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EJSO the Journal of Cancer Surgery

EJSO xx (2017) 1–8 www.ejso.com

Factors associated with degree of tumour response to neo-adjuvant radiotherapy in rectal cancer and subsequent corresponding outcomes

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Accepted 18 July 2017

Available online ■ ■ ■

Abstract

Background: Tumour response to neo-adjuvant radiotherapy for rectal cancer varies significantly between patients, as classified by Tumour Regression Grade (TRG 0–3), with 0 equating to pathological complete response (pCR) and 3 denoting minimal/no response. pCR is associated with significantly better local recurrence rates and survival, but is achieved in only 20–30% of patients. The literature contains limited data reporting factors predictive of tumour response and corresponding outcomes according to degree of regression.

Methods: All patients with rectal cancer who received neo-adjuvant radiotherapy, entered into the National Cancer Database (NCDB) in 2009–2013, were included. Data were analysed on procedure performed, tumour details, pathological findings, chemo-radiotherapy regimens, patient demographics, outcomes and survival. Multivariate regression analysis was used to identify factors independently associated with pCR.

Results: Of 13,742 patients, 32.4% achieved pCR/TRG0 (4452). Factors associated with pCR (vs. TRG3) included adenocarcinoma rather than mucinous adenocarcinoma histology; well/moderately differentiated grade; lower clinical tumour (cT_1, cT_2, cT_3) and nodal (N_0 and N_1) stage, and the addition of neo-adjuvant chemotherapy. Elevated CEA levels were associated with TRG3. pCR patients had higher rates of local excision, shorter mean length of stay and lower unplanned readmission rates, than TRG3. R0 resection rates and overall survival were significantly higher in all grades of regression, compared to TRG3 ($p < 0.0001$).

Conclusion: Tumour regression correlates with outcomes. Identifying factors predictive of response may facilitate higher pCR rates, the tailoring of therapy, and improve outcomes.

Keywords: Rectal cancer; Neo-adjuvant radiotherapy; Tumour response; Regression grade; Pathological complete response

Introduction

The aim of neo-adjuvant radiotherapy in rectal cancer is to minimise the risk of local recurrence, reduce tumour bulk to facilitate resection with clear margins (R0 resection) and to increase sphincter preservation [1,2]. While neo-adjuvant treatment has been demonstrated to improve oncological outcomes [3–6], the relative success of such therapy, in terms of tumour response, varies significantly between patients.

One of the earliest studies advocating the use of neo-adjuvant radiation was that carried out by the European Organization for Research and Treatment of Cancer (EORTC) in the late 1970s, which reported a significant reduction in local recurrence but not survival with 34.5 Gy pre-operative radiation, compared to surgical resection alone [7]. The Swedish Rectal Cancer Study further highlighted the benefits of Short Course Pre-operative Radiotherapy (SCPRT); reducing local recurrence to 11%, compared with 27%

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http://dx.doi.org/10.1016/j.ejso.2017.07.024

Please cite this article in press as: Gash KJ, et al., Factors associated with degree of tumour response to neo-adjuvant radiotherapy in rectal cancer and subsequent corresponding outcomes, Eur J Surg Oncol (2017), http://dx.doi.org/10.1016/j.ejso.2017.07.024

for surgical resection alone ($p < 0.001$), and improving five-year survival to 58% vs. 48% ($p = 0.004$) [3]. Interestingly, although other studies have also demonstrated improvements in oncological outcomes with the addition of SCPRT [5,8], including a reduction in local recurrence at five-years from 10.9% to 5.6% in equivalently staged patients ($p < 0.001$), this has not translated to a demonstrable difference in five-year survival between the two treatment modality groups (63.5% vs. 64.2%) [8]. The addition of pre-operative fluorouracil-based chemotherapy to neo-adjuvant radiotherapy has been shown to reduce local recurrence rates to 7.6% vs. 17.1%, but had no significant effect on survival [4]. For tumours with an involved or threatened circumferential resection margin (CRM), down-staging treatment is recommended with Long-course Chemo-Radiotherapy (LCRT) [1]. This has been shown to enhance tumour regression, increase R0 resection rate and improve local control, when compared to neo-adjuvant radiation alone [8,9].

