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The role of adjuvant chemotherapy on survival and recurrence after curative rectal cancer surgery on patients who are histologically node negative after neoadjuvant chemoradiotherapy

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Abstract

Aim:

The aim of this study is to evaluate whether adjuvant chemotherapy will affect recurrence rates, disease free and overall survival in patients with rectal adenocarcinoma who were staged with MRI node positive disease (mrN+) preoperatively and underwent neoadjuvant chemoradiotherapy with curative rectal cancer surgery and their pathological staging was negative for nodal disease (ypN0). There is no consensus on the role of adjuvant chemotherapy in these patients.

Method: Patients who received neoadjuvant chemoradiotherapy and underwent curative rectal cancer surgery for rectal adenocarcinoma staged as [mrTxN+M0] on MRI staging and on pathological staging were found to be [ypTxN0M0] were retrospectively identified from 01/2008-12/2012 from two tertiary referral centers

(Royal Marsden Hospital and Saint-Andre Hospital).

Results: 163 patients were recruited and after propensity matching at a ratio of 2:1 n=80 patients were divided into adjuvant (n=28) and no adjuvant treatment (n=52) respectively. A comparison of adjuvant chemotherapy vs no adjuvant therapy showed that the mean overall survival was 2.67 vs 3.60 years (p=0.42), disease free survival was 2.27 vs 3.32 years (p=0.14).

Conclusion: This study found no significant difference in survival or disease recurrence between patients who received adjuvant chemotherapy and patients who did not. There is no clear evidence to support or dismiss the use of adjuvant chemotherapy for patients who have been node positive on pre-operative MRI and node negative on histopathological staging. Further multicenter prospective randomised trials are needed to identify the appropriate treatment regime for this group of patients.

What does this paper add to the literature? There is no consensus on the benefit of giving adjuvant chemotherapy to patients with rectal adenocarcinoma and positive lymph nodes on preoperative mrN+, who received neoadjuvant chemoradiotherapy and underwent R0 resection with pathological ypN0. This paper found no difference. A randomised controlled trial is required to be definitive on the benefits of adjuvant chemotherapy in this scenario.

Introduction

Colorectal cancer is the third most common in the world and rectal cancer accounts for 30-40% of these malignancies [1,2]. In rectal cancer with nodal disease neoadjuvant chemoradiotherapy followed by total mesorectal excision (TME), aiming to harvest 12 or more lymph nodes in the specimen, is the standard of treatment recommended[3].

The use of adjuvant chemotherapy especially in the context of previous neoadjuvant treatment is controversial [4,5]. Fluoropyrimidine based adjuvant chemotherapy has been widely used and the addition of oxaliplatin was based on data from patients with colon cancer [2,6]. For many years colonic and rectal cancers were considered as a single entity [6,7,8] and much of the evidence looking at the use of adjuvant therapy in rectal cancer is taken from studies looking colonic and rectal cancer together. This was based on the logic that they are histologically similar and are in organ continuity [6,7,8,9]. However, they should be considered separately as the rectum is deep in the pelvis and is covered by surrounding tissue on all sides. It has a different lymphatic drainage, it responds to chemotherapy in a different way and historically has a higher rate of local recurrence [6,7,9].

Studies in locally advanced rectal cancer have shown a benefit to neoadjuvant chemoradiotherapy by reducing significantly the recurrence rates [10,11,12], although this has not been conclusively followed by an improvement in overall survival [6,10,11,12]. In the event of a complete pathological response to neoadjuvant chemoradiotherapy there is improved local and distal control with an overall and disease free survival benefit [13]. Conversely patients with tumours that are refractory to neoadjuvant therapy, where the T stage is not reduced, have a much poorer outcome [14]. Lymph node non-response after neoadjuvant chemotherapy is associated with increased distant metastasis and is an independent risk factor for decreased 5-year disease free survival [15,16].

