International Journal of Radiation Oncology biology • physics

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Clinical Investigation

Dose Escalation Using Contact X-ray Brachytherapy After External Beam Radiotherapy as Nonsurgical Treatment Option for Rectal Cancer: Outcomes From a Single-Center Experience

Arthur Sun Myint, FRCR,[*,†] Fraser McLean Smith, FRCSI,[‡] Simon Gollins, FRCR,[§] Helen Wong, PhD,[*] Christopher Rao, PhD,[‖] Karen Whitmarsh, FRCR,[*] Raj Sripadam, MD,[*] Paul Rooney, FRCS,[‡] Michael Hershman, FRCS,[¶] and D. Mark Pritchard, FRCP[†,‡]

The Clatterbridge Cancer Centre, Liverpool, United Kingdom; [†]Institute of Translational Medicine, University of Liverpool, Liverpool, United Kingdom; [‡]The Royal Liverpool and Broadgreen University Hospital National Health Service Trust, Liverpool, United Kingdom; [§]North Wales Cancer Treatment Centre, Rhyl, United Kingdom; [‖]Department of Surgery, University Hospital Lewisham, London, United Kingdom; and [¶]New Cross Hospital, Wolverhampton, United Kingdom

Received Jun 8, 2016, and in revised form Oct 6, 2017. Accepted for publication Oct 12, 2017.

Summary

The present study reviewed the outcomes from 83 rectal cancer patients treated with a contact x-ray brachytherapy (CXB) boost for residual tumor ≤3 cm after external beam radiation therapy (EBRT). Of these 83 patients, 53 (63.8%) achieved a clinical complete response

Purpose: To review the outcomes of rectal cancer patients treated with a nonsurgical approach using contact x-ray brachytherapy (CXB) when suspicious residual disease (≤3 cm) was present after external beam chemoradiation therapy/radiation therapy (EBCRT/EBRT).

Methods and Materials: Outcome data for rectal cancer patients referred to our institution from 2003 to 2012 were retrieved from an institutional database. These patients were referred after initial local multidisciplinary team discussion because they were not suitable for, or had refused, surgery. All selected patients received a CXB boost after EBCRT/EBRT. Most patients received a total of 90 Gy of CXB delivered in 3 fractions over 4 weeks.

Results: The median follow-up period was 2.5 years (range 1.2-8.3). Of 345 consecutive patients with rectal cancer referred to us, 83 with suspicious residual disease

Reprint requests to: Arthur Sun Myint, FRCR, Clatterbridge Cancer Centre, Papillon Suite, Wirral CH63 4JY, UK. Tel: (51) 482-7826; E-mail: sun.myint@nhs.net

The present study was previously presented at the European Society for Radiotherapy and Oncology 35th Annual Meeting, Turin, Italy, April 29 to May 3, 2016; abstract selected for oral presentation at "high lights of proffered papers" and oral presentation at American Brachytherapy Society World Brachytherapy Congress, San Francisco, June 27-29, 2016.

The present study was entirely funded by the National Health Service. Conflicts of interest: none.

Acknowledgments—The authors wish to thank Jean Pierre Gerard (Lyon/Nice) for his inspiration. Mark Lodge (Oxford), Zsolt Fekete (Cluj Napoca), Amandeep Dhadda (Hull), Alex Stewart (Guildford), Jamie Mills (Nottingham), Mike Brada (Clatterbridge), Vivek Misra (Christie Hospital, Manchester), Mike Davies (Cardiff), and Stephanie Bartlett for their help and advice with the manuscript.

Int J Radiation Oncol Biol Phys, Vol. 100, No. 3, pp. 565–573, 2018
0360-3016/$ - see front matter
https://doi.org/10.1016/j.ijrobp.2017.10.022

(cCR). Local regrowth after cCR was low at 11.3%. All patients underwent successful salvage surgery. At a median follow-up period of 2.5 years, 63 patients (83.1%) were cancer free. This approach could provide a nonsurgical treatment option to reduce local regrowth after external beam chemoradiation therapy (EBCRT) in patients not suitable or who wish to avoid surgery.

(≤3 cm) after EBCRT/EBRT were identified for a CXB boost. Their median age was 72 years (range 36-87), and 58 (69.9%) were men. The initial tumor stages were cT2 (n = 28) and cT3 (n = 55), and 54.2% were node positive. A clinical complete response (cCR) was achieved in 53 patients (63.8%) after the CXB boost that followed EBCRT/EBRT. Of these 53 patients, 7 (13.2%) developed a relapse after achieving a cCR, and the 6 patients (11.6%) with nonmetastatic regrowth underwent salvage surgery (100%). At the end of the study period, 69 of 83 patients (83.1%) were cancer free.

