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Original Research

Planned organ preservation for early T2-3 rectal adenocarcinoma: A French, multicentre study

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Abstract ***Background:*** Neoadjuvant chemoradiotherapy (nCRT) and watch-and-wait policy as reported by Habr-Gama are references for organ preservation in rectal cancer. To increase the clinical complete response (cCR) and reduce the local recurrence rates, we report a retrospective analysis of a prospective cohort of selected T2-3 tumours treated in three French institutions using contact X-ray brachytherapy (CXB) with nCRT.

Methods: Tumour selection was based on digital rectal examination (DRE), rigid rectoscopy, magnetic resonance imaging (MRI) and/or endorectal ultrasound. Adenocarcinoma T2-3 < 5 cm largest diameter, M0 were treated, all with organ preservation intent. CXB delivering 90 Gy/3 fractions/4 weeks was combined with CRT (capecitabine 50). Strict evaluation of tumour response using DRE and rectoscopy ± MRI was performed at regular interval with prolonged surveillance.

Findings: Between 2002 and 2016, 74 consecutive patients were treated (median age: 74 years. T2: 45 and T3: 29). A cCR or near-cCR (mainly rectal wall ulceration) was noted at week 14 in 71 patients (95%). A local excision was performed in 13 patients. Of three partial responses (PRs), one salvage anterior resection was performed. With a median follow-up of 3 years, local

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recurrence (mainly in the rectal wall) was seen in seven patients. The 3-year local recurrence rate was 10%, and the cancer-specific survival, 88%. Two patients underwent radical proctectomy for PR or local recurrence and 96% preserved their rectum. Grade III acute toxicity was recorded in five patients. Rectal bleeding was the main late toxicity (grade III in 12%). Bowel function was scored as good or excellent in 85% of patients.

Interpretation: Combining CXB and nCRT in selected early T2-T3 rectal cancers may safely provide a high rate of cCR, organ preservation, and good bowel function with a risk of local recurrence below 15%. Such an approach could be offered to operable patients as a planned option for organ preservation.

1. Introduction

Surgery is the standard treatment for cT2-3 rectal cancers [1]. However, after low anterior resection (LAR), quality of life is often affected [2]. Habr-Gama has demonstrated that when clinical complete response (cCR) is achieved after neoadjuvant chemoradiotherapy (nCRT), a watch-and-wait policy can preserve the rectum [3]. This approach is attracting growing interest, and most series report a cCR and local recurrence rates close to 40% and 25%, respectively [4,5]. These suboptimal data are explained by the relative radioresistance of rectal adenocarcinoma, a dose above 90 Gy being necessary to sterilise only 50% of T3 tumors [6,7]. Endoluminal radiation dose escalation is a strategy to increase the cCR rate [8,9]. Contact X-ray brachytherapy (CXB) was pioneered in the 1970s by Papillon [10] and was used in Europe and the US [11]. The Lyon R 96-02 randomised trial proved that when compared with neoadjuvant external beam radiotherapy (EBRT) alone, a CXB boost combined with EBRT was able to increase cCR and sphincter preservation rates [12,13]. In 2009, a renaissance of CXB was made possible with the design of a new CXB Papillon 50 ™ system [14]. In France, three institutions are performing CXB following the Lyon principles with two main end-points: clinical response and local recurrence, which are key parameters for organ preservation. We report their results in selected cT2-3 tumours.

