ISSN- O: 2458 - 868X, ISSN–P: 2458 – 8687
Index Copernicus Value: 68 . 16
PubMed - National Library of Medicine - ID: 101731606

International Journal of Medical Science and Innovative Research (IJMSIR)
IJMSIR : A Medical Publication Hub
Available Online at: www.ijmsir.com
Volume – 5, Issue – 5, September - 2020, Page No. : 196 - 202

Prognostic factors affecting clinical and pathological response after neoadjuvant chemoradiation for locally advanced carcinoma rectum

[1]Dr. Preeya V, Associate Professor, Department of Radiation Oncology, Government Medical College, Kottayam, Kerala, India.

Corresponding Author: Dr. Preeya V, Associate Professor, Department of Radiation Oncology, Government Medical College, Kottayam, Kerala, India.

Citation this Article: Dr. Preeya V, "Prognostic factors affecting clinical and pathological response after neoadjuvant chemoradiation for locally advanced carcinoma rectum", IJMSIR- September - 2020, Vol – 5, Issue - 5, P. No. 196 – 202.

Type of Publication: Original Research Paper

Conflicts of Interest: Nil

Abstract

Background: Neoadjuvant chemoradiation (NACRT) for rectal cancers helps in tumor downstaging and improved survival.Pathological complete response is a forerunner of improved outcomes.We investiagated various variables influencing clnical & pathological response.

Methods: 60 biopsy proven rectal cancer patients underwent NACRT from august 2012 to june 2015.All of them received long course radiation with concurrent capecitabine .4 to 6 weeks after completion of NACRT ,those eligible clinically and radiologically ,were taken up for surgery. Pathologic response to neoadjuvant treatment was evaluated by comparing pathologic TN (tumour and nodal) staging (yp) with pre-treatment clinical staging .Association of various patient related variables in pathological complete responders were investigated.

Results: Among 60 patients, 87% patients had an Ro resection,4.8% patients resisted surgery,R1 resection in 9. 5%.Complete radiological response was present in 35.7% and poor response in 14%.Complete pathological response was present in 10% patients.. In our study,3-year crude disease survival rate was 87.7% and 3-year metastases free survival rate was 100% in pCR group. Of the 4 (10%) patients achieving complete pathological (pCR) response,none failed locally or distally. Factors influencing pCR were advanced T and N stage of the disease , preopCEA and histological type.

Conclusions: All the patients with pathological complete response were of well differentiated adenocarcinoma with preop CEA of less than 5ng/ml and node negative status. Pathological complete response in turn confer survival advantage with improved rates of local and distant disease control .pCR of our patients (10%) and factors influencing pCR are comparable to that of World literature .

Keywords: neoadjuvant chemoradiotherapy (NACRT), carcino-embryonic antigen level (CEA level), microscopically margin-negative resection (R0 resection), microscopic margins positive (R1 resection), pathological complete response (PCR).

Introduction

Colorectal cancer accounts for world's third most commonly diagnosed cancer. In India, with lifestyle changes colorectal cancer is on increase. Now it accounts for 6th most common digestive tract cancer[1,,2] About 95% are adenocarcinomas followed by mucinous and adenosquamous carcinomas[1] The purpose of neoadjuvant chemoradiation as emerged from previous several randomized trials include downstaging of higher stage disease with preservation of sphincters ,especially of lower distal tumors.[3,4]When compared to postop adjuvant chemoradiation ,preop treatment is associated with fewer toxicities. The response to treatment varied among patients in the treatment group. This variation has led us to study various factors which influenced the response as well as disease free survival and overall survival in patients who received treatment from our institution from 2012 to 2015.

Materials And Methods

A. Patient Selection

This study included sixty patients who received long course preop chemoradiation for biopsy proven rectal cancers from August 2012 to june 2015.The patients included were more than 18 years of age with Eastern cooperative oncology group (ECOG)performance status of 0 or 1, T3–T4TUMORS, locally unresectable T1–T2, low-lying T2, and/or node-positive rectal cancer, adenocarcinoma confirmed histologically by endoscopic biopsy, superior extent of the tumor located within 15 cm from anal verge and with adequate bone marrow, liver and renal function. Patients with history of any form of treatment received for this disease, except those who have undergone a diverting colostomy, Synchronous colon cancer, Systemic disease(cardiovascular, renal, hepatic, etc) precluding the patient from receiving chemotherapy and those with metastatic disease are excluded from the study.