In the event that a patient is diagnosed preoperatively as being lymph node positive, mrTany N+ M0, and after neoadjuvant therapy becomes lymph node negative, ypTany N0 M0, there is a paucity of evidence as to the benefits of treatment with adjuvant therapy [4,7,17]. As a result, a clear consensus is lacking, with no guidelines, [4,7,17] leading to a variation in practice [4,7,17]. Previously studies have shown that adjuvant therapy is of little benefit in ypT0-2 N0 patients but its benefits in ypT3-4 N0 are less understood and are controversial [2,5]. Practice includes blanket policies of ‘yes to all’ or ‘no to all’, or an individualised case by case plan based on high risk features, such as the presence of extramural vascular invasion (EMVI) or high T stage [8,17,18,18]. If adjuvant chemotherapy is not

given when there was preoperative evidence of nodal metastasis (mrN+) an early recurrence would raise the question of under treatment. However, giving chemotherapy with no clear benefit, risks over treating patients and subjecting them to the side effects of chemotherapy [7,9].

This is a retrospective look at a selected group of patients aiming to investigate the merits, in terms of overall survival and disease free survival, of adjuvant chemotherapy in the event that mrTany N+ M0 becomes ypTany N0 M0 after neoadjuvant therapy.

Methods

A retrospective analysis of patients with rectal cancer that received neoadjuvant treatment in two tertiary referral centres (Saint-Andre Hospital, University of Bordeaux, France and The Royal Marsden Hospital, London, UK) between the dates of January 2008 and December 2012 was performed. Patient identification number, sex, age, body mass index (BMI) and American Association of Anesthesiologists (ASA) grade and preoperative and pathological staging were obtained. Patients with rectal cancer, regardless of T stage, who were initially lymph node positive without metastasis, (mrTany N+ M0) on preoperative imaging, were identified. A subgroup of patients that had a full lymph node response and so had no cancer positive lymph nodes (ypTany N0 M0) in the postoperative pathological specimen were selected. These patients were divided into two groups on the basis of whether or not they received adjuvant chemotherapy.

The primary endpoint is the reduction of local and distant cancer recurrence rate postoperatively. The secondary endpoints are the effects on overall and disease free survival.

All patients were evaluated initially with a full history, physical examination and blood tests, followed by an endoscopy and biopsy. Patients were imaged with computed tomography (CT) of the chest, abdomen and pelvis followed by a pelvic magnetic resonance imaging (MRI) scan. If there was any suggestion of metastasis then a positron emission tomography (PET) scan was used to assess this further. All patients were discussed and the treatment planned in a multidisciplinary team meeting.

Neoadjuvant treatment was given according to European Guidelines. The patients received radiation of 50 Greys in 25 fractions over 5 weeks with concomitant chemotherapy of 5-florouracil (5-FU). During the second half of the study period patients received induction chemotherapy in addition to the long course chemoradiotherapy based on double or triple cytotoxic therapy of 5-FU and oxaliplatin or 5-FU, oxaliplatin and irinotecan respectively.

Surgery was performed with curative intent in all patients and was undertaken 6-8 weeks after neoadjuvant therapy in one of the two tertiary colorectal centres listed above, by a consultant lead team experienced in advanced and complex rectal cancer surgery.

The decision to administer adjuvant chemotherapy was made locally on a case by case basis in the multidisciplinary team meeting and there was no randomisation. Factors affecting the decision included the overall health of the patient in conjunction with risk factors for recurrence that was in keeping with previous local practice. If deemed necessary then 5-FU and oxaliplatin was administered.

Outcome data for the two groups were obtained retrospectively from the physical and computerised records. Type of operation, anastomosis technique, height of anastomosis, resection status, pathological TNM staging, the number of lymph nodes in the specimen and the number of positive lymph nodes, the time to local and distant recurrence and post-operative survival were all recorded.

Statistical Analysis

The two groups were propensity matched at a ratio of two to one based on patient age, pathological tumour stage, resection margin, extramural vascular invasion (EMVI) and tumour grade.