2. Method

2.1. Study design and participants

Between 2002 and 2016, 74 consecutive patients were treated in three French institutions (Lyon-Villeurbanne, Mâcon, Nice) with organ preservation intent by radiation oncologists with long experience of CXB treatments (J.D., J.-P.G., K.B., N.B., and R.C.). This is a retrospective analysis of a prospective cohort. Patients were selected based on the following: with adenocarcinoma; accessible to digital rectal examination (DRE); T2, T3, N0-1 and M0 (UICC tumour-node-metastasis 7th classification); tumour diameter < 5 cm; less than half rectal circumference extension and no infiltration of the anal canal. Only N1 tumours with node < 1 cm were included. Workup was always performed with a DRE and rigid rectoscopy in the knee-chest position, by colonoscopy, endorectal ultrasound (ERUS) and/or magnetic resonance imaging (MRI), thoraco-abdominopelvic computed tomography (CT) scan (and/or positron-emission tomography [PET]-CT scan), routine serum biology and carcino-embryonic antigen (CEA) serum level tests. The performance status and operability were assessed. Half of the patients were referred by surgeons, and high surgical risk was often an argument to propose the option of non-radical surgery approach which explains a high mean age of this cohort. All patients gave informed consent for this conservative treatment after a multidisciplinary team (MDT) discussion.

2.2. Procedures

Until 2009, CXB was performed in Nice using the RT50 ™ (Philips, NL) machine, which was later replaced by the Papillon 50 ™ (Ariane, UK), which delivered the same performances and has been used in the three participating centres since 2010. The previously described [11,14] CXB treatment was ambulatory using a stainless steel applicator 3 cm in diameter positioned in the rectum, with the patient in the knee-chest position. This system allowed precise tumour targeting. The 50 kVp X-ray beam was delivered after insertion of the X-ray tube, and the dose (at the exit surface of the applicator) was 30–35 Gy for the first fraction in 2–3 min. A 2-week interval was allowed between fractions. Depending on the tumour shrinkage, dose (25-15 Gy) and size of the applicator (2.5–2.2 cm) could be reduced. The total dose ranged between 90 and 110 Gy in 3–4 fractions, delivered over 4 to 6 weeks.

CXB was the initial procedure for tumours < 3.5 cm. Chemoradiotherapy was started 1 or 2 weeks after the end of CXB. In tumours > 3.5 cm, CRT was the first

treatment, and CXB was initiated 2 weeks after CRT (Fig. 1). EBRT used 15–18 MV photon beam with a 3D conformal technique in Nice and intensity modulation radiation therapy (IMRT) in the two other centres. The clinical target volume (CTV) encompassed the gross rectal tumour, mesorectum, presacral nodes, and lateroposterior pelvic nodes. The upper limit extended to the S2/S3 level (S1/S2 for T3 in the middle rectum). The anal canal was not included in the CTV, except for the upper segment if the tumour had reached the anal canal. The anterior limit was behind the plane of the ureters. The CTV usually did not exceed 1 L. The dose was 50 Gy in 25 fractions over 5 weeks with a cone-down boost after 44 Gy. Concurrent capecitabine was given on radiation days (800 mg/m^2 twice daily). In frail patients, chemotherapy could be omitted, and EBRT could be delivered on a short course schedule (25 Gy/5 fractions/5 days).

Transanal local excision (TLE) was decided on an individual basis, either after cCR or after near-cCR (ncCR) (usually small residual ulcer). It was performed electively 4–6 weeks after end of irradiation. TME surgery was proposed for fit patients in case of partial response (PR) or local recurrence. No adjuvant chemotherapy was given. Overall duration of treatment (when no TLE was proposed) was close to 11 weeks (slightly shorter when CXB was the first treatment).

Follow-up was performed by the radiation oncologist. During CXB treatment, tumour response was assessed at each fraction using DRE and rectoscopy. One month after completion of the whole treatment, the first follow-up visit was scheduled. In case of cCR, the next visits were planned every 3 months for the first 3 years and then, every 6 months. In case of ncCR, the interval between visits was shortened to 1 or 2 months. Follow-up was often combined with flexible sigmoidoscopy by a gastroenterologist, and an MRI with diffusion-weighted imaging (DWI) was performed every 3 or 6 months during the first year and once a year from then on. When the patient was operable, a surgeon always participated in the follow-up for tumour response evaluation and joined the MDT for any decisions regarding surgery. Once a year, a general workup was performed using thoraco abdomino pelvis (TAP)-CT scan, CEA level and serum blood test. PET-CT was prescribed on an individual basis.