Conclusions: Our data suggest that a CXB boost for selected patients with suspicious residual disease (≤3 cm) after EBCRT/EBRT can be offered as an alternative to radical surgery. In our series, patients with a sustained cCR had a low rate of local regrowth, and those with nonmetastatic regrowth could be salvaged successfully. This approach could provide an alternative treatment option for elderly or comorbid patients who are not suitable for surgery and those with rectal cancer who wish to avoid surgery.

Introduction

Although a decade ago, nonoperative management of rectal cancer with a clinical complete response (cCR) to neoadjuvant chemoradiation therapy seemed anathema, it is has recently been gaining acceptance (1-5). This approach is relevant for individuals for whom the potential risks of surgery outweigh the benefits, such as elderly comorbid patients with rectal cancer. The incidence of rectal cancer is increasing as a proportion of all cancers diagnosed owing to national bowel cancer screening programs (6, 7). With conventional external beam chemoradiation therapy (EBCRT) regimens, the true level of the pathological complete response is low, occurring in ~10% to 30% of patients who received fluoropyrimidine with radiation (8-10). In addition, published data have shown that ~15% to 40% of those with an initial cCR will develop regrowth locally and require surgical salvage for cure (8-10). Therefore, a need exists to increase the clinical complete response rates and reduce local regrowth to enable more patients to benefit from the watch-and-wait approach after EBCRT.

At our center, we have adopted the strategy of offering patients escalated doses of radiation delivered directly to the tumor site in an effort to increase the cCR rate using a contact x-ray brachytherapy (CXB) boost. The advantage of this approach is that it can deliver up to an additional 90 Gy of radiation, with minimal collateral damage to the surrounding normal tissues (11). In the present report, we describe the treatment outcomes of this approach from our center.

Methods and Materials

Patient selection

A total of 83 patients were identified from a prospectively maintained institutional database of 345 consecutive patients with rectal cancer who had been referred to our center for CXB from January 2003 to November 2012. No ethics approval was necessary for our retrospective audit because CXB has been used since 1993 and is not regarded as an experimental treatment at our institution. However, our regional audit committee approved the present retrospective audit (approval no. 01-02/26).

A histologic diagnosis of adenocarcinoma was confirmed in all patients before treatment. The baseline pretreatment assessment included endoscopy; digital rectal examination (DRE); magnetic resonance imaging (MRI); computed tomography of chest, abdomen, and pelvis; and endorectal ultrasonography (if MRI was not possible owing to the presence of a cardiac pacemaker). The baseline assessment was performed at the patients' local referring hospitals. The initial local T and N stage using the TNM staging system (American Joint Committee on Cancer/International Union Against Cancer, version 7) was determined from the MRI findings for 87.9% of the patients (Table 1). Patients agreed to receive treatment after informed consent and counseling. All the patients were fully aware that we did not treat all those who had been referred, that we only selected suitable individuals for the CXB boost, that curative treatment might not be possible, and that if residual disease or local regrowth developed at a later date, salvage surgery might be feasible, provided they did not have distant metastases and that they were fit and agreed to surgery.

Inclusion and exclusion criteria

We included patients with persistent abnormal findings suspicious of residual cancer, either endoscopically on DRE or radiologically, that was ≤3 cm after EBCRT or EBRT for consideration of a CXB boost in those patients who were not suitable for surgery or had refused surgery. Individuals who had achieved a true cCR after EBRT or EBCRT were excluded from our present study, because that group comprised patients in whom no mucosal abnormality had

been seen or palpated and hence no target was available at which to direct the CXB boost. Some of those referred for consideration of a CXB boost had bulkier residual tumor (>3 cm) or tumor that involved one-half of the rectal circumference (poor responders to EBRT/EBCRT). They were offered high-dose-rate endoluminal brachytherapy using a rectal applicator (Elekta, Stockholm, Sweden) and were also excluded from the present study (n = 46). Patients with metastatic disease or tumors with regrowth after EBRT/EBCRT were treated palliatively (n = 86) and were excluded from the present analysis. Patients with cT1 or early cT2 tumors who had received CXB alone (n = 17), patients with cT1 or cT2/cN0 tumors that were mainly adenomas with a small focus of cancer ≤3 cm who had received CXB before EBRT (n = 26), and all other cT1 and cT4 patients (n = 6) were excluded from our study. In addition, all patients who had received CXB within 4 weeks of completing EBCRT/EBRT (n = 26) were excluded from our study to improve the homogeneity of our cohort (Fig. 1). Finally, patients with missing data (n = 61) were also excluded.