Log-Rank (Mantel-Cox) was used to compare the two groups in terms of time to distant recurrence, overall and disease free survival. For tumour down staging and complete pathological tumour response Pearson's Chi-Squared test was used to compare proportions between the groups except if one of the cells had a value of less then 5 in which case Fisher's Exact Test was used. 0.05 was the threshold for statistical significance throughout.

All data were collated using Microsoft Excel (2007. Redmond, WA, USA) and all statistical analysis was performed on Statistical Package for the Social Sciences (SPSS) (Armonk, New York, USA).

Results

A total of 163 patients were enrolled in the study. 124 patients had no adjuvant chemotherapy and 39 patients had adjuvant therapy. After propensity score matching, at a ratio of 2 to 1, 80 patients were included in the analysis, 52 patients did not receive adjuvant chemotherapy and 28 patients received adjuvant chemotherapy.

The patients that were included were operated on between February 2008 and December 2012 at Saint-Andre Hospital, University of Bordeaux, France and The Royal Marsden Hospital, London, UK. In both groups 29 were female and 51 were male, the mean (range) age was 59.7 (36-84) years and the mean BMI was 26.0 (18.7–38) kg/m^2. Demographics are displayed according to the groups in Table 1. Preoperative and post-operative tumour staging data are shown in Table 2.

All 80 patients were selected as being specifically lymph node positive on preoperative MRI scans (N1: 70/80 and N2: 10/80) and pathologically having no cancer remaining in the lymph nodes post-operatively.

The median number of lymph nodes harvested was 13 (range 2-26) in the adjuvant group and 17 (range 4-34) in the no-adjuvant group. In the adjuvant group 21/28 (75%) were anterior resections, 5/28 (18%) were abdominoperineal excisions of rectum and 2/28 (7%) were pelvic exenterations. In the no-adjuvant group 46/52 (88%) were anterior resections, 3/52 (6%) were abdominoperineal excisions of rectum, 2/52 (4%) were total pelvic exenterations and 1/52 (2%) was a Hartmann's operation. All patients in both groups underwent a complete (R0) resection.

The tumour response to neoadjuvant chemotherapy between the two groups showed that 16/28 (57%) and 36/52 (69%) patients had a reduced T stage (p=0.28) and 4/28 (14%) and 6/52 (12%) had a pathological complete response (p=0.73) in the adjuvant versus the no-adjuvant groups respectively (Table 3). The mean length of follow up of the entire cohort was 3.28 years with a range of 0.02 -7.32 years.

Recurrence outcomes

In the group that received adjuvant chemotherapy (n=28) there were 6 recurrences and one death; four distant recurrence and two with both local and distant recurrence. There was one death after two years and 11 months with both distant and local recurrence.

In the group that received no-adjuvant chemotherapy (n=52) there were 8 recurrences, which were all distant, with an average time to recurrence of 3.32 (0.10 – 6.88) years. There were five deaths; two with distant recurrence, both after 2.2 years and three deaths with no recurrence after 0.1, 2.9 and 6.3 years. There was no statistically significant difference in distant recurrence rates (p=0.14) between the groups that did and did not receive adjuvant chemotherapy. There was no local recurrence in the group that did not receive adjuvant chemotherapy.

Survival outcomes

Comparison between the groups of adjuvant therapy vs no-adjuvant therapy showed no statistically significant difference in the overall survival (p=0.42) and no difference in disease free survival (p=0.14). The mean overall survival of the two groups, adjuvant vs no adjuvant, was 2.67 (0.02 – 7.32) years vs 3.60 (0.10 –6.88) years and mean disease free survival was 2.27 (0.02 – 7.3) years vs 3.32 (0.10 –6.88) years respectively (Table 4 and Figures 1 and 2).

Discussion

This analysis showed better overall survival, disease free survival and time to distant recurrence in the group with no-adjuvant treatment; however the differences were not statistically significant. The limitations of this work are that it is retrospective in nature, with no randomisation and unequal groups. There were significantly more ASA I patients in the group that did not receive adjuvant therapy and the specific types of rectal cancer operation in each group are not precisely matched, which may have an affect on survival. Despite looking at two tertiary centres both of which treat large numbers of patients with rectal cancer, the specific patients being selected in terms of lymph node status are few, which leaves small sample sizes that may limit the statistical analysis. The preoperative radiological and postoperative pathological staging were undertaken by a consultant working in a specialised colorectal centre, but there was no secondary analysis checking for agreement on staging. Both groups showed down staging of T stage with some complete pathological responses noted, although there was no significant difference between the groups.