2.3. Outcomes

Clinical tumour response was classified according to the Response Evaluation Criteria in Solid Tumours: (1) cCR was defined as the complete disappearance of the tumour on rectoscopy (sigmoidoscopy) showing a normal mucosa (sometimes with a flat, white scar or inflammatory superficial capillaries) with a soft rectal wall on DRE with no suspicious firm areas, nodularities or ulcers; (2) ncCR was reported when a small superficial ulcer (≤2 cm) was found with regular edges, a smooth induration on DRE or a minor residual nodularity; (3) PR was the presence of any visible (or palpable) residual tumour in the rectal wall revealed by DRE or endoscopy and occasionally by biopsy. The MRI regression score [15] was the following: tumour regression grade (TRG)1: no visible tumour and normal rectal wall; TGR2: moderate isolated rectal wall fibrosis or rectal wall thickening with no restriction on DWI [16] and TRG 3–5: any significant visible tumour.

Pathological classification after any surgery was performed using the ypTNM classification, UICC 7th edition, and the Dworak score [17]: Dworak 4 = no residual cancer cell; Dworak 3 = only very few residual cancer cells and Dworak 2 and 1 = residual cancer cells in moderate or large amounts.

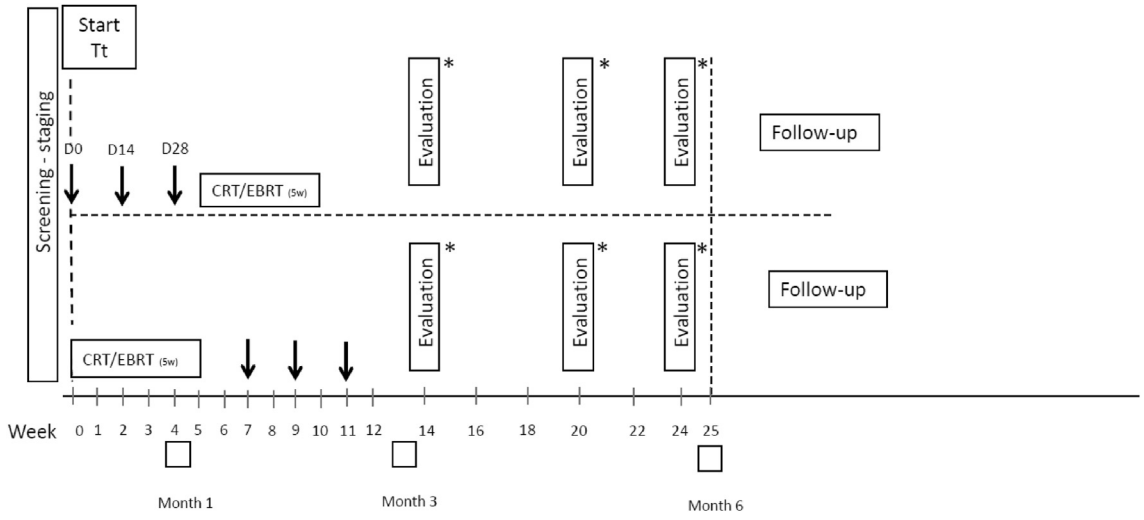


Fig. 1. **Study treatment and follow-up protocol.** *According to tumour response at time of evaluation: follow-up (surveillance) or surgery (TME or local excision). Tt, treatment; D, day; CRT, chemoradiotherapy; EBRT, external beam radiotherapy; w, week.

Local recurrence was any local relapse of the tumour after cCR or ncCR. It was intraluminal when the recurrence was located in the rectal wall, perirectal when in the mesorectum and pelvic when occurring in the pelvis outside the mesorectum. **Local control** was the absence at the last examination (or death) of any cancer in the pelvis, either after cCR, local excision or TME surgery. Organ preservation was the absence of any radical TME surgery (with or without local cancer evolution).

