Influence of Organ Invasion in Clinical Outcomes for Locally Advanced Rectal Cancer

FRANCESCA DE FELICE¹, DANIELA MUSIO¹, ILARIA BENEVENTO¹, ANNALISA MAGNANTE¹,
NADIA BULZONETTI¹, CAIAZZO ROSSELLA¹ and VINCENZO TOMBOLINI^{1,2}

¹Department of Radiotherapy, Policlinico Umberto I Sapienza University of Rome, Rome, Italy;

²Spencer-Lorillard Foundation, Rome, Italy

Abstract. Aim: To evaluate whether patients with external sphincter invasion have a better prognosis than patients with invasion of other organs. Patients and Methods: Patients with cT4b adenocarcinoma of the rectum were treated with a tri-modality approach, including neo-adjuvant chemoradiotherapy (CRT), surgery and adjuvant chemotherapy. Patients with external sphincter invasion were classified as cT4b1, whereas patients with invasion of other organs as cT4b2. Survival curves were compared for cT4b sub-stage. Results: Between January 2008 and December 2014, a total of 21 consecutive patients with cT4b disease (14 with cT4b1 and seven with cT4b2) were treated with CRT, followed by surgery and adjuvant chemotherapy. In total, the overall survival rate at 5 years was 57.4%, whereas 5-year disease-free survival was 52%. The 5-year overall survival rates were 65.3% and 44.4% for patients with cT4b1 and cT4b2 disease, respectively. Conclusion: External sphincter invasion seems to be associated with a better prognosis when compared to primary lesion with extension to other organs.

Tumor and lymph node staging are paramount to treatment choices in patients with locally advanced rectal cancer (LARC). In rectal cancer, the stage system is still based on depth of penetration through the rectal wall (T), the presence and the number of metastatic lymph nodes (N), and the presence of distant metastasis (M). Throughout the years, minor changes have been made in relation to the T classification. In the seventh edition of the American Joint Committee on Cancer (AJCC) staging, T4 was stratified into

T4a (tumor penetrates to the surface of the visceral peritoneum) and T4b (tumor directly invades or is adherent to other organs or structures), due to a 10% improvement in 5-year overall survival (OS) in patients with T4a compared to T4b lesions (1). However, cT4b appears to be grossly classified considering that invasion of other organs is merged with involvement of structures by virtue of extension beyond the *muscularis propria* (2). Thus, the placement of all patients with cT4b disease in the same T sub-stage, independently of invasion of organs, such as prostate, uterus, bladder or bowel, and structures including external sphincter, describes a heterogeneous group of lesions. This does not provide complete clinical information, and this feature could have a different prognostic significance and influence treatment decisions.

The aim of this work was to determine whether patients with external sphincter invasion (cT4b1) have a better OS than those with invasion of other organs (cT4b2).

Patients and Methods

Patients. This study was approved by the Institutional Review Board (Prot. 464/16) and all patients signed an informed consent. A retrospective analysis of patients treated at our institute between January 2008 and December 2014 for cT4b adenocarcinoma of the rectum was performed. The main inclusion criteria were age over 18 years, no previous medical history of radiotherapy to the pelvic region, no metastatic disease at diagnosis, and clinical evidence of stage cT4b adenocarcinoma of the rectum. Local staging of disease was made by endorectal ultrasound and abdominal-pelvic computerized tomography (CT) with/without pelvic magnetic resonance imaging (MRI). Data were collected on local tumor invasion of organs or structures at the pre-treatment examination.

The seventh AJCC Staging System was used for the TNM classification (3). Extension to the external sphincter was recorded as cT4b1, whereas tumor directly invading organs, including prostate, seminal vesicles, cervix or vagina, was defined as cT4b2.

Pre-treatment investigation also included a chest CT scan. For all cases, demographic data (such as sex, age, smoking, alcohol, performance status) and primary tumor parameters (including localization, tumor stage, treatment modality, toxicity) were collected.