Table 1 Patient characteristics

Characteristic	n (%)
Age (y)	
Median	72
Range	36-87
Sex	
Female	25 (30.1)
Male	58 (69.9)
Performance status	
0	35 (42.2)
1	34 (41.0)
2	9 (10.8)
3	3 (3.6)
Not known	2 (2.4)
Differentiation	
Well	3 (3.6)
Moderate	58 (69.9)
Poor	1 (1.2)
Not known	21 (25.3)
Tumor stage	
cT2	28 (33.7)
cT3	55 (66.3)
Nodal stage	
cN0	38 (45.8)
cN1	32 (38.6)
cN2	12 (14.5)
Not known	1 (1.2)
Metastasis stage, M0	83 (100)
Tumor size (cm)	
≤3	47 (56.6)
>3	23 (27.7)
Not recorded	13 (15.7)
Distance from anal verge (cm)	
<7	61 (73.5)
7-11	16 (19.3)
Not recorded	6 (7.2)

External beam radiation dose and schedule

EBCRT consisted of 45 Gy in 25 fractions over 35 days with concurrent chemotherapy using a 5-fluorouracil infusion 1 g/m^2/day from days 1 to 4 in weeks 1 and 5 at the beginning of the study. In a later period of our study, chemotherapy was changed to oral capecitabine 825 mg/m^2 twice daily (Monday through Friday) throughout radiation therapy (n = 71). A small number of patients who were not suitable for chemotherapy (because of poor renal function) received EBRT alone (n = 12). The patients were assessed at 4 to 6 weeks after EBRT/EBCRT in the earlier period of the present study. However, more recently, the practice in the United Kingdom has changed to assessing patients slightly later at 6 to 8 weeks. This time point is in line with most international watch-and-wait protocols (10). The cases of all patients were discussed again at the local colorectal multidisciplinary team meeting after their assessment. The assessment, performed at their local colorectal units, included endoscopy, DRE, and restaging MRI scans to evaluate their response. The interval between EBRT/EBCRT and CXB varied, because the patients underwent EBRT/EBCRT at their local cancer units and were subsequently referred to our specialist cancer center for consideration of CXB. In most cases, the interval was within 4 to 6 weeks during the earlier period of our study and 6 to 8 weeks in the later stages, with a median of 39 days (range 28-174).

CXB setup, dose, schedule, and rationale

CXB was delivered using a 50-kVp Therapax (Gulmay, UK) machine from 2003 to 2009 and, after 2009, using a Papillon 50 (Ariane, Alfreton, UK; Fig. 2). The comparisons between these 2 machines (12) and the CXB treatment protocol used in the present study have been previously described (13-16). CXB was administered on an outpatient basis every 2 weeks. At each visit, 30 Gy of 50-kVp x-rays (HVL 0.64 Al, 2.7 mA) was delivered through a rectal treatment applicator (size 30, 25, or 22 mm) at a focal source surface distance of 29, 32, or 38 mm (depending on the applicator size chosen). Radiation was targeted straight onto the tumor with a 5-mm margin under direct vision (Fig. 2). Most patients received a total of 90 Gy (surface dose) delivered in 3 fractions (days 0, 14, and 28) over 4 weeks.

Response assessment and surveillance protocol

The most intensive monitoring occurred within the first 2 years when the risk of tumor recurrence was greatest. Patients were seen every 3 months for DRE and sigmoidoscopy. MRI scans were performed every 4 to 6 months, and computed tomography of the chest, abdomen, and pelvis was undertaken at 12, 24, and 36 months. A cCR was defined according to the published criteria as a

