RESEARCH ARTICLE

# Risk factors effecting development of metachronous liver metastasis in rectal cancer patients after curative surgical resection. Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore experience

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## Abstract

**Objective:** To determine risk factors affecting development of metachronous liver metastasis in rectal cancer patients after curative surgical resection.

**Method:** The retrospective cohort study was conducted at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, and comprised data of patients with histologically proven rectal carcinoma admitted to the department of surgical oncology from January 2005 to December 2015. Clinical data of all patients, including age, gender, clinical presentation, clinical and pathological tumour-nodes-metastasis classification, neoadjuvant chemo-radiotherapy, surgery, adjuvant chemotherapy, pre- and postoperative carcinoembryonic antigen levels, histopathological findings and tumour recurrence were analysed. SPSS 23 was used for data analysis.

**Results:** Of the 434 patients, 26(6%) developed liver metastasis. Of them, 18(69%) were male and 16(61.5%) were aged below 50 years. On clinical staging, 2(7.7%) patients had stage II disease, 22(84.6%) had stage III, and 2(7.7%) patients had stage IV disease. At last follow-up, 2(7.7%) patients were alive without disease, 7(27%) had expired, while 17(65.4%) were alive with disease.

**Conclusion:** Tumour depth, lymph node metastasis, postoperative carcinoembryonic antigen levels, complete tumour response on histopathology were found to be responsible for metachronous liver metastases in rectal cancer patients following curative resection.

**Key Words:** CEA, Carcinoembryonic antigen, T stage, Tumour depth of invasion, ChemoXRT, Chemotherapy with radiotherapy. (JPMA 69: 201; 2019)

## Introduction

Rectal cancer is one of the most commonly diagnosed cancers worldwide and is counted among the leading causes of cancer-related deaths. The prognosis is closely related to the extent of disease at presentation as determined by Dukes[1,2] and American Joint Committee on Cancer (AJCC)[3] classifications. Metastases from colorectal cancers are common and develop in 40-60% patients. The existence of metastases classifies patients into M1 and stage IV of AJCC classification.[4]

The most common metastases site from rectal cancer is liver and about 50% patients develop hepatic metastases during the course of their disease, with 20-25% of these presenting with synchronous liver metastases. In about 1/3rd of the patients with synchronous or metachronous liver metastases, and the liver is the only site of metastatic disease.[5-7] In particular, the median survival for patients with untreated colorectal cancer liver metastases ranges from 4.5 months to 21 months with a survival rate of only 0-3%.[8,9] Advances in adjuvant treatment after primary curative surgical resection of colorectal cancer have shown the potential of a decrease in the number of metastatic cases even though the two-year survival is limited to 40% at best. These results explain that metastatic liver lesions, if resectable, should be excised as it will completely eliminate the source and, hence, would reduce further spread of the tumour.[10,11]

However, only 10-20% of the patients with liver

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metastases are candidates for surgical resection at presentation[12,13] while the rest are ineligible for surgery because of the tumour location, size, number of liver lesions, the residual normal liver and extra-hepatic disease progression.[14,15]

The current study was planned to identify the risk factors responsible for the development of metastatic lesions in liver after curative surgical resection of the primary rectal carcinoma.

## Methods

The retrospective cohort study was conducted at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, and comprised data of patients with histologically proven rectal carcinoma admitted to the department of surgical oncology from January 2005 to December 2015. Approval was obtained from the institutional review board.

Rectal cancer was defined as histologically-proven adenocarcinoma within 15cm of the anal verge and staged according to the 7th edition of AJCC staging system.[4] Records of patients were included if they had received neoadjuvant chemo-radiation therapy 4-6 weeks before surgery. Curative surgical treatment was defined as any gross residual tumour not having remained in the surgical bed and a surgical resection margin that was pathologically negative for tumour invasion. Patients with hepatic insufficiency, end-stage lung disease, irresectable primary tumour at presentation and multiple primary cancers were excluded. Staging work-up included full colonoscopy, contrast enhanced computed tomography (CT) scan of thorax and abdomen, and magnetic resonance imaging (MRI) of pelvis in all cases to exclude patients with evidence of distant metastasis at initial diagnosis.

Clinical data of all patients, including demographic variables (age, gender), clinical variables (clinical presentation, tumour location, tumour staging, clinical and pathological tumour-nodes-metastasis (TNM) classification, neoadjuvant chemo-radiotherapy (chmoXRT), surgery, adjuvant chemotherapy, pre- and postoperative carcinoembryonic antigen (CEA) levels at 3 and 6 months, histopathological findings, specimen resection margin status, local and distant tumour recurrence was collected from patients' records. Follow-up for five years from the date of surgery was observed for tumour recurrence.

