 (20.9%)	17 (19.8%)	
Sex			
Males	24 (27.9%)	43 (50.0%)	0.361
Females	9 (10.4%)	10 (11.6%)	
Tumour location			
Mid–third	3 (3.5%)	5 (5.8%)	0.958
Lower–third	30 (34.9%)	48 (55.8%)	
Clinical T stage			
≤ T3	28 (32.5%)	39 (45.4%)	0.392
T4	5 (5.9%)	14 (16.3%)	
Clinical N stage			
Node positive	27 (31.4%)	48 (55.8%)	0.238
Synchronous limited metastases [#]	2 (2.3%)	8 (9.3%)	0.204
Preoperative treatment			
Long-course chemoradiation	27 (31.4%)	42 (48.8%)	0.242
Short-course radiation	6 (7.0%)	7 (8.1%)	
No treatment	0 (0%)	4 (4.7%)	
Surgery			
APR	19 (22.1%)	42 (48.8%)	0.132
LAR	6 (7.0%)	5 (5.8%)	
ISR	6 (7.0%)	3 (3.5%)	
Exenteration	2 (2.3%)	3 (3.5%)	
Lateral pelvic node dissection	1 (1.2%)	3 (3.5%)	0.573
Grade			
Moderately differentiated	21 (24.4%)	22 (25.6%)	0.046
Poorly differentiated ± signet ring cell	12 (14.0%)	31 (36.0%)	
Pathological T stage			
≤ pT3	28 (32.6%)	45 (52.3%)	0.994
pT4	5 (5.8%)	8 (9.3%)	
pN stage*			
pN0	15 (17.4%)	14 (16.3%)	0.136
pN1	11 (12.8%)	19 (22.1%)	
pN2	7 (8.1%)	20 (23.3%)	
Tumour regression grade			
≥ grade 3	24 (27.9%)	43 (50.0%)	0.361
Perineural invasion			
Yes	7 (8.1%)	15 (17.4%)	0.464

All percentages in the table represent a fraction of all eligible patients (i.e. 86 patients). *APR* abdomino-perineal resection, *LAR* low anterior resection, *ISR* inter-sphincteric resection

[*] Mean lymph nodal yield was 13 nodes

[#] 5—liver-limited metastases, 1—unilateral, unilobar lung metastases and 4—low volume retroperitoneal nodal metastases (para-aortic region)

index surgery. Only 1 patient underwent revision surgery whilst the other 8 received chemotherapy.

Of the 4 patients who underwent upfront surgery, one received adjuvant chemoradiation therapy and 3 patients received chemotherapy in view of synchronous resected metastatic disease.

5. Analysis of patterns of failure

Of the 86 patients, 53 patients (61.6%) had recurrence at a median follow-up of 25 months. Recurrences were detected by asymptomatic rise of CEA on follow-up in 18 patients (20.9%), by asymptomatic finding on per protocol follow-up imaging in 13 patients (15.1%) and by symptomatic presentation in 22 patients (25.6%).

As shown in Table 2, systemic recurrences were more often detected either by imaging or serum testing for CEA in an asymptomatic patient (20.1%) while local (13.1%) and peritoneal (13.2%) recurrences were more often symptomatic (p=0.000).

6. Salvage of recurrent disease

Of the 53 patients that had recurrence, 6 patients (11.3%) were lost to follow-up while 16 (30.2%) were declared unfit for any salvage treatment and were given supportive care. Twenty (37.7%) patients were given only chemotherapy while 11 patients (20.8%) were offered combination treatment with either surgery or radiation for the recurrent disease along with chemotherapy.

Follow-up after salvage treatment for recurrent disease:

Salvage treatment with curative intent was offered in 11 (20.8%) patients. Of these, 9 patients followed up till subsequent relapse. The mean time interval till the subsequent relapse was 11.2 months. All these 9 patients eventually had systemic relapse.

7. Survival analysis

a Median follow-up was 25 months. The 2-year overall survival (OS) and disease-free survival (DFS) of the cohort is 82.4% and 74.0%. The projected 3-year OS and DFS is 68.6% and 64.5% respectively. Median LRFS was 10.3 months (Fig. 2).

b Cox regression univariate and multivariate analysis

Various pathological and treatment variables were analysed to assess the impact of survival. Table 3. On multivariate analysis, only N2 nodal status was consistently found to influence survivals. pCRM positivity lost its predictive power when controlled for other tumour characteristics.

