Research and Reports of Medicine

Research Article

Pathologic Complete Response in Locally Advanced Rectal carcinoma after Neo-adjuvant chemo radiation –A Single Institutional Study

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Received: January 18, 2018; **Accepted**: January 23, 2018; **Published**: January 25, 2018

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Abstract

The study aims to assess pathologic complete response (pCR) and its clinical significance in patients treated with pre-operative chemo-radiotherapy for locally advanced rectal carcinoma in Regional Cancer Centre, Trivandrum, during 2008-2012 (n= 114), followed-up till 2014. Pre-operative radiation was given using external beam radiation (50.4Gy in 28#), with concurrent chemo radiation. 94% had tumor down staging and 14% had a complete response to pre-operative chemo radiation. In pCR group, histological subtype was well differentiated adeno in 45%, moderate in 45%, poorly-differentiated in 5% and remaining 5% showed carcinoma of other histologic types. The corresponding values among non-pCR group were 48% (well), 40% (moderate), 7% (poorly differentiated) and 5% (others), respectively. 95% had no recurrence in pCR and 81% in non-pCR group.

Highlights

Neo-adjuvant chemo radiation can result in tumor down staging in more than 90% of patients. But the pathologic complete response is less than 20%. Complete responders show better survival compared to partial responders.

Keywords: pCR; Locally Advanced Rectal Adenocarcinoma; Pre-operative Chemo radiation

Introduction

Locally advanced rectal carcinoma is treated with pre-operative chemo radiation followed by surgery (total mesorectal excision) and adjuvant chemotherapy. The German CAO/ARO/AIO 94 trial comparing pre-operative and post-operative chemo-radiotherapy has shown better local control and reduced acute and chronic toxicity in the pre-operative setting. Majority of patients show down staging of tumor. After chemo radiation and surgery, 15–27% of the patients have no residual viable tumour at pathological examination, i.e. a pathological complete response (pCR) [1]. Many studies have suggested that pathological complete response (pCR) is associated with favourable outcome in terms of local control, distant recurrence, disease free survival and overall survival [2,3]. With pre-operative chemo radiation, down staging of disease has significantly improved and pCR was below 10% with preoperative radiation alone in historic series. Now it has improved to 15-30% with the practice of preoperative chemo radiation [4-6].

The clinical implication of pCR has been suggested in several studies [7-10]. It is associated with a favourable outcome with regards to local control, distant recurrence, disease-free survival and overall survival. As of now, published studies have reported a trend towards a favourable prognosis for patients who attained a pCR. But, this trend was often not significant statistically. The most probable reason was due to small sample size in these studies [5]. Many studies compared responding patients with non-responding patients and did not differentiate between pCR and other degrees of response [10-12].

The results of the pooled analysis of 3105 patients from 14 study data sets reported by Maas and co-workers suggested the prognostic value of pCR, which was associated with significantly improved disease-free and overall survivals [13]. However, most of these studies were non-randomised trials and many were retrospective in nature.

However, response to treatment and the effect of radiation might not be the only deciding factors for achieving pCR. Bulkier or more locally advanced tumours have less chance to resolve completely, whereas a longer interval between completion of preoperative radiotherapy and resection might provide more of an opportunity for better response. The present study assessed the incidence of pathologic complete response and analyzed its clinical significance in patients who were treated with pre-operative chemo-radiotherapy for locally advanced rectal carcinoma.

Materials and Methods

One hundred and fourteen patients treated in the Regional Cancer Centre, Trivandrum with preoperative chemo-radiation for rectal carcinoma during the period 2008-2012 were included in this study. All patients were followed up until July 2014. The median follow-up period was 37 months. All patients were histologically confirmed and staged using radiological investigations including CECT/MRI pelvis, X-ray chest/CECT thorax. Pre-operative radiation was given using external beam radiotherapy to the dose of 45-50.4 Gy in 1.8-2 Gy per fraction, 5 days a week along with concurrent capecitabine on days of radiation. Statistical measures such as frequency and relative proportion for categorical variables were provided.

Results

Among the 114 patients included in the analysis, 74 were male and 40 female. The histological subtypes among the patients analysed were well-differentiated adeno

(48%), moderately-differentiated adeno (40%), poorly-differentiated adeno (8%) and carcinoma of other histology's (4%). Six percentages of patients had history of intestinal obstruction before starting the treatment. Dose of the pre-operative radiotherapy (RT) was 45-50.4 Gy given at 1.8-2 Gy per fraction along with concurrent chemotherapy. Ninety four percentages of the patients had tumor down staging after pre-operative chemo-RT. Twenty patients (14%) had a complete pathological response to preoperative chemo-RT.

Relationship between histology and pCR rate was that 45% of patients had well differentiated histology, 45% had moderately differentiated type and 5% each were poorly differentiated and other histologic types and the corresponding percentage among non pCR group was observed to be 48, 40, 7 and 5% respectively. In the pCR group, 95% had no recurrence while it was 81% in non pCR group during the follow-up period. Only one patient had recurrence in the pCR group, the recurrence being in brain with no other sites of disease including local site.

Discussion

Pre-operative chemo radiation has been considered as the standard of care for locally advanced rectal carcinoma for many years. Surgery remains the standard of care after neo-adjuvant chemo radiation irrespective of extent of response. European randomized trials of neo-adjuvant chemo radiation showed pCR rate of 11–16% [1,14,15] which is significantly greater than pre-operative radiation alone. Phase IIb randomized studies showed a pCR rate ranging from 24 -36% [5,16,17].

Chari and co-workers reported that patients with pCR after chemo radiation for locally advanced rectal carcinoma had better long term outcome than those who had not attained pCR [7]. pCR after chemo radiation could be an indicator of prognostically favorable tumor biology. Patients who attained pCR have low incidence of local recurrence and distant metastasis and thereby better survival than the patients who did not attained pCR.

Fourteen percent of patients in our study had a pathological complete response to pre-operative chemo-radiotherapy. Complete responders had better outcome compared to partial responders. Down staging of pre-operative chemo-radiation has an impact on pathological response and outcome. Our study confirms that patients undergoing pre-operative chemo radiation who undergo pathological response has better outcome compared to non-responders. The present study did not analyze factors like clinical stage, bulk of the tumor, type of surgery done, interval between surgery, chemo-radiation and the site of tumor and their effects on the rate of pCR.

In conclusion, patients with pCR after pre-operative chemo radiation had better outcome irrespective of the initial stages and this shows heterogeneity of tumor behavior in this population of locally advanced disease. There is definitely a role for future studies aiming at improving tumor response before surgery. Imaging techniques could play an important role in predicting pathological tumor response, thereby selecting patients for conservative surgery. This would also help radiation oncologists to tailor treatment in a more personalized way, depending upon the tumor behavior.

Conflicts of Interest

The authors declare that there is no conflict of interest.

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