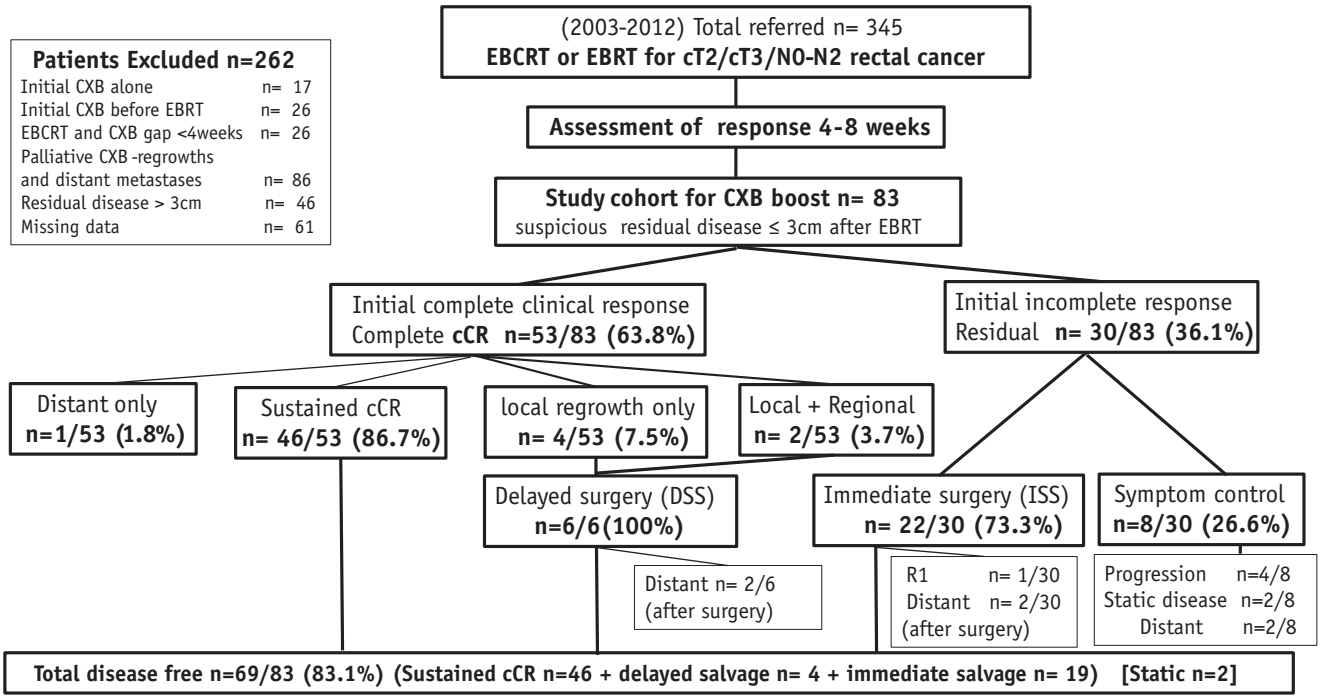

Fig. 1. Patient care pathway flow chart. *Abbreviations:* cCR = clinical complete response; CXB = contact x-ray brachytherapy; DSS = delayed salvage surgery; EBCRT = external beam chemoradiation therapy; EBRT = external beam radiation therapy; ISS = immediate salvage surgery.

complete absence of palpable, endoscopic, or radiologic evidence of residual tumor (17). Importantly, the time point used to establish a true clinical incomplete response was 6 months after the last CXB dose, because, in our experience, further tumor regression will not usually be observed beyond that point. If a suspicious mucosal abnormality progressed endoscopically, or an induration was palpated on DRE, or suspicious changes were observed on MRI, the patients were referred for immediate salvage surgery (ISS) provided they agreed and were fit for treatment (18). Less importance was given to isolated subtle abnormalities seen on MRI scans or mucosal abnormalities noted on endoscopy that did not change over time (19). These were regarded as static disease and kept under review with

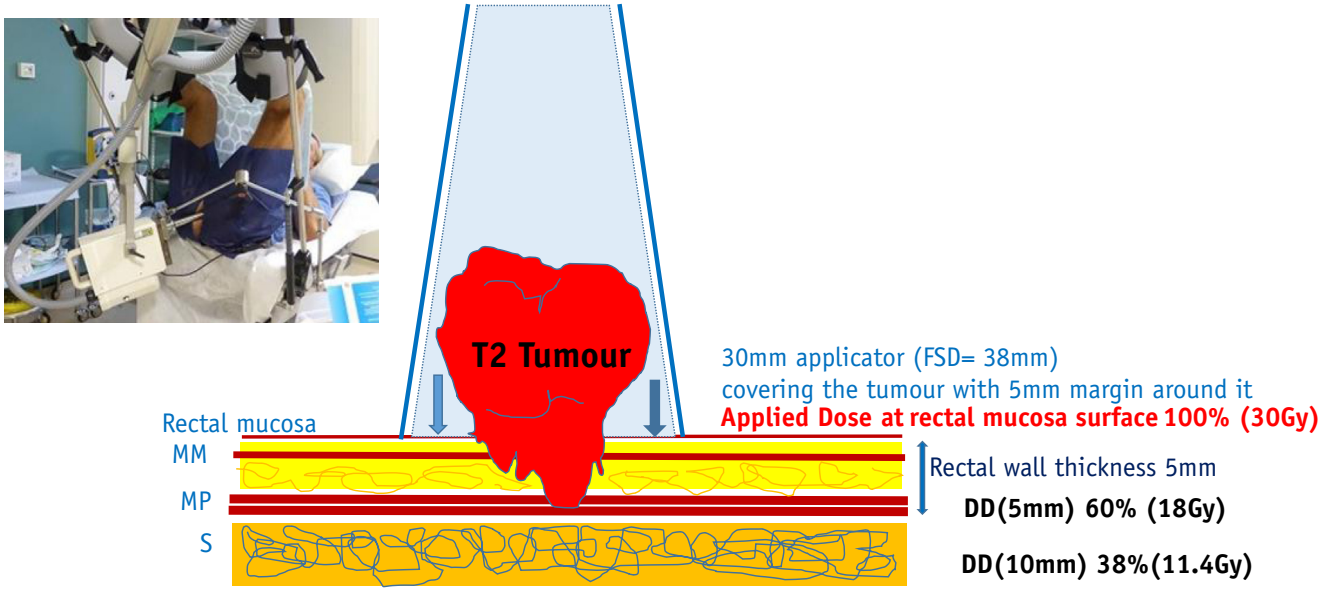

Fig. 2. Contact x-ray brachytherapy treatment position and schematic diagram. *Abbreviations:* DD = depth dose; FSD = focal source surface distance; MM = muscularis mucosa; MP = muscularis propria; S = serosa; T2 = stage T2 tumor infiltrating into MP (TNM).

regular endoscopic and radiologic assessments at 3-month intervals.