Correspondence to: Francesca De Felice, Department of Radiotherapy, Policlinico Umberto I Sapienza University of Rome, Viale Regina Elena 326, 00161 Rome, Italy. Tel: +39 0649973411, Fax: +39 0649973411, e-mail: fradefelice@hotmail.it

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Table I. Patient and tumor characteristics.

Characteristic	Patients (%)		
	Total	Stage	
		cT4b1	cT4b2
Gender			
Male	13 (61.9)	8 (57.1)	5 (71.4)
Female	8 (38.9)	6 (42.9)	2 (28.6)
Age, years			
Mean (range)	63.6 (51-76)	63 (51-74)	64.7 (52-76)
Performance status			
0-1	21 (100)	14 (100)	7 (100)
Smoker			
No	10 (47.6)	8 (57.1)	2 (28.6)
Yes	11 (52.4)	6 (42.9)	5 (71.4)
Distance from anal verge			
<5 cm	14 (66.7)	10 (71.4)	4 (57.1)
≥5 cm	7 (33.3)	4 (28.6)	3 (42.9)
Nodal classification			
Negative	1 (4.8)	1 (7.1)	0 (0)
Positive	20 (95.2)	13 (92.9)	7 (100)

cT4b1: External sphincter invasion; cT4b2: other organ invasion.

Treatment. All patients were treated with a tri-modality approach. Long-course chemoradiotherapy (CRT) was performed. RT was delivered with a 3D-conformational multiple-field technique at a dose of 45 Gy (1.8 Gy/fraction) to the whole pelvis plus 9 Gy (1.8 Gy/fraction) to the tumour volume, with 6-15 MV energy photons. Chemotherapy consisted of weekly oxaliplatin (50 mg/m²) and fluoruracil (200 mg/m²/day). Surgery was scheduled 7-9 weeks after the end of CRT. The type of surgery was left at the surgeon's discretion, and the type of adjuvant chemotherapy to the oncologist's.

Follow-up. During CRT, patients were evaluated daily. Toxicity was evaluated using the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0 (4). After surgery, all patients were monitored at three-month intervals for the first year and at six-month intervals for the subsequent years. Follow-up data were updated in September 2015.

Statistical analysis. Standard descriptive statistics were used to evaluate the distribution of each factor. Continuous data are given as the median (range), and categorical data as the number of observations and ratios. OS and disease-free survival (DFS) were calculated in months from the date of the end of CRT to the first event, including date of the last follow-up or death (OS), or relapse (DFS). Pathological complete response (pCR) was defined as the absence of any residual tumor cells detected in the operative specimen, including the primary tumor area, the whole mesorectal fat and the resected lymph nodes.

OS and DFS were estimated using the Kaplan–Meier method and survival curves were compared using the log-rank test (5). The following variables were investigated: age in years at diagnosis (<65 vs. ≥65), sex (male vs. female), clinical T4b sub-classification

Figure 1. Overall survival according to cT4b sub-classification (cT4b1: external sphincter invasion; cT4b2: other organ invasion)

(cT4b1 vs. cT4b2), clinical nodal status (positive vs. negative), pathological T classification (pT0-2 vs. pT3), pathological nodal status (positive vs. negative), and pCR (yes vs. no). Variables associated with a *p*-value of less than 0.20 were included in a multivariate survival Cox regression analysis. All reported *p*-values are two-sided, and *p*-values lower than 0.05 were considered significant. Statistical analysis was performed using RStudio-0.98.1091 software (RStudio, Inc., Boston, MA, USA).

Results

Baseline characteristics. Between January 2008 and December 2014, a total of 21 consecutive patients with cT4b disease were treated with tri-modality approach. Baseline patient and tumor characteristics are shown in Table I. All patients but one were classified as having stage IIIC disease with no evidence of distant metastasis (M0). cT4b1 tumors accounted for 66.7% (n=14) of cases, cT4b2 for 33.3% (n=7).