Statistical analysis was done using SPSS 23. For categorical variables, frequencies and percentages, and for continuous variables mean and standard deviation (SD) were reported. Bivariate analysis was done using chi-square test or Fisher exact test where appropriate to establish association between two categorical variables with $p<0.05$ being the cut-off marker for statistical significance. Logistic regression model was applied for identification of risk factors responsible for the development of metastatic lesions in the liver.

## Results

Of the 434 patients identified, 26(6%) developed liver metastasis. Of them, 18(69%) were male and 16(61.5%)

**Table-1:** Descriptive statistics with bivariate analysis.

| Variables | | Liver metastasis | | *p*-value |
|---|---|---|---|---|
| | | Yes | No | |
| | | 26 (6.0%) | 408 (94.0%) | |
| Age | <50 YEARS | 16 (7.4%) | 201 (92.6%) | 0.832 |
| | >50 YEARS | 10 (4.6%) | 207 (95.4%) | |
| Sex | MALE | 18 (6.3%) | 266 (93.7%) | 0.225 |
| | FEMALE | 8 (5.3%) | 142 (94.7%) | |
| cTNM | STAGE I | 0 (0%) | 5 (100%) | 0.299 |
| | STAGE II | 2 (4.7%) | 41 (95.3%) | |
| | STAGE III | 22 (5.9%) | 354 (94.1%) | |
| | STAGE IV | 2 (20%) | 8 (80%) | |
| Clinical nodal status | N 0 | 1 (1.8%) | 56 (98.2%) | 0.039 |
| | N 1 | 5 (5.4%) | 88 (94.6%) | |
| | N2 | 19 (6.7%) | 264 (93.3%) | |
| | N 3 | 1 (100%) | 0 | |
| Pre-operative CEA*levels | NORMAL | 15 (5%) | 286 (95%) | 0.212 |
| | RAISED | 9 (8.3%) | 100 (91.7%) | |
| NEOADJUVANT TREATMENT | NO | 4 (9.8%) | 37 (90.2%) | 0.292 |
| | YES | 22 (5.6%) | 371 (94.4%) | *** |
| pTNM | NO DISEASE | 1 (1.1%) | 88 (98.9%) | 0.006 |
| | STAGE I | 3 (4.8%) | 59 (95.2%) | |
| | STAGE II | 2 (2.8%) | 70 (97.2%) | |
| | STAGE III | 18 (8.8%) | 187 (91.2%) | |
| | STAGE IV | 2 (33.3%) | 4 (66.7%) | |
| COMLPETE RESPONSE | NO | 25 (7.2%) | 320 (92.8%) | 0.03 |
| | YES | 1 (1.1%) | 88 (98.9%) | *** |
| MARGIN CLEARENCE | NO | 1 (3.4%) | 28 (96.6%) | 0.47 |
| | YES | 25 (6.2%) | 380 (93.8%) | *** |
| Histopathology status | WELL DIFF | 3 (5.1%) | 56 (94.9%) | 0.133 |
| | MOD DIFF | 19 (7.9%) | 223 (92.1%) | |
| | POOR DIFF | 3 (6.2%) | 41 (93.8%) | |
| | NO RESIDUAL | 1 (1.2%) | 88 (98.8%) | |
| POSTOPERATIVECEA* LEVELS | NORMAL | 12 (3.4%) | 339 (96.6%) | 0.001** |
| | RAISED | 12 (21.1%) | 45 (78.9%) | |
| OUTCOME STATUS | ALIVE | 2 (0.7%) | 271 (99.3%) | 0.001** |
| | DEAD | 7 (18.9%) | 30 (81.1%) | |
| | DISEASED | 17 (15.3%) | 94 (84.7%) | |
| | LOST F/U | 0 | 13 (100%) | |

*Carcinoembryonic antigen, **Adjusted p-values as per editor comments, ***Fisher exact test is applied on these results (if you have a 2x2 frequency table with small number of expected frequencies less than 5 you should perform fisher exact test . reference: Altman DG (1991) Practical statistics for medical research. London: Chapman and Hall. Book info)