All patients who continued with the so-called watch-and-wait pathway after 6 months were reassessed as described every 3 months for the first 2 years. If any active tumor regrowth was suspected or detected after an initial cCR, the patient underwent restaging and was offered delayed surgical salvage (DSS), provided no inoperable distant metastases were detected and they were fit and agreed to surgery (Fig. 1). Throughout the disease-monitoring process, clinicians were encouraged not to perform a biopsy of the scar if no obvious cancer remained owing to the known low-negative predictive value of negative histologic features (19, 20). When cCR was maintained, the frequency of assessment was reduced to every 6 months in year 3 and every year thereafter for $\leq$5 years.

Data integrity and statistical analysis

Because our data were retrospective and had been accrued over many years, an external independent validator was commissioned to ensure their accuracy and integrity. This process indicated that 94% of the initial data entries were accurate. All identified inaccuracies were corrected. The data were analyzed using SPSS, version 21 (IBM, Portsmouth, UK). The objective of our report was to describe the outcomes of CXB used as a boost after EBCRT or EBRT. We chose our main endpoint as local regrowth in those who had achieved a cCR following CXB after EBCRT or EBRT. Furthermore, disease-free survival was estimated using the Kaplan-Meier survival method (Fig. 3). Univariate and multivariate analyses using logistic regression were used to identify possible clinical factors associated with treatment response and local regrowth (Table 2).

Results

Study group and demographic data

Our institutional database identified 83 patients who fulfilled our inclusion and exclusion criteria. The baseline demographics of the study group are listed in Table 1, and their outcomes are shown in Fig. 1.

Clinical complete response

A cCR after the CXB boost in patients with suspicious residual disease after EBCRT/EBRT was observed in 53 patients (63.8%). Univariate logistic regression analysis showed that attainment of a cCR was not related to the pretreatment performance status (P = .62), age (P = .74), cT stage (P = .31), tumor size (P = .27), CXB dose (P = .82), or EBRT modality with or without chemotherapy (P = .56). Importantly, a cCR was also not related to the pretreatment clinical nodal status (P = .10).

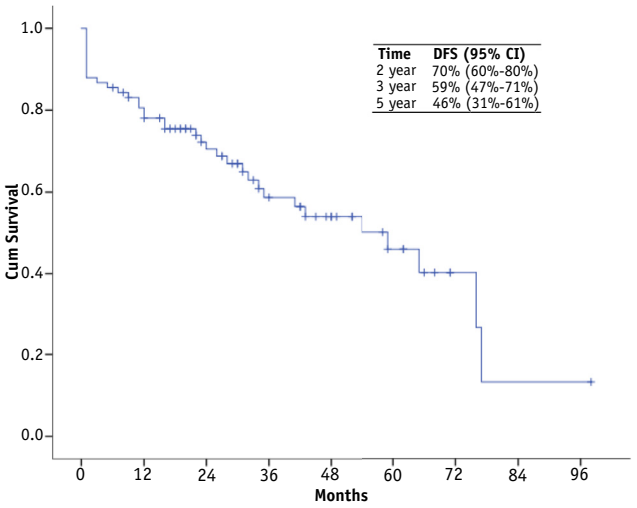

Fig. 3. Disease-free survival (DFS). *Abbreviations:* CI = confidence interval; Cum = cumulative.

Clinical incomplete response

Of the 83 patients, 30 (36.1%) had a clinical incomplete response 6 months after the last dose of CXB. Of these 30 patients, 22 (73.3%) subsequently underwent surgery, because it was presumed that they had residual cancer. However, 5 of these 22 patients (22.7%) actually had no residual tumor with a pathologic stage of ypT0. Eight patients did not proceed to ISS, mainly because of advanced age and comorbidities; however, 2 patients chose not to undergo surgery.

Local regrowth after initial cCR

At the study cutoff date, 7 of the 53 patients (13.2%) who had achieved an initial cCR after the CXB boost following EBRT developed either local regrowth or distant relapse. Thus, 46 of the 53 patients (86.7%) who had achieved a cCR had a sustained cCR. The median interval to relapse was 16 months (range 4.0-113). Univariate analysis showed that tumor regrowth was not associated with pretreatment performance status (P = .99), age (P = .69), cT stage (P = .81), cN stage (P = .98), original tumor size (P = .75), treatment modality (P = .10), or CXB dose (P = .25; Table 2).