Treatment compliance. All patients completed the programmed CRT. All patients received the prescribed RT total dose, while only two patients (9.5%) suspended chemotherapy, due to acute toxicity. Proctitis was the most common acute side-effect (n=14, 66.7%), classified as grade 3 in only one patient. Overall, severe acute toxicity (grade 3-4) was recorded in two cases (9.5%). All patients underwent surgery, with a sphincter-preservation approach in the vast majority of cases (n=14, 66.7%). Miles' surgery was performed in seven patients (33.3%). A complete resection with negative margin was possible in all cases. pCR was achieved in 28.6% of patients (n=6).

Overall survival analysis. Thirty-eight percent of patients (n=8) had died by study end; 75% (n=6) of these patients died of their disease, whereas non cancer deaths were related

Table II. Univariate analysis of prognostic factors for overall survival.

Prognostic factor	Univariate analysis	
	HR (95%CI)	p-Value
Sex (male <i>vs.</i> female)	3.43 (0.04-2.38)	0.22
Age (<65 <i>vs.</i> ≥65 years)	0.75 (0.33-5.45)	0.69
cT4b sub-classification (cT4b1 <i>vs.</i> cT4b2)	0.64 (0.37-6.67)	0.55
Nodal status (positive <i>vs.</i> negative)	1.81 (0.76-4.93)	0.45
Pathological T classification (pT0-2 <i>vs.</i> pT3)	0.70 (0.36-5.75)	0.61
Pathological N classification (positive <i>vs.</i> negative)	1.64 (0.12-3.21)	0.56
pCR (yes <i>vs.</i> no)	0.67 (0.22-2.02)	0.09

HR: Hazard ratio; CI: confidence interval; cT4b1: external sphincter invasion; cT4b2: other organ invasion; T: tumor; N: nodes; pCR: pathological complete response.

to comorbidities (n=2). The 2- and 5-year OS rates for the entire population were 79.5% [95% confidence interval (CI)=54%-92%] and 57.4% (95% CI=29-78%), respectively. No prognostic factors for OS were found, although pCR was the strongest predictor of survival on univariate analysis (hazard ratio=0.67, 95% CI=0.22-2.02; $p=0.09$) (Table II).

OS curves were compared for patients stratified by cT4b sub-stage. The 2-year OS rates for patients with cT4b1 disease was 85.7% (95% CI=54%-96%) and 66.7% (95% CI=20-90%) for those with cT4b2 disease; whereas the 5-year OS rates were 65.3% (95% CI=31-87%) and 44.4% (95% CI=6-78%), respectively (log rank $p=0.55$) (Figure 1).

Disease-free survival. Six patients (28.6%) developed distant metastasis and one patient (4.8%) presented locoregional recurrence. Two- and 5-year DFS for patients overall were 60.7% (95% CI=34-79%) and 52% (95% CI=25-73%), respectively. No prognostic statistical analysis was performed due to the low rate of both local and distant recurrences, precluding the identification of any prognostic factor.

The estimated 5-year DFS was 56.3% (95% CI=24-80%) for the cT4b1 group and 44.4% (95% CI=6-78%) for the cT4b2 group (log rank $p=0.93$).

Discussion

Our study showed that patients with cT4b rectal cancer achieve a high rate of local control after tri-modality approach. The vast majority of patients had developed distant metastasis. The overall prognosis was relatively high, with a 5-year OS and DFS estimated at 57.4% and 52%, respectively. In an attempt to provide a more reliable survival evaluation, patients with external sphincter involvement (cT4b1) and other organ invasion (cT4b2) were examined separately. The 2-year OS rates were 85.7% for

those with cT4b1 tumors and 66.7% for those with cT4b2 tumors. Five-year follow-up indicated the persistent benefit in OS of 65.3% (cT4b1) *versus* 44.4% (cT4b2). This describes the probable adverse effect on survival of organ invasion, even if there was no significant difference between cT4b1 and cT4b2 categories ($p=0.55$). However, patients with only sphincter involvement had a 36% better probability of survival at 5 years than those with primary tumor that invaded adjacent organs (hazard ratio=0.64; 95% CI=0.37-6.67). It was also associated with a small improvement in 5-year DFS (56.3% *versus* 44.4% for cT4b1 and cT4b2, respectively).