Table 2 Sites of recurrence and the method of detection

	Locoregional recurrence	Systemic recurrence	Peritoneal recurrence	Locoregional and systemic recurrence	Total
CEA rise only	6 (11.3%)	9 (16.9%)	0 (0.0%)	3 (5.6%)	18 (33.9%)
Radiological detection only	3 (5.6%)	7 (13.2%)	1 (1.9%)	2 (3.7%)	13(24.5%)
Symptomatic	7 (13.2%)	4 (7.5%)	7 (13.2%)	4 (7.5%)	22 (41.5%)
Total	16 (30.2%)	20 (37.7%)	8 (15.1%)	9 (16.9%)	53 (100.0%)

CEA carcino-embryonic antigen

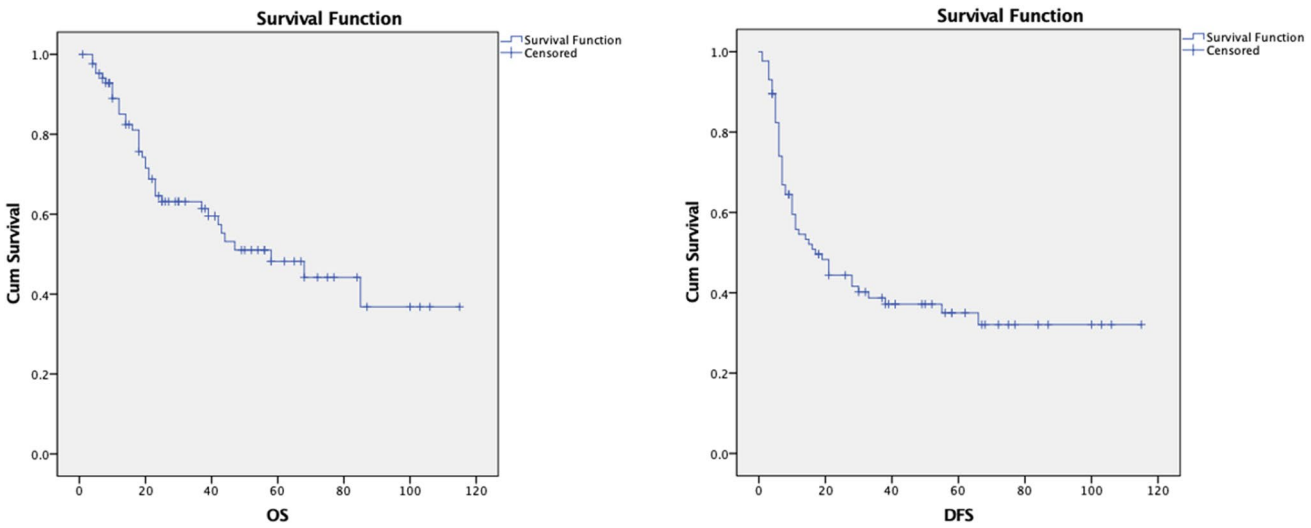

Fig. 2 Kaplan Meier curves for overall survival and disease-free survival

Table 3 Univariate and multivariate Cox regression analyses assessing the impact on overall survival and disease-free survival

	Overall survival		Disease-free survival	
	Univariate	Multivariate	Univariate	Multivariate
Variable	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age	0.98 (0.95–1.02)		**0.98 (0.96–0.99)**	0.98 (0.97–1.001)
Sex (male)	1.5 (0.65–3.4)		1.54 (0.77–3.07)	
Synchronous metastases	1.58 (0.61–4.1)		**2.23 (1.03–4.8)**	**2.26 (1.005–5.1)**
Preoperative treatment	Ref		Ref	
None	2.39 (0.32–17.6)		0.72 (0.26–2.01)	
Long-course chemoradiation	3.94 (0.47–33)		1.09 (0.31–3.7)	
Short-course radiation				
Sphincter preservation	0.47 (0.19–1.15)		0.43 (0.2–0.9)	
Poorly differentiated	**2.05 (1.05–4.008)**	1.8 (0.82–3.9)	**1.8 (1.04–3.1)**	1.73 (0.92–3.3)
pT4	0.62 (0.19–2.04)		0.95 (0.45–2.03)	
N stage				
pN0	Ref	Ref	Ref	Ref
pN1	2.15 (0.84–5.5)	2.4 (0.91–6.0)	1.73 (0.87–3.5)	1.73 (0.85–3.5)
pN2	**6.05 (2.4–14.9)**	**4.6 (1.7–12.2)**	**3.12 (1.5–6.2)**	**2.3 (1.09–4.85)**
Extracellular mucin	1.26 (0.65–2.44)		0.97 (0.56–1.67)	
Perineural invasion	**2.25 (1.09–4.6)**	1.9 (0.88–4.5)	1.64 (0.9–3.01)	
Tumour regression grade ≥ 3	1.7 (0.75–3.9)		1.7 (0.85–3.37)	
pCRM*				
Node	Ref	Ref	Ref	
Primary	**0.16 (0.05–0.5)**	0.3 (0.08–1.15)	0.57 (0.13–2.3)	