Distant metastasis was any relapse outside the pelvis, either in lymph nodes or in distant organs.

Survival was analysed in terms of cancer-specific survival (CSS), any death related to cancer and overall survival (OS), any death.

Toxicity was reported using the common terminology criteria for adverse events (CTCAE) V4 classification and described as early when occurring within 1 year after the end of treatment and as late when occurring later. **Bowel function** was analysed using the Memorial Sloan Kettering cancer center (MSKCC) 4-category score: excellent, good, fair and poor [18]. Since 2014, all patient bowel functions have been assessed using the LARS score [2].

2.4. Statistical analysis

Data entry and management were performed using CSOnline (Ennov Clinical®) and were analysed with R 3.2.2 for Windows®. Quantitative data were described by using median and range, and qualitative data, by using absolute and relative frequencies. Survival time was defined between the first radiotherapy date and the event onset date. OS, CSS, and local recurrence cumulative rate were respectively estimated and presented graphically using the Kaplan–Meier method with 95% confidence intervals (CIs). Patients still alive at the last visit were censored at the date of the last follow-up. Median follow-up with 95% CIs was calculated by reverse Kaplan–Meier method. The survival curves were compared using the log-rank test. The date of data analysis was December 2017, and the median follow-up time was 37 months (95% CI: 29–44). All P values inferior to 0.05 (two sided) were considered statistically significant.

2.5. Role of the funding sources

The funders of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the report.

3. Results

A total of 74 consecutive patients was treated with organ preservation intent between March 2002 and September 2016 in three French CXB institutions (Mâcon: 10; Lyon-Villeurbanne: 15 and Nice: 49). Patients and tumour characteristics at the baseline are given in Table 1. Median age was 74 years (39–98), with 34 patients (46%) considered operable. Most tumours were T2 (45 patients) in the distal rectum (51 patients). Median tumour diameter was 3.1 cm (1.8–5.2) with eight tumours exceeding 4 cm in diameter. Combined CXB and CRT were given to most patients (49 patients). Two patients with T2N0 tumours were treated with CXB alone: one achieved cCR after three CXB fractions but was considered too frail for EBRT (he died a year later from intercurrent disease with no evidence of cancer); the other died 3 weeks after CXB from ischaemic cerebral accident before EBRT initiation. Owing to frailty, three patients received accelerated EBRT (25 Gy/5 fr). CXB was the first treatment in 53 cases, usually for tumours not exceeding 3.5 cm. A local excision was made after irradiation in 13 patients (Table 2).

3.1. Tumour response

When CXB was the initial treatment, cCR was observed on day 28 in 14/53 patients, a ncCR in 29 and a PR in 10 (Fig. 3). Of the 74 patients, cCR was observed at the end of the entire radiotherapy treatment (week 14 ± 1) in 31 patients, an ncCR in 40 (ulceration, induration and nodularity in, respectively, 34, three and three patients) and a PR in three. Two patients with an ncCR underwent a local excision and achieved local control. Overall cCR and ncCR were observed in 71/74 patients (95%) at week 14. When an ncCR was seen at week 14, it usually evolved spontaneously to cCR within 2–3 months. Six months (week 24 ± 2) after treatment initiation, a cCR was noted in 64 patients (86%) and an ncCR in seven. Six of these seven patients achieved cCR with time; one developed a local recurrence 1 year later, which was treated palliatively. Of three patients with PR (week 14), one underwent anterior resection (ypT0N2) with local control at 2 years. The two others, owing to their poor general condition, were given palliative treatment not requiring a derivative stoma (see Fig. 2).

Since 2011, MRI has been performed 3–6 months after treatment initiation in 36 patients, with DWI in 30. The TRG score in patients with cCR or ncCR was TRG1 in 24 (Fig. 3), TRG 2 in 10 (rectal wall thickening and fibrosis) and TRG 3 in one (hypersignal on DWI, which became TRG1 6 months later). Among the three patients with PR, one underwent MRI, which showed TRG3.