Nowadays the tri-modality approach, including neo-adjuvant CRT followed by surgery and adjuvant chemotherapy, represents the standard of care in LARC. This treatment has dramatically improved patient outcomes but seems not to be completely effective on distant control, especially in the high-risk prognostic group. The risk of distant metastasis remains high (approximately 25%) and a more advanced clinical stage is associated with worse outcomes (6-9). This was consistent with the results of our analysis that demonstrated a distant metastasis incidence of 28.6%, underlining the potential negative impact on survival of cT4b disease. Nevertheless, the vast majority of distant metastasis (n=5; 83.3%) occurred in patients with cT4b1 disease. The individual data of these patients did not help to explain the exact cause of this dissemination.

In recent years, in order to improve OS, a novel treatment strategy of induction chemotherapy followed by standard therapeutic approach has been investigated in this setting of patients (2, 10). The rationale for giving induction chemotherapy is to prevent or eradicate tumor cell dissemination. The choice of induction chemotherapy highlights the value of accurate staging at diagnosis in order selectively to treat patients with worse prognosis and therefore reduce the risk of overtreatment (11). Our results

Table III. Overall survival outcomes by tumor and node (TN) category analysis (1).

TN Category	5-Year overall survival
T3	
N0	64%
N1	52.4%
N2a	42.5%
N2b	32%
T4b	
N0	44.7%
N1	24.3%
N2a	18.5%
N2b	12.3%

have shown that there may be a subset of cT4b tumors that might not be eligible for additional intensification of therapy. In fact, it should be noted that in our cohort, patients with cT4b1 disease had a 5-year OS rate that compared favourably to the OS rates reported in patients with cT3 lesions in prior published Surveillance, Epidemiology, and End Results (SEER) data, which ranged from 64% to 32% (Table III) (1, 12). The small number of patients did not allow for a solid comparison between N sub-groups, even if all cases but one had positive lymph nodes at diagnosis. Our patients with cT4b1 lesions (5-year OS=65.3%) performed better than SEER patients with cT4b lesions, independently of combinations of N classification (T4bN0=44.7%; T4bN1=24.3%; T4bN2a=18.5%; T4bN2b=12.3%), whereas our cT4b2 category had outcomes more akin to these values. This finding questions whether patients with external sphincter invasion benefit from more aggressive treatments. Literature data did not exist for patients with cT4b1 and cT4b2 disease and the continued use of heterogeneous cT4b stage without the potential benefit of its sub-staging could be judged as inadequate. The limited subset of patients with cT4b1 disease may have an excellent outcome with standard treatment, but there are no randomized data to support this assumption. It appears that accurate local extent of disease is critical for the assessment of efficiency of treatment and predicting prognosis of these patients. We believe that the cT4b1 category is indicative of a favorable cT4b profile than for patients with organ invasion. Considering the positive trend in survival for cT4b1, the indications for induction chemotherapy should, therefore, be restricted to patients with cT4b2 disease.

In the literature, several clinical and histological tumor characteristics were identified as predictive of survival. In order of importance these are: primary lesions confined to the rectal wall and clinical node status, followed by negative lateral/circumferential margins and histological grade of the

cancer (13-14). This study was restricted to patients with cT4b disease and there was a correlation of survival with the extent of tumor invasion, albeit not significantly. With this assumption, clinical tumor invasion at diagnosis may play an important role in both outcome and choice of management. Our results were from a single-institute experience with a relatively small sample size. Due to this limitation we failed to find any strong factors predictive of survival, including well-established prognostic variables. Moreover data were not adequate for our analysis to have sufficient power for drawing definitive conclusions about oncological outcomes. However, these promising early results could provide the background for multi-institutional phase III trials to determine whether this new classification will help to confirm our observation.

Extension of the primary tumor to other organs, including urethra, vagina, or prostate, seems to be associated with a poorer prognosis when compared to those lesions with external sphincter invasion alone. The significance of this should be reflected in the stage assignment of patients, in view of the different treatment strategy. The addition of sub-staging for stage T4b should be validated by further pooled analysis of rectal cancer.

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