Management of local regrowth

Of the 7 patients (13.2%) who had developed tumor regrowth after an initial documented cCR, 1 (1.8%) had distant metastases only. Only 4 patients (7.5%) had local regrowth only, and 2 patients (3.7%) had regional nodal regrowth in addition to their local regrowth. All 6 patients with potentially salvageable nonmetastatic local regrowth (100%) underwent DSS. However, 1 of these 6 patients (16%) had no pathologic evidence of residual tumor (ypT0).

Table 2 Prognostic factors related to treatment response and local regrowth

		Treatment response			Local regrowth		
Prognostic factor	Patients (n)	HR	95% CI	*P* value	HR	95% CI	*P* value
Performance status				.62			.99
0	35	Ref	NA		Ref	NA	
1	34	0.43	0.14-1.35		0.62	0.08-4.64	
2	9	1.19	0.2-6.94		0.00	0-0	
3	3	1.22	0.07-21.03		0.00	0-0	
Not known	2	1.09	0.03-42.78		0.00	0-0	
Age group (y)				.74			.69
<70	33	Ref	NA		Ref	NA	
70-79	30	0.66	0.2-2.18		2.49	0.3-20.38	
80-89	20	1.03	0.24-4.36		1.41	0.08-24.77	
Tumor stage				.31			.81
cT2	28	Ref	NA		Ref	NA	
cT3	55	1.87	0.56-6.18		0.76	0.08-6.98	
Nodal stage				1.00			.98
cN negative	38	Ref	NA		Ref	NA	
cN positive	44	1.01	0.32-3.19		1.25	0.11-13.58	
Not known	1	0.00	0-0		0.00	0-0	
Distant from anal verge (cm)				.32			.63
<7	61	Ref	NA		Ref	NA	
7-11	16	0.43	0.1-1.84		3.34	0.28-39.96	
Not known	6	0.23	0.02-2.85		0.00	0-0	
Tumor size (cm)				.27			.75
≤3	31	Ref	NA		Ref	NA	
>3	34	0.61	0.19-2		0.39	0.03-4.9	
Not recorded	18	1.99	0.46-8.62		0.88	0.06-12.91	
Treatment modality				.56			1.00
Chemo-RT	71	Ref	NA		Ref	NA	
RT alone	12	0.58	0.1-3.51		0.00	0-0	
Papillon total dose (Gy)				.82			.25
≤90	79	Ref	NA		Ref	NA	
>90	4	0.74	0.05-9.99		8.65	0.22-347.01	

Abbreviations: Chemo-RT = chemoradiation therapy; CI = confidence interval; HR = hazard ratio; NA = not applicable; Ref = reference; RT = radiation therapy.

Distant metastases

A total of 7 patients (13.2%) developed distant metastases. This included 1 patient who developed distant metastases after achieving a cCR and 2 patients who had developed distant metastases after ISS for residual disease. Two patients developed a relapse with distant metastases after DSS for local regrowth. Two patients in the initial incomplete response group with persistent tumor developed distant metastases in addition to their local disease (Fig. 1). Of those who developed distant metastases, 3 underwent metastectomy, and the others received palliative treatments.

Disease-free survival

The Kaplan-Meier probabilities of disease-free survival for the whole group were 70% (95% confidence interval [CI] 60%-80%) at 2 years, 59% (95% CI 47%-71%) at 3 years, and 46% (95% CI 31%-61%) at 5 years (Fig. 3). These data mainly reflect the elderly nature of this population, who also had medical comorbidities and, in many cases, died of causes unrelated to their cancer.

Toxicities and adverse effects of therapy

No patient had to stop CXB because of gastrointestinal toxicity. Rectal ulceration (grade 1) developed in 30% of patients after CXB, but this usually healed within 3 to 6 months. Of the 83 patients, 23 (28%) developed bleeding (grade 1) due to telangiectasia and 5 (6%) required argon beam therapy (grade 2) for hemostasis (Common Toxicity Criteria Score, version 4.0) (21, 22). No patients required colostomy to treat late gastrointestinal toxicity (grade 3). No deaths were reported related to CXB.

Disease status

At the end of our study period with median follow-up duration of 2.5 years, 69 of 83 patients (83.1%) were free of cancer. This included those who had undergone salvage

surgical treatment (Fig. 1). Of the 27 patients who died, 16 (60%) had no documented evidence of residual or recurrent cancer and had died of other causes.