In locally advanced rectal cancer, neoadjuvant chemoradiotherapy with a total mesorectal excision is the standard of treatment, as it can downstage the disease [6,10,11,12,14,15,16]. Furthermore, reduction in the lymph node staging is seen in 30-60% of lymph node positive patients [16,20,21,22,23]. This overall down staging of tumour and lymph nodes leads to an improvement in local and distant control and in the disease free and overall survival [7,13,14,15,16]. It is shown that failure to be down staged in terms of T stage, N stage or both is a very poor prognostic sign [16,24]. A study by Kim et al [24] noted a 5-year disease free survival of 84%, 68% and 27% of ypN0, ypN1 and ypN2 respectively which raises the question as to whether or not patients that remain ypN+ should be given adjuvant chemotherapy in an attempt to improve outcome [16,24]. Bujko et al in 2007 [15] stated that lymph node positivity leads to such a poor outcome that these patients should be considered for adjuvant chemotherapy [15] but a systematic review in 2010 noted that none of the trial data on this topic supported a survival benefit when given for rectal cancer [9].

There have been four clinical randomised trials [25,26,27,28] looking into the use of adjuvant chemotherapy in advanced rectal cancer and none have shown an overall or disease free survival benefit. However, some of the data are lacking, with poor accrual and high drop out rates and they do not all use the same cytotoxic agents or regimes [25,26,27,28]. Kiran et al [29] conducted a similar study to ours in 2012 and found no benefit from giving adjuvant therapy to patients who had a curative resection and were lymph node negative after neoadjuvant therapy. A randomised controlled European Organisation for Research and Treatment of Cancer (EORTC) trial showed no benefit from giving adjuvant therapy after neoadjuvant chemoradiotherapy, even in the presence of node positive disease [9,10,18,27].

In America the Mayo/North Central Cancer Treatment Group have recommended adjuvant treatment with 5-FU with T3 N1-2 disease since 1990 [7]. In 2009 the European Society for Medical Oncology recommendations stated that stage III and ‘high risk’ stage II should be given adjuvant chemotherapy and acknowledged that the evidence for it is ‘less’ and that it is based on data from colonic cancer [8]. In 2015 the National Comprehensive Cancer Network guidelines recommended postoperative chemotherapy for all patients undergoing preoperative chemoradiation, regardless of the surgical pathology results [19].

The lack of direct evidence on this topic to support the current guidelines has led to a varied practice internationally and this makes studying this topic difficult. However the question is relevant and of interest, as under and over treatment present difficulties [4,7,8,17].

In conclusion, the question posed in this paper is clinically relevant, as targeting cytotoxic therapies appropriately is vital. The literature and the guidelines are juxtaposed and this has created variation in practice. The data we used have some flaws that have been discussed, but they are in agreement with the published literature in not showing any significant overall survival or disease free survival benefits to giving adjuvant chemotherapy in this setting. A sufficiently powered and randomised controlled trial is required to be definitive on the benefits of adjuvant chemotherapy in this scenario.

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Table 1: Patient Demographics

	Adjuvant Treatment n=28	No Adjuvant Treatment n=52	P Value
Male	16	35	(included in propensity match)
BMI (kg/m^2)	26.7 (21-34)	25.6 (18.7-30.0)	(included in propensity match)
ASA 1	7	28	0.01*
ASA 2	15	21	0.26*
ASA 3	6	3	0.06^

Table 2: Tumour Characteristics

	Adjuvant Treatment n=28	No Adjuvant Treatment n=52
Preoperative imaging		
mrT1	0	0
mrT2	5	0
mrT3	16	48
mrT4	7	4
mrN1	28	52

Postoperative stage		
ypT0	4	6
ypT1	0	4
ypT2	12	23
ypT3	9	19
ypT4	3	0
ypN+	0	0
EMVI	2	3
Lymph Node	**Median (Range)**	**Median (Range)**
Number In Specimen	13 (2-26)	17 (4-34)

Table 3. Tumour response to neoadjuvant treatment.