All patients underwent a detailed history taking, clinical examination with proctosigmoidoscopy, including biopsy for knowing extent , nature and histological type and grade of primary tumor. Contrast enhanced computed tomography (CECT) abdomen and pelvis and chest X-ray are done as a part of intial staging evaluation. Those patients with perirectal fat stranding are labelled T3 and ,T4 are those with definite invasion of surrounding organ. Digital rectal examination are done in all to note the distance of tumor from anal verge. To rule out medical comorbidities ,all patients underwent a complete blood count ,renal function test ,liver function test and random blood sugar examination. Serum Carcino-embryonic antigen estimation (S.CEA) also done in all patients.

B. Treatment Protocol

All patients received radiation at adose of 50.4 Gy ,1.8Gy per fraction 5 days a week for 5.5 weeks. Concurrent capecitabine,at a dose of 825mg/m2 twice daily was administered till the end of radiation. Post concurrent chemoradiation, reassesment was considered 3 weeks later with per rectal examination and contrast enhanced CT scan of abdomen and pelvis. If found operable ,they were taken up for total mesorectal excision with low anterior resection or abdominoperinel resection . Postoperatively pathological specimen was evaluated for tumor size ,nodal status ,pathological response ,margin status and tumor regression score. Adjuvant chemotherapy was planned for node positive ,T4tumors with either CAPOX three weekly for 6 cycles or FOLFOX two weekly for 12 cycles.Those who were inoperable after intial reassessment ,were continued with chemotherapy

with two weekly FOLFOX with reassessment after 4 cycles for operability. If found operable then ,taken up for surgery or else, continued with chemotherapy until disease progression.

C. Follow-Up

During chemoradiation all patients were reviewed weekly for toxicities blood count and clinical examination of irradiation site for radiation related acute toxicities. Toxicities were graded with common toxicity criteria for adverse events version 3(CTCAE). Surgical complication rates like wound healing, colostomy dysfunctioning ,if any are recorded. Post surgery patient's follow up were done every 3 monthly for first two years with clinical examination &serum c.e.a .In case of serial elevation of serum C.E.A, contrast enhanced C.T of abdomen and pelvis with or without biopsy was advised ,to rule out recurrence.

Statistical Analyses

The factors which influence pathological responses to chemoradiation were analysed with SPSS software. These include tumor stage, size, nodal status, age, histology, grade and preop CEA. Disease free survival and overall survival of these patients were also assessed till date.

Results

Sixty patients included in our study underwent chemoradiation as neoadjuvant treatment. Median age was 58 years with 54% males , outnumbering females.

Patient and disease characteristics at presentation N=60

Characteristic	N	%
Age		
Median	58years	
<50yrs	9	15%
>_50yrs	51	85%
Sex		
Male	32	54%
Female	28	46%
Distance from anal verge		
0-5 cm	25	42%
>5cm	35	53%
S.CEA		
<5ng/ml	34	57%
>/=5ng/ml	26	43%
Adeno carcinoma		
Grade 1	47	78%

Grade 2	11	18%
Grade 3	2	4%
T Stage		
T2	6	10%
T3	37	62%
T4	17	28%
N Stage		
N0	11	18%
N1	36	60%
N2	13	22%

Almost all patients received concurrent chemoradiation with capecitabine. After concurrent chemoradiation, 87% patients had an Ro resection, 4.8% patients resisted surgery, R1 resection in 9. 5%.Complete radiological response was present in 35.7% patients and poor response in 14%.Complete pathological response was present in 10% patients. Factors influencing response to treatment were advanced T stage of the disease and histological type.

A. Toxicity

Toxicity were graded as per CTCE .version 3.Haematological toxicity was reported in 9.5% patients and gastrointestinal toxicity in 7% .Wound complication in the form of wound infection was noted in 9.5%.

B. Survival

60 patients were identified with ca rectum fulfilling our criteria in the study period. Of these, 18 patients were of lost follow up. Remaining ,42 patients were analysed .2 patients died ,one of myocardial infarction and other of post-surgical wound infection with disease progression.40 patients were alive with DFS of 85% and OS of 90% at the end of three years.