**Table-2:** Logistic Regression Model-Multivariate Analysis.

| Variables | Categories | Unadjusted Or(Ci), P-value | Adjusted Or(Ci), P-value |
|---|---|---|---|
| Age In Years | Upto 50 | Ref | Ref |
| | Above 50 | 0.61 (0.27 1.37), 0.23 | 0.54 (0.22 1.35), 0.19 |
| Sex | Male | Ref | Ref |
| | Female | 0.83 (0.35 1.96), 0.67 | 0.48 (0.17 1.37), 0.17 |
| Preoperative Cea* Levels | Normal | Ref | Ref |
| | Raised | 1.72 (0.73 4.04), 0.22 | 1.16 (0.44 3.03), 0.76 |
| Complete Response | N0 | Ref | Ref |
| | Yes | 0.14 (0.021.09), 0.06 | 0.21 (0.03 1.65), 0.14 |
| Postoperative Cea* Levels | Normal | Ref | Ref |
| | Raised | 0.75 (3.19 17.80), 0.001 | 6.34 (2.50 16.13), 0.001 |

were aged below 50 years. On clinical staging, 2(7.7%) patients had stage II disease, 22(84.6%) had stage III, and 2(7.7%) patients had stage IV disease. Pre-op CEA levels were missing in 2(7.6%) cases, 15(57.6%) had normal and 9(34.6%) had raised serum CEA levels. All the 26(100%) patients received neoadjuvant chemoXRT. On histopathology, 18(69%) patients had stage III disease. Specimen resection margins were negative for disease in 25(96%) patients. Post-op CEA levels were also missing in 2(7.6%) patients, while 12(46%) patients each had raised and normal CEA levels at 6-month follow-up. Only 1(3.8%) patient had complete tumour response on histopathology. At last follow-up, 2(7.7%) patients were alive without disease, 7(27%) had expired, while 17(65.4%) were alive with disease.

Results showed that tumour depth (T-stage), lymph node metastasis, post-op serum CEA levels and complete tumour response on histopathology were the risk factors responsible for the development of metastatic lesions in liver after curative resection of primary rectal carcinoma (Table 1).

When multivariate analysis was run on these results only post-op serum CEA levels (p=0.001) was identified as a significant risk factor (Table 2).

## Discussion

Rectal tumours are associated with increased mortality rate even after complete curative surgical resection of the primary tumour and it is mostly due to tumour recurrence. Almost half of patients undergoing resection for primary rectal cancer develop metastasis at some point during their surveillance. Primary metastatic site is liver and accounts for almost 50% of the cases. Even after improvement in chemotherapeutic and biological agents, chances of recurrence cannot be reduced and patient's survival is rarely longer than 3 years. After curative surgical resection of primary rectal cancer, if patients develop hepatic metastasis the chances of curative treatment still exist and it depends upon the disease status, its extent and available treatment options.[16-18]

During the past two decades, the five-year survival rates for hepatic rectal metastases patients have almost doubled from 30% to 60%.[19] The introduction of new chemotherapeutic agents and the shift in the criteria of surgical resection were the main factors in this progress.[20-23] Current criteria of liver resection for a metastatic liver lesion depend only on what should be left after hepatic resection. The amount of liver remnant after resection should not be less than 20% of total liver volume for normal patients and about 30% or more for cirrhotic patients.[24,25]

Our study showed that recurrent liver metastasis after curative primary rectal cancer surgery depends on several factors like T stage of the tumour, lymph node metastasis (N stage of tumour) and post-op serum CEA levels. Advanced T stage, positive lymph node metastasis on histopathology of the specimen and post-op raised serum CEA levels are responsible for the recurrence of tumour after complete curative surgical resection of primary rectal cancer. If no residual tumour is identified on histopathology and complete tumour response is achieved, then chances of recurrence are minimal. These results when compared with international studies were found similar.[26, 27]

Early detection of these risk factors for tumour recurrence will increase the chances of surgical cure and adjuvant treatment will in turn increase overall survival of these patients. Hence, we recommend that such patients should have an extended surveillance programme. In terms of limitations, the current study is retrospective in nature with a small sample size at a single institution. We recommend multi-centre prospective studies with large number of patients to validate these results.

## Conclusion

Tumour depth, lymph node metastases, post-op serum CEA levels and complete tumour response on histopathology can affect the development of metachronous liver lesions in patients having umdergone curative surgical resection for rectal cancers. Hence, we recommend that such patients should have an extended

surveillance programme and should potentially be treated for recurrence at an earlier stage of the disease.

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