	Adjuvant Treatment n=28	No Adjuvant Treatment n=52	P Value
Tumour (T) Down Staged	16	36	0.28*
Tumour (T) Complete Response	4	6	0.73^

Table 4: Outcome Data

	Adjuvant Treatment n=28	No Adjuvant Treatment n=52	P Value
Overall Survival (Years)	2.67 (0.02 – 7.32)	3.60 (0.10 - 6.88)	0.42[&]
Disease Free Survival (Years)	2.27 (0.02 – 7.32)	3.32 (0.10 - 6.88)	0.14[&]
Time To Distant Recurrence (Years)	2.27 (0.02 – 7.32)	3.32 (0.10 - 6.88)	0.14[&]

Legend:

*: Pearson's Chi-Squared Test

^ Fisher's Exact Test

[&] Log-Rank (Mantel-Cox)

Figure 1: Kaplan-Meier Curve of overall survival

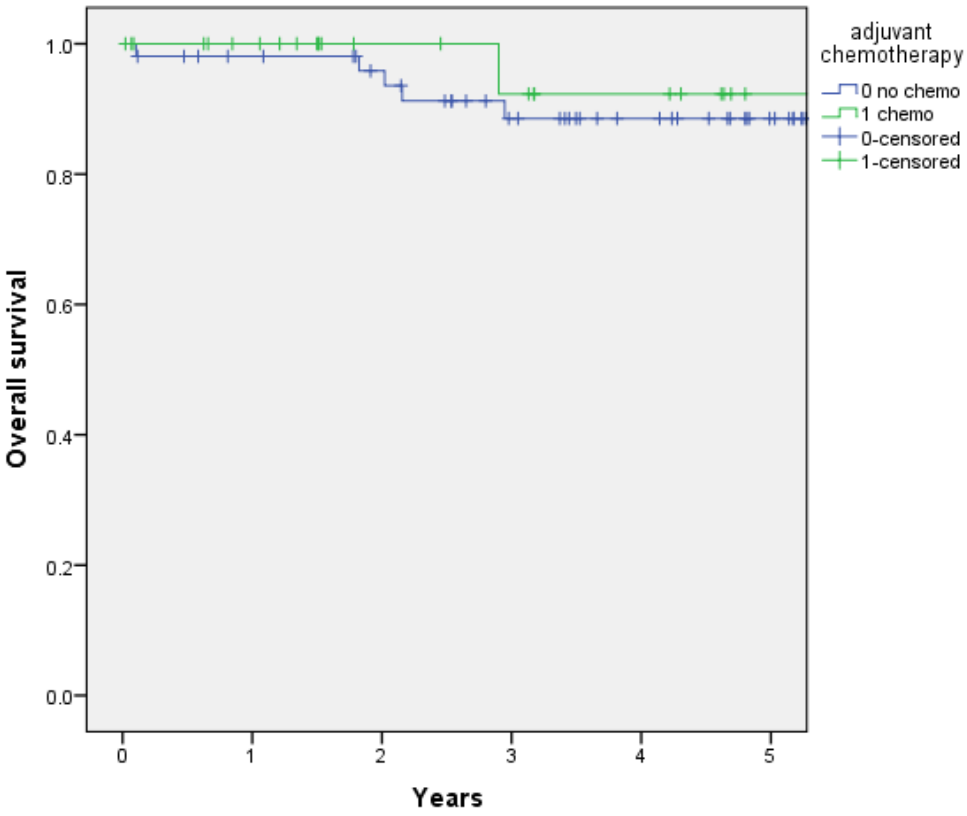

Figure 2: Kaplan-Meier Curve of disease free survival