*Involvement of pCRM either by lymph node or by primary tumour

c Patients with recurrence were analysed separately to assess the impact of any kind of treatment received. Patients with relapse who received some treatment for relapse (chemotherapy or surgery or both) had significantly superior survival, 43.7 (32.1–55.4) months compared to those who did not receive any treatment for relapse, 20.4 (13.5–27.2) months, $p = 0.002$.

d Patients with recurrence were also separately analysed to study the impact of the pattern of relapse on the survival outcomes. Patients with peritoneal recurrence fared the worst when compared with the ones having locoregional and systemic recurrences (p value for OS < 0.01, p value for DFS < 0.01).

e Sub group analysis: outcomes of node-negative or node-positive pCRM patients

Patients with node-negative disease (n=29) were compared with the ones with node-positive disease (n=57). No difference was seen with regards to the patterns of relapse between the two groups (p=0.346).

Discussion

Rates of curative rectal resections with positive pCRM ranges from 1 to 28%, varying across institutions according to the used defining criteria and varying pathology reporting standards [1, 4, 6, 7]. The rate of margin positive resections at our institute is 5.83% suggestive of an adequate surgical quality control.

Strategies for management of a positive pCRM resection include chemotherapy with or without post-operation radiotherapy boost or a revision surgery (in cases of sphincter preservation surgery). T.R. de Paul et al. analysed 1607 patients of rectal cancer with a positive pCRM from the National Cancer database and found that 65% patients did not receive any adjuvant treatment [8]. Adjuvant chemotherapy improved the survival outcomes in these patients with T3N0 tumours who had clear margins preoperatively but had unexpected positive pCRM involvement (3 year OS, 88.6% versus 84.6%; p=0.027%). As a standard protocol at our institute, all patients with

a positive pCRM after an adequate TME surgery are offered adjuvant chemotherapy. However, the decision for administration of additional therapy like radiation boost to the tumour bed or revision surgery in case of an index sphincter preservation surgery is more complex and often involves a multi-disciplinary discussion.

The compliance to adjuvant treatment after rectal resections has been noted to be low (~50%) across the globe [9, 10]. Poor patient rehabilitation after chemoradiation and surgery, patient comorbidities accompanied by varying physician practices account for these low rates. Completion of the entire treatment provides with the best chance at survival. The cohort analysed in this study included only those patients who had completed adjuvant treatment after the surgery. Patients with a margin positive sphincter preserving surgery are evaluated for a revision surgery, subject to recovery from index surgery and patient compliance. Likely delay in initiation of chemotherapy because of a revision surgery often precludes the use of this option. In the current cohort, only 1 out of 9 patients with inter-sphincteric resections underwent a completion abdomino-perineal resection while the remaining 8 received chemotherapy either because of delayed recovery (n=2) or because of patient preference to avoid a second surgery (n=6).

Marijnen et al conducted a subgroup analysis of the Dutch TME trial, analysing the rectal cancer patients operated upfront (without preoperative radiotherapy) having a positive pCRM (CRM <1mm) and concluded that post-operative radiotherapy does not compensate for positive margins. [11]. However, these derivations from the Dutch TME trial are subject to several statistical flaws. As of now, there is no evidence on the use of re-radiation for a pCRM following preoperative RT and TME surgery. This leads to an uncertain role of post-operative radiotherapy in cases of a positive pCRM after an preoperative radiotherapy and surgery [12]. Hence, it is not practiced routinely at our institute considering the increased toxicity with doubtful survival benefit.

Kim et al conducted a propensity score matched analysis to assess the impact of positive pCRM on the patterns of relapse [13]. A total of 43 out of 72 patients with positive pCRM developed recurrences at a median follow-up time of 46 months. Of these, 54.9% had distant recurrence, 14.4% had regional recurrence and 7.3% had local recurrence. When compared with R-0 resections, group with R+ resections had a trend towards inferior distant metastases-free survival and inferior overall survival with equivalent local relapses. Denost et al. in a recent analysis of 42 patients with R1 rectal resections have raised concern regarding a higher rate and short interval to distant relapse after a positive pCRM [14]. This study shows that amongst the positive pCRM resections, 18.6% patients had only locoregional recurrence, 23.3% had only systemic recurrence, 9.3% had recurrence in peritoneal cavity while 9 patients 10.5% had simultaneous recurrence both at locoregional and systemic sites. Hence, a higher rate of distant relapse should be anticipated after rectal resections with a positive pCRM and the adjuvant treatment in such cases should focus more on systemic control.