Discussion

We performed a retrospective analysis of patients from a single institution who had undergone nonoperative watch-and-wait management for rectal cancer. Our study had limitations, uncertainties, and a potential selection bias in our data, which could have skewed the initial cCR rate. The difference between the present series and most other reported series is that all patients received an additional boost of CXB in an attempt to treat any remaining cancer cells that persisted after EBCRT or EBRT, with the aim of reducing local regrowth. A further important difference was that the patients included had not had a classic cCR because, by definition, this would have meant nothing visible on the mucosa or MRI scan and nothing to palpate and thus nothing to target for CXB. All the patients in our series had a residual mucosal abnormality; thus, they had not had a classic cCR after EBCRT/EBRT. However, although our patients all had a "clinical incomplete response" after EBCRT/EBRT, we found that after CXB, another 63.8% achieved a classic cCR with no mucosal abnormalities suspicious for residual disease. Of those who achieved a cCR after the CXB boost, only11% developed local regrowth, and, this, in turn, was salvageable in all 6 nonmetastatic patients.

Although CXB has been in clinical use for >80 years, it has not been regarded by many clinicians as a standard of care in Europe (13, 23-26) or in the United States (27, 28). Its use has been restricted to only a few specialist centers owing to decommissioning of the Phillips RT50 machine in the 1970s. However, since then, interest in CXB has revived with the availability of the Papillon 50 machine (Ariane, Alfreton, UK), and 15 centers in Europe now offer CXB for rectal cancer in suitable patients (14). We found that our referrals were mostly elderly patients and those who were either unsuitable for surgery or had refused surgery. We have also found an increasing numbers of young and fit patients who wish to explore alternative options to radical surgery because of its side effect profile and the likelihood of a stoma.

As the population ages and because rectal cancer is being diagnosed in more patients through national bowel cancer screening programs, the number of patients with rectal cancer who are suitable and likely to benefit from CXB will increase. Therefore, expansion of the number of centers offering CXB is needed to meet this increasing demand in the future.

A Brazilian research group was one of the first to report the results of a watch-and-wait policy for rectal cancer (10). They reported on 183 patients who received intensified chemoradiation therapy (54 Gy in 28 fractions over 38 days), followed by 4 cycles of chemotherapy, and achieved a high cCR (49%). However, 31% of these patients who had achieved a cCR later developed local regrowth requiring surgical salvage (Table 3). The most comparable group to our cohort was reported in the OnCoRe (Oncological Outcomes after Clinical Complete Response in Patients with Rectal Cancer) study. The geographic coverage of the patients referred to our center was similar to that of the patients in the OnCoRe study. The patients in the OnCoRe study were those who had achieved a cCR and were not referred to our center for a CXB boost. However, 38% of the 129 patients included in a watch-and-wait approach after EBRT required surgical salvage for local regrowth. A meta-analysis of watch-and-wait trials recently reported showed a lower local regrowth rate of 15% at a short follow-up period of 2 years (31). However, most patients in the studies reviewed had much earlier stage rectal cancer, unlike the patients in the OnCoRe and in our study, which included much more advanced-stage cancer (70% and 66.3% with stage T3, respectively) with a longer follow-up period of 33 and 29 months, respectively. In our series, despite including a heterogeneous group of patients, many of whom were elderly with locally advanced disease, 6 (11%) developed locoregional regrowth, of whom 4 (7.5%) had developed local regrowth at only a median follow-up period of 2.5 years after an initial cCR. Our data, therefore, appear to be very favorable compared with other reported series of nonoperative management involving standard neoadjuvant protocols using 50 Gy in 25 fractions over 5 weeks with fluoropyrimidine, in which approximately 15% to 40% of patients developed local tumor regrowth (8-10).

Several reasons for the high levels of a sustained cCR observed in our study are possible (Table 3). We believe that dose escalation with the CXB boost is an important contributing factor (11). The advantage is that any viable

Table 3 Comparison of initial response and local regrowth after cCR

Investigator	Patients (n)	Treatment modality	Initial response	Local regrowth
Habr-Gama et al (10)	183	EBCRT 45 Gy + EBRT boost 9 Gy	90/183 (49)	28/90 (31) at 5 y
Appelt et al (2)	51	EBCRT 60 Gy + HDR 5 Gy	40/51 (78)	9/40 (25.9) at 2 y
Renehan et al (9)	129	EBCRT 45 Gy	NA	44/129 (38) at 3 y
Frin et al (29)	45	EBCRT 50 Gy + CXB 90 Gy	43/45 (98)	3/43 (11) at 5 y
Dhadda et al (30)	42	EBCRT 45 Gy + CXB 90 Gy	NA	5/42 (12) at 2 y
Present study	83	EBCRT 45 Gy + CXB 90 Gy	53/83 (63.8)	6/53 (11.3) at 2.5 y

Abbreviations: cCR = clinical complete response; HDR = high-dose-rate brachytherapy; NA = not available.
Data presented as n/N (%).

tumor cells beneath the surface of the residual mucosal abnormality (which is usually ≤20 mm) receive a further, very high, yet localized, dose of targeted radiation therapy that sterilizes them. The tumor was shaved off layer by layer at each 2-week application until the tumor had regressed to its base. The total dose of 90 Gy seems quite high; however, most of this dose was delivered directly onto the tumor, using low-energy x-rays with limited range of penetration. Thus, the surrounding normal tissues, including those at a depth, received very little of this radiation dose, reducing the collateral damage, which minimized the side effects (15, 16).