C. Factors Affecting Local and Distant failures

Of the 40 operated patients 4 (10%) failed locally and 2(5%) failed locally and distally. The majority of distant failures were in lung (5%), rest in liver (2.5%) of the 3 patients whose circumferential resection margin was positive, 1(33%) failed locally of the 4 (10%) patients achieving complete pathological (PCR) response, none failed locally or distally.

Discussion

All the patients with pathological complete response were of well differentiated adenocarcinoma with preop CEA of less than 5ng/ml and node negative status .Response to neoadjuvant chemoradiation of advanced stage vary with preop CEA level and histological type. Among the histological type ,signet ring cell variant of adenocarcinoma occuring in patients of younger age carries a grave prognosis[5,14]. So aggressive treatment stratigies need to be considered for this subgroup of patients.This was supported by data from U.S National cancer data base,Korean National registry[1,2]).

Pathological complete response as per our study was also influenced by preop CEA level .CEA causes loss of anchorage to extracellular matrix and thereby

inhibits cell death. In our study preop CEA level of <5ng/ml was associated with a higher 3-year DFS and OS rates. Pathological complete reponse rate is a predictor of response to concurrent chemoradiation. Thus preop CEA level of <5ng/ml was associated with improved PCR ,DFS and OS rates. In a multi-institutional analysis by Lee etal.in Asian population the definitive role of pretreatment CEA level as a predictor of poor tumor response and distant recurrence was well depicted.(5).Moreno etal. stressed the prognostic value of CEA level in rectal cancer patients treated with chemoradiotherapy.(6)

Two other important variables which influenced PCR and survival rates of our study were pathological T and N stages. Of these ,pathological N stage was more significant .This was supported by studies by Huebner et.al(7,8,15).According to the study by Huebner et.al [8] , TRG and nodal status ($P < 0.001$) were the most significant predictors associated with outcome. In our study ,two patients with distant failure had advanced nodal stage . pN stage serves as a good marker post neoadjuvant treatment, indicating a need for more aggressive adjuvant chemotherapy regimens to tackle distant metastasis[9,14] .In the present study,out of 5 patients who failed locally ,three patients(60%) had inadequate lymph node sampling ,1 deferred surgery ,1 with advanced nodal stage .Out of 3 with inadequate lymph node sampling ,two were associated with high risk features of local failure namely margin positivity and involved circumferential resected margin. This in turn emphasis the importance of intensifying all efforts from involved subspecialities (i.e. surgeons and pathologists) to reach the benchmark harvest of 12 resected lymph nodes according to current guidelines. But in a systematic review by Awwad et.al[10]and Robert Mechera et.al[11],it has been seen that long-course preoperative radiotherapy appears to reduce lymph node yield in patients with rectal cancer without causal relationship between lymph node yield and survival .

A recent report from Hwang showed pathological stage in patients after neoadjuvantchemoradiotherpy can predict their prognosis.(16).In a recent metaanalysis with 3000 patients,it was demonstrated that 1)5-year crude disease survival rate in patients with pathological complete response and those without were 88% and 66% respectively2)that the 5-year distal metastases-free survival rate was 89% in the pCR group and 75% for non-pCR ($P < 0.0001$) . Maas et al[13].in a recent metaanalysis of 3105 patients demonstrated

- a 5 year crude disease survival rate of 83% in patients with pathological complete responders(pCR)Vs 66% with no pCR and
- 5 year distant metastase free survival of 89% in pCRVs 75% in no pCR group.

pCR is achievable in a proportion of patients and that response to pre-operative CRT can be used as a predictor of tumour recurrence rate and long-term outcome.(12,13,15,16)

In our study,3-year crude disease survival rate is 87.7% and 3-year metastases free survival rate is 100% in pCR group.

Conclusion

The response to NACRT can vary among patients with locally advanced rectal cancers and thus affect survival. Among all the pCR patients, mucinous adenocarcinoma patients had the worst survival compared patients with common adenocarcinoma. Present study showed that histology and clinical advanced N stage were independent risk factors.

Mucinous adenocarcinoma, positive pre-treatment serum CEA results, and clinical T4 and advanced N

stages may impart difficulty for patients to achieve pCR. Mucinous adenocarcinoma and clinical N2 stage might be indicative of a prognostically unfavorable biological tumor profile with a greater propensity for local or distant recurrence and decreased survival.