3.2. Local excision

Two patients with an ncCR underwent local excision: operative specimens showed one ypT1 and one ypT2, R0 and Dworak 3 in both cases. Eleven other patients underwent elective local excision (LE) after cCR.

Table 1
Patient and tumour characteristics at the baseline.

Centre		Lyon-V	Macon	Nice	Total
Total		15	10	49	74
Gender	Male	8	9	36	53
	Female	7	1	13	21
Age	Mean (range)	73.9 (57–71)	66.5 (46–82)	75.7 (39–93)	74 (39–93)
	<75	9	7	19	35
	≥75	6	3	30	39
Operable	Yes	9	6	19	34
	High risk	2	2	23	27
	Inoperable	4	2	7	13
Histology	Well diff	10	5	24	39
	Moderate	4	3	16	23
	Poor	0	1	2	3
	Unspecified	1	1	7	9
Exam-TN staging	ERUS	4	4	18	26
	MRI	4	2	9	15
	ERUS + MRI	7	4	22	33
T	T2	11	6	28	45
	T3a	2		1	3
	T3b	1		11	12
	T3c			3	3
	T3d	1		1	2
	T3x		4	5	9
N	N0	10	7	34	51
	N1a	1	1	8	10
	N1b	4	2	4	10
	N2a			1	1
	N2b			1	1
Tumour diameter (mm)	(0–20)	2	1	7	10
	(21–30)	11	8	18	37
	(31–40)	2	1	16	19
	(≥41)			8	8
Mobility	Mobile	9	3	17	29
	Tethered	2	5	16	23
	Unspecified	4	2	16	22
Clinical aspect	Polypoid sessile	9	3	15	27
	Polypoid with ulceration	5	3	24	32
	Fungating (deep ulceration)	1	3	9	13
	Unspecified		1	1	2
Distance anal verge (cm)	(0–5)	13	7	31	51
	(5.1–6)	1	2	5	8
	(6.1–10)	1	1	13	15
CEA	Normal	3	0	18	21
	Elevated	1	1	3	5***
	Not done	11	9	28	48
pT (y) after loc. exc.	T0			6	
	T1			5*	
	T2			2**	
CRM	R0			11	
	R1			0	
	Unspecified			2	
TRG (Dworak)	No residual (4)			6	
	Very few (3)			6	
	Residual (2-1)			1	

Lyon V, Lyon-Villeurbanne; diff, differentiated; ERUS, endorectal ultrasound; MRI, magnetic resonance imaging; CEA, carcinoembryologic antigen serum level; CRM, circumferential rectal margin; TRG, tumour regression grade; loc. exc, local excision.
*4/5 with very few residual cancer cells.
**2/2 with very few residual cancer cells (Dworak 3).
***All patients with elevated CEA were T3.

Table 2
Treatments.

Centre		Lyon. V (15)	Macon (10)	Nice (49)	Total (74)
CXB					
Machine	Philips RT			22	22
	Papillon 50	15	10	27	52
Dose	50–79	2	5	10	17
	80-110	13	5	27	52
	>110			12	5
EBRT dose					
25/5				3	3
44–50		15	10	45	70
<44				1	1
Conc. Chemo (EBRT)					
Capecitabine		10	7	29	46
FUFOL				3	3
CXB followed by EBRT		10	7	36	53
EBRT followed by CXB		5	3	11	19
CXB alone				2*	2
Local excision				13	13

CXB, contact X-ray brachytherapy; EBRT, external beam radiotherapy; Conc Chemo, concurrent chemotherapy.
*Two patients received no EBRT: one cCR after CXB and too frail to receive EBRT; one died from cerebro-vascular accident 3 weeks after CXB before EBRT start; one patient discontinued EBRT after 22 Gy.

Pathological evaluation showed ypT0 in six patients, ypT1 in four and ypT2 in one. The Dworak score was 4 in six patients, 3 in four and 2 in one. No reoperation was performed. All patients achieved local control except one (ypT1 R0), who developed a perirectal recurrence 7 years later.