The randomized trial Lyon 96-02 provided supportive evidence for an improved clinical response (24% vs 2%) and pathologic response (57% vs 34%) in favor of a CXB boost, in addition to EBRT, for more advanced bulky stage T2 and T3 rectal cancer cases (26). More recently, histologic data after EBRT for earlier stage cT1, cT2, and cT3a tumors have been reported from 2 independent trials. One study from the United Kingdom of cT1 and cT2 rectal cancer cases showed a 32% pathologic complete response after 8 to 10 weeks after short-course radiation therapy. A similar Dutch study reported a 44% pathologic complete response rate after EBCRT for cT1, cT2, and cT3a tumors (32, 33). Histologic evidence of residual tumor was found in 68% and 56% of the patients in both trials. Transanal endoscopic microsurgery provided the histologic status after either neoadjuvant short-course radiation therapy or EBCRT. Our data suggest that the residual disease that remained could be sterilized by CXB to reduce local regrowth to 11%. Our data concur with those from a reported prospective study of a well-defined group of patients at a single center (Hull, UK) treated under a strict protocol, which showed a reduction in local regrowth to 12% (n = 5) when a CXB boost was offered in addition to EBRT (33). Moreover, a recent report from Nice, France, showed an 11% predicted local regrowth at 5 years in patients with more advanced cT2/cT3 tumors treated by a combination of EBCRT at a higher dose of 50 Gy in 25 fractions over 5 weeks and CXB at 90 Gy in 3 fractions (30). Both these studies used a CXB boost similar to that received by our patients; however, both were prospective studies involving patients treated under strict protocol at single institutions. Both studies showed low rates of local regrowth, similar to our series, which suggests that CXB is a significant contributor to the reduction of local regrowth (Table 3). We are assessing this hypothesis further in an ongoing European multicenter phase III randomized trial, which started in 2015; to date, 45 patients have been randomized.

We believe another important clinical finding from our results is that most of our patients (16 of 27 patients [60%]) who died had no documented evidence of cancer (ie, they died of other medical causes). As such, our data highlight the importance of competing oncologic outcomes against physiologic risk involved in decision making for rectal cancer in comorbid and elderly patient groups, who are increasing in number owing to the aging population (26). Furthermore, in patients with an initial cCR who subsequently developed local and regional regrowth, DSS was possible for all 6 patients (100%) without distant metastatic disease (18). These results mirror those from other specialist centers, with reported surgical salvage rates of ~90% (9, 10, 31).

Our study had further limitations because our study was a retrospective analysis of patients treated over many decades with all the accompanying drawbacks. We also did not compare our outcomes with those from patients who had received radical surgery, the current reference standard treatment. However, the OnCoRe study did perform such a comparison. The OnCoRe study compared the oncologic outcomes of 129 patients who received a watch-and-wait approach (38% required surgical salvage because of local regrowth) with a propensity score-matched group of patients who underwent index radical surgery and showed no difference in their survival outcomes (9).

We acknowledge that our follow-up was relatively short, and we also have not included outcome data concerning bowel function. However, we are in the process of formally and prospectively recording functional data for our patients through a national data set as recommended by the National Institute of Health and Care Excellence. In addition, a review of acute and long-term toxicities of CXB was performed by National Institute of Health and Care Excellence, and their findings were reported as Interventional Procedure Guidance 532 (34). Their findings of acceptable safety and toxicity profiles in patients not suitable for surgery were consistent with our experience.

We also accept that our data were not a part of a formal clinical study, that our patients were not randomized, and that it was, essentially, a retrospective observational study with all the inherent limitations. This is because until recently nonoperative management was deemed anathema to conventional treatment of rectal cancer, and very few patients were referred for a CXB boost after EBRT/EBCRT. We aim to rectify these issues in a European multicenter phase III randomized trial, for which we have started recruiting patients. The primary endpoint is organ preservation with local control at 3 years (35).

Conclusions

Our study, with all its limitation and uncertainties, has shown that patients with a clinical incomplete response to ECBRT/EBRT can still achieve a cCR after a CXB boost. Of those who achieved a cCR, only 11% developed local regrowth, and this percentage is low compared with those from other series. All 6 patients with nonmetastatic local regrowth could be salvaged. However, this technique ideally should be assessed in a clinical trial, one of which is under way. We believe that CXB is particularly pertinent for older or comorbid patients with rectal cancer who are not suitable for surgical salvage and for younger stoma-averse patients who wish to avoid surgical salvage (if possible) in the event of local regrowth after EBCRT/EBRT.

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