Locally advanced rectal cancers with signet ring cell histology are aggressive with poorer survival compared to other common histologies. This warrants more intensive chemoradiation strategies with induction chemotherapy followed by chemoradiation possibly with radiation dose escalation and aggressive surgical resections aiming at R0 resection. Addition of biologicals can also be considered for this subgroup aiming at pCR and a better outcome.

Acknowledgements: I would like to thank Dr.Rema, Professor of Radiation Oncology, Dr.Aneesh.K.Soman, Junior consultant, Mrs. Ancy, Statistician for their significant contribution towards the manuscript. I would also thank the authors whose articles were selected for reference and was a constant help while preparing the manuscript.

References

1. Hyngstrom JR, Hu CY, Xing Y, et al. Clinicopathologyand outcomes for mucinous and signet ring colorectaladenocarcinoma: analysis from the National Cancer Data Base. Ann SurgOncol 2012;19:2814-21.
2. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2014 accessed on 16/01/2015 . Available from:http//globcan.iarc.fr.
3. Kang H, O'Connell JB, Maggard MA, et al. A 10-yearoutcomes evaluation of mucinous and signet-ring cellcarcinoma of the colon and rectum. Dis Colon Rectum 2005;48:1161-8.
4. Silberfein EJ, Kattepogu KM, Hu CY, et al. Long-term survival and recurrence outcomes following surgery for distal rectal cancer. Ann Surg Oncol 2010;17:2863-9.
5. Lee JH, Kim SH, Jang HS, et al. Preoperative elevation ofcarcinoembryonic antigen predicts poor tumor responseand frequent distant recurrence for patients with rectalcancer who receive preoperative chemoradiotherapy and total mesorectal excision: a multi-institutional analysis inan Asian population. Int J Colorectal Dis 2013;28:511-7.
6. Moreno García V, Cejas P, Blanco Codesido M, et al.Prognostic value of carcinoembryonic antigen level inrectal cancer treated with neoadjuvant chemoradiotherapy.Int J Colorectal Dis 2009;24:741-8.
7. Pacelli F, Sanchez AM, Covino M, et al. Improvedoutcomes for rectal cancer in the era of preoperativechemoradiation and tailored mesorectal excision: a series of 338 consecutive cases. Am Surg 2013;79:151-61.
8. Huebner M, Wolff BG, Smyrk TC, et al. Partial pathologicresponse and nodal status as most significant prognosticfactors for advanced rectal cancer treated with preoperativechemoradiotherapy. World J Surg 2012;36:675-83.
9. Mathis KL, Nelson H, Pemberton JH. Can unresectable colorectal cancer be cured? Adv Surg 2009;43:211-9
10. G.E.H Awwad etal.Prognostic significance of lymph node yield after long-course preoperative radiotherapy in patients with rectal cancer: a

systematic review. Colorectal Dis . 2013 Apr;15(4):394-403.

11. Robert Mechera et.al . Lymph node yield after rectal resection in patients treated with neoadjuvant radiation for rectal cancer: A systematic review and meta-analysis .Eur J Cancer . 2017 Feb;72:84-94.
12. Peng J, Lin J, QiuM,Wu X, Lu Z, Chen G, et al. Clinical factors of post-chemoradiotherapy as valuable indicators for pathological complete response in locally advanced rectal cancer. Clinics. 2016;71(8):449-454
13. Maas M, Nelemans PJ, Valentini V et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 2010;11:835–44.
14. Reena Engineer et.al Factors influencing response to neoadjuvant chemoradiation and outcomes in rectal cancer patients: tertiary Indian cancer hospital experience. J Gastrointest Oncol 2015;6(2):155-164.
15. Mashid Jalilia et.al Pathologic response to neoadjuvant treatment in locally advanced rectal cancer and impact on outcome. Journal of Gastrointestinal Oncology. 2016 Aug; 7(4): 603–608.
16. Kyungyeon Hwang etal, Impression of prognosis regarding pathologic stage after preoperative chemoradiotherapy in rectal cancer; World journal of Gastroenterology: 2015 Jan 14; 21(2): 563–570