3.3. Local recurrence

Of 71 patients with cCR or ncCR at 6 months, a local recurrence was observed in seven cases (five before 3 years, one at 6 years and one at 7 years). Six were intramural and one perirectal. Two of them (with late recurrence) were treated with EBRT alone with acceptable radiation toxicity and short-term stable disease. One patient was salvaged using abdominoperineal resection surgery and achieved local control but died from distant metastases 1 year after surgery. The four others received only palliative treatment and died without derivative stoma. The 3-year (and 5-year) cumulative rate of local recurrence was 10% (95% CI: 1–19) (Fig. 4). There was no isolated pelvic recurrence.

Local control was achieved (irradiation alone ± local excision or TME surgery) in 66/74 patients (89%). Eight patients presenting PR (2) or local recurrence (6) were not operated on because of refusal or frailty.

Organ preservation was achieved in 72 patients (97%). Two patients underwent TME surgery for PR or local recurrence. Among patients with organ preservation, 64 were free from rectal tumour, and eight presented intrarectal progressive tumour, after either PR or local recurrence. No salvage surgery was proposed due to frailty or refusal. None of these patients required stoma, and all experienced acceptable bowel function.

Distant metastases developed in ten patients, two being associated with local relapse and one with PR. The 3-year cumulative rate of metastasis was 19% (95 CI: 7–29).

Death occurred in 25 cases. This was due to cancer in nine cases and to intercurrent disease in 16 cases. The OS rate was 74% (95% CI: 62–88) at 3 years. CSS was 88% (95% CI: 79–98) at 3 years (Appendix).

3.4. Early toxicity

Early grade III toxicities related to EBRT or CRT were observed in seven patients (9%) (constipation, diarrhoea, proctitis and cardiac pain). All these toxicities subsided after several weeks. Eight patients (11%) developed late grade III toxicities due to rectal bleeding in seven (1 to 2 years after treatment), which were successfully treated using plasma argon coagulation. One patient had grade III transient incontinence and urgencies. Rectal bleeding grade I–II was observed in 34% of patients, usually starting 6 months after treatment and lasting for 1 or 2 years and not requiring treatment. After local excision, postoperative grade III toxicity was recorded in three patients (pain in two and bleeding in one). One patient had a long-lasting deep ulceration in the anterior rectum, and one presented an irregular scar, making clinical surveillance difficult. No special grade III toxicity was observed after the two TME salvage surgeries.

3.4.1. Bowel function

At the last follow-up in 64 patients with organ preservation and who were free from rectal tumour, the MSKCC score was excellent in 30, good in 20, fair in 12 and poor in two. The LARS score in 25 patients was good in 20, average in four and poor in one.

3.5. Some prognostic factors

Some prognostic factors were outlined: in 27 patients with T2 $\leq$ 3 cm in diameter treated with CXB first, tumour response on day 28 was cCR in 16 and ncCR in 11. There was no PR. All 27 patients achieved local control after full combined treatment and preserved their rectum. Two developed distant metastases. No difference between the three centres was noted in terms of classification at the baseline, tumor response, local recurrence or metastasis. Two parameters where significantly correlated with local recurrence estimate at 3 years. Tumour size, $\leq$ 3 cm: 8.5% (95% CI: 0–11) vs $>$ 3 cm: 13% (95% CI 0.26–26) $p = 0.04$ and T classification, T2: 3% (95% CI: 0–8) vs T3: 20% (95% CI: 1–35) (Appendix).