The AJCC criteria [10], is commonly used to classify tumour regression following neo-adjuvant LCRT. It classifies regression as 0–3, where TRG0 equates to a pathological complete response (pCR), i.e. no viable tumour cells remaining; TRG1 represents a single or small group of tumour cells remaining; TRG2 is recorded where the residual cancer is outgrown by fibrosis and TRG3 represents minimal or no tumour response. pCR is achieved in around 20–30% of patients [11] and is associated with lower rates of local recurrence and greater disease-free and overall survival [11,12], highlighting the importance of optimising tumour response.

However, there is significant disparity in tumour regression between patients following pre-operative radiotherapy [13,14], with some tumours demonstrating complete regression, and others exhibiting no response [15]. The reasons for such variations in regression are poorly understood, with previous studies that investigated predictors of response not having demonstrated distinct, consistent associations [16,17]. We therefore aimed to identify factors associated with tumour response to neo-adjuvant radiotherapy, using a nationwide cancer database.

Methods

The USA National Cancer Database (NCDB) was used to identify patients with rectal cancer and investigate outcomes for those who received neo-adjuvant radiotherapy. The NCDB currently records data from more than a million cancer cases per year, incorporating the clinical oncology data for patients from over 1500 hospitals (each Commission on Cancer [CoC] accredited facilities), from across the USA [18]. It is jointly sponsored by the American College of Surgeons and the American Cancer Society and represents approximately 70% of all newly diagnosed cancer cases nationwide and 30 million historical records [19]. Data is collated locally in each CoC program, but is replicated nationally with highly standardized coding and core outcomes recorded from centres across 49 states. Since 1992 it has been mandatory that all cancer cases are reported to state cancer registries [20]. Any data submitted undergoes a series of data integrity checks, by way of quality assurance. Consequently the NCDB provides large volumes of quality data for research analysis and is a valuable asset for such studies. There are nearly 100,000 cases of colon cancer and over 40,000 of rectal cancer each year in the USA [21]. Over 30,000 cases of rectal cancers are reported to the NCDB per year, accounting for 76% of all such tumours [18].

All patients in the NCDB diagnosed with rectal cancer from 2009 to 2013, who received neo-adjuvant radiotherapy, were included. Datasets were assembled from NCDB on the operation performed, tumour details, pathological findings, chemo-radiotherapy regimens, as well as patient demographics and survival. Institutional Review Board (IRB) approval was obtained from Columbia University Medical Center. Statistical analysis was performed using SPSS® for Windows®. Propensity score matching was used to create cohorts of different treatment types and data was assessed using t-tests, Chi-squared tests and Wilcoxon rank sum tests as appropriate. Multivariate regression analysis was used to identify factors independently associated with pCR.

Results

Overall, 13,742 patients received neo-adjuvant radiotherapy for rectal cancer and had a Tumour Regression Grade (TRG) recorded in the NCDB. Regression varied considerably: 32.4% TRG0 (4452), 35.9% TRG1 (4931), 21.4% TRG2 (2948), 10.3% TRG3 (1411). Basic patient demographics are outlined in Table 1; of note, of those patients achieving TRG 0 (pathological complete response, pCR), significantly fewer were uninsured (4.1%) compared to those with a poor/no tumour response (TRG3), (6.0%, $p < 0.0038$) and a greater proportion of patients with private insurance had tumours which had pCR rather than TRG3 (50.8% vs. 47.0%, $p < 0.01$). Importantly, there was no significant difference in patient co-morbidities (Charlson–Deyo Score) between tumour response groups (Table 1).

Tumour factors – Table 2

Tumours histologically classified as adenocarcinomas were more likely to undergo complete regression (94.1%, $p < 0.0001$), or TRG1 (91.9%, $p < 0.03$) or TRG2 (93.2%, $p < 0.0003$) than have no response to radiotherapy (TRG3, 90.0%). Mucinous adenocarcinomas accounted for more tumours in the non-responsive group (TRG3) 8.40%, compared to all other groups: TRG2 5.2%; TRG1 5.8%, TRG0 2.4%, (all $p \leq 0.0003$). Tumour grade (differentiation) also varied among regression groups,

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