Systemic recurrences are often detected first on routine follow-up in otherwise asymptomatic patients while the peritoneal and locoregional recurrences are more often symptomatic. Analysis revealed that 26% patients recurred within 6 months which indicates the need for a more stringent surveillance protocol in this cohort of patients which is at higher risk of both systemic and local failure. PROPHYLOCHIP trial which evaluated the strategy of HIPEC in high-risk rectal cancers utilised a more intensive surveillance protocol of imaging every 3 months in the control arm and showed that around 52% patients developed recurrence within 6 months [15]. This probably hints towards instituting a more intensive and stringent follow-up imaging protocol, possibly imaging every 3 monthly, for high-risk rectal cancers, although it is subject to further research if earlier detection of recurrences would translate into overall survival benefit.

In this study, only 11 of 53 patients (20.75%) with recurrent disease could be offered salvage treatment with a curative intent. We postulate that patients with locoregional and peritoneal recurrences are more often symptomatic and possibly unfit to receive any salvage treatment for the relapse. Local failure despite an adequate initial surgery probably is a predictor of an aggressive disease destined for higher chance of systemic failure. There is an unmet need of identifying such high-risk patients at the time of treatment initiation and then tailor the neoadjuvant and subsequent surgical treatment for such patients to possibly improve the survival outcomes.

An inadequate surgery leading to a positive pCRM should be avoided and be differentiated from an adequate good-quality surgery leading to an inadvertent positive pCRM when evaluating oncological outcomes. Emphasis should be laid on an adequate MRI-directed surgery to achieve the most superior results [3, 16, 17].

Majority of the patients in this study with a positive pCRM had low-lying tumours (90.7%) requiring a sphincter sacrificing surgery in 76.7% patients. Signet ring cell adenocarcinoma (SCRA) histology was seen in a disproportionately higher fraction of this cohort (34.9%). SRCA histology has been found to be a predictive factor for a positive pCRM [18, 19]. Previous study from the institute showed that SRCA comprised 15.1% of the overall rectal cancer patients at the institute and a higher proportion of these patients (23%) have a poor response to neoadjuvant chemoradiation [20]. We postulate that an apparent higher rate of positive pCRM can be attributed to diffuse submucosal and radial infiltration by the signet ring cells. Such patients with low-lying tumours and poor differentiation

often necessitating an abdomino-perineal resection, have an inherent biologically aggressive disease.

Patients having low-lying tumours with poor differentiation and needing abdomino-perineal resection have a biologically aggressive disease [21]. Cox regression analyses in this study points towards inferior outcomes for patients with poorly differentiated tumours and node-positive tumours. The impact of a positive pCRM was reduced when controlled for pathological factors constituting the disease biology. This seems to follow a similar trend as that of a decreasing requirement of a longitudinal distal resection margin in rectal resections [22]. Kazi et al. have shown that long-term oncological outcomes after rectal resections are equivalent even with sub centimetric distal resection margin, unless accompanied by an inferior tumour response to preoperative chemoradiation (again reflective of a poor disease biology) [23].

These patients require special attention at the time of treatment planning to improve the survival outcomes. Poor disease biology should take precedence over margin involvement alone during the course of treatment planning, even the need for wide distal margin during rectal resections has now been superseded

Strengths of the study include it being the largest single-centre experience of patients with a positive pCRM involvement, thus ensuring uniform surgical expertise across the database. The cohort includes patients managed in the modern era of preoperative radiation therapy and good-quality MRI-directed rectal surgery, as reflected by overall comparable rates of institutional positive pCRM rate (~5.8%). Patient follow-up used was quite exhaustive with meticulous data retrieval from the electronic database or after telephonic patient follow-up.

Limitations of the study include the retrospective nature of the analysis. Comparison with entire cohort of patients of rectal cancer surgery would shed more light on the factors predictive of margin involvement and on the compliance to post-operative treatment modalities. Positive pCRM resulting after an inadequate surgery could not be objectively differentiated from a positive pCRM after a good-quality surgery. There is need for further research into locoregional treatment approaches after a positive pCRM in node-negative disease with relatively good disease biology, where chances of distant failure are minimum.

Conclusion

Patients with a positive pCRM have high relapse rates (as high as 61.6%), failing both locally and distally. Systemic relapses are more often asymptomatic as compared to peritoneal or locoregional relapse and detected on follow-up surveillance. Identification of such recurrences while still salvageable via an intensive imaging surveillance protocol is desirable. Early identification of patients at a higher risk of a positive pCRM right at the time of treatment initiation using appropriate radiological staging may provide a window for treatment intensification via systemic therapy or an extended surgery.

Author contribution The authorship has been decided in accordance with CRediT taxonomy.

Data availability The data used in the manuscript will be available upon request from the corresponding author.

Code availability Not applicable.

Declarations

Ethics approval Not applicable as retrospective analysis.

Consent to participate Not applicable.

Consent for publication. Not applicable.

Conflict of interest The authors declare no competing interests.

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