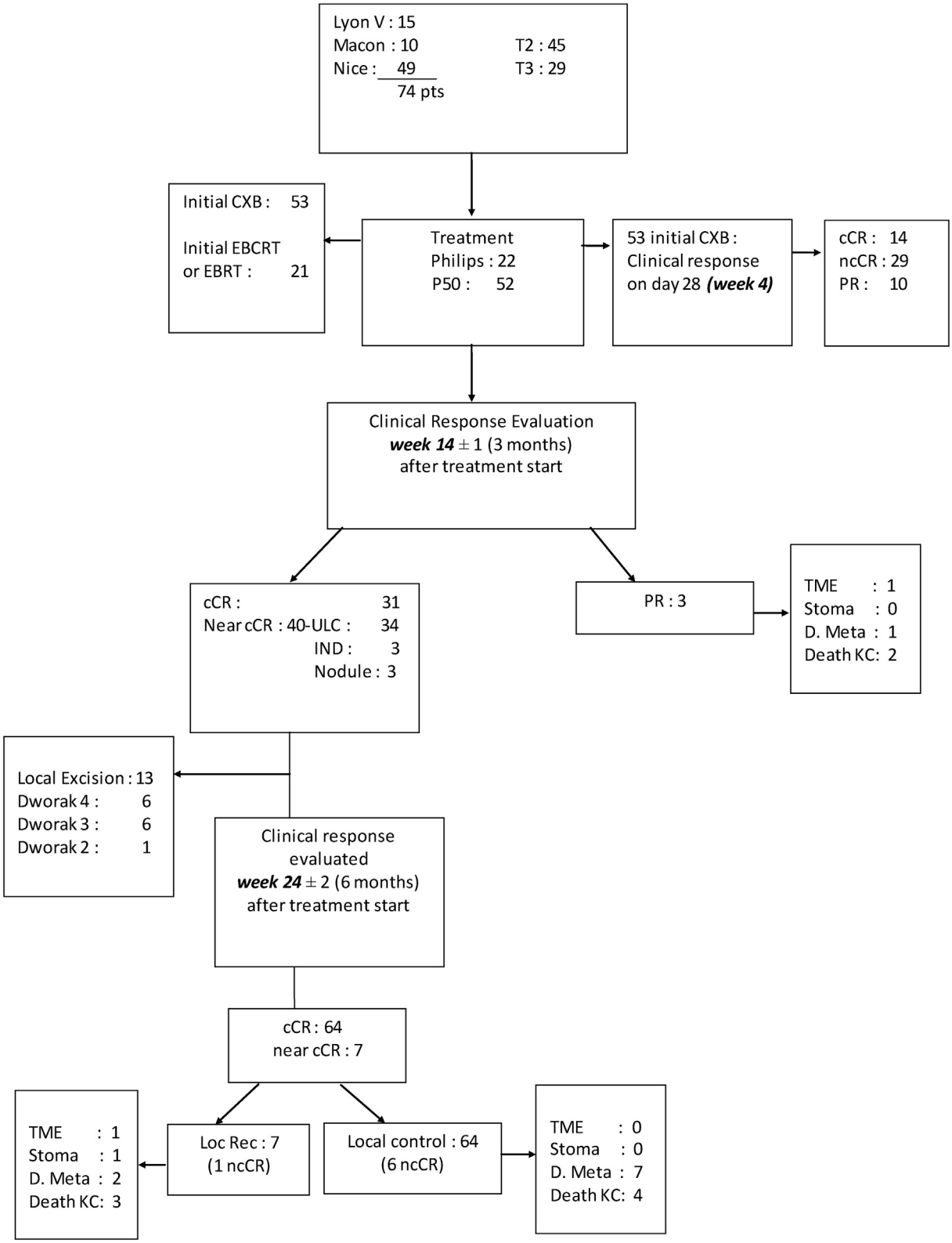


Fig. 2. **Patient care pathway**. Lyon V, Lyon-Villeurbanne; CXB, contact X-ray brachytherapy; EBRCT, external beam radiochemotherapy; EBRT, external beam radiotherapy; P50, Papillon 50 ^{TM} machine; cCR, clinical complete response; ncCR, near-clinical complete response; PR, partial response; ulc, ulceration; Ind, induration; TME, total mesorectal excision; D Meta: distant metastasis; KC, cancer; Loc Rec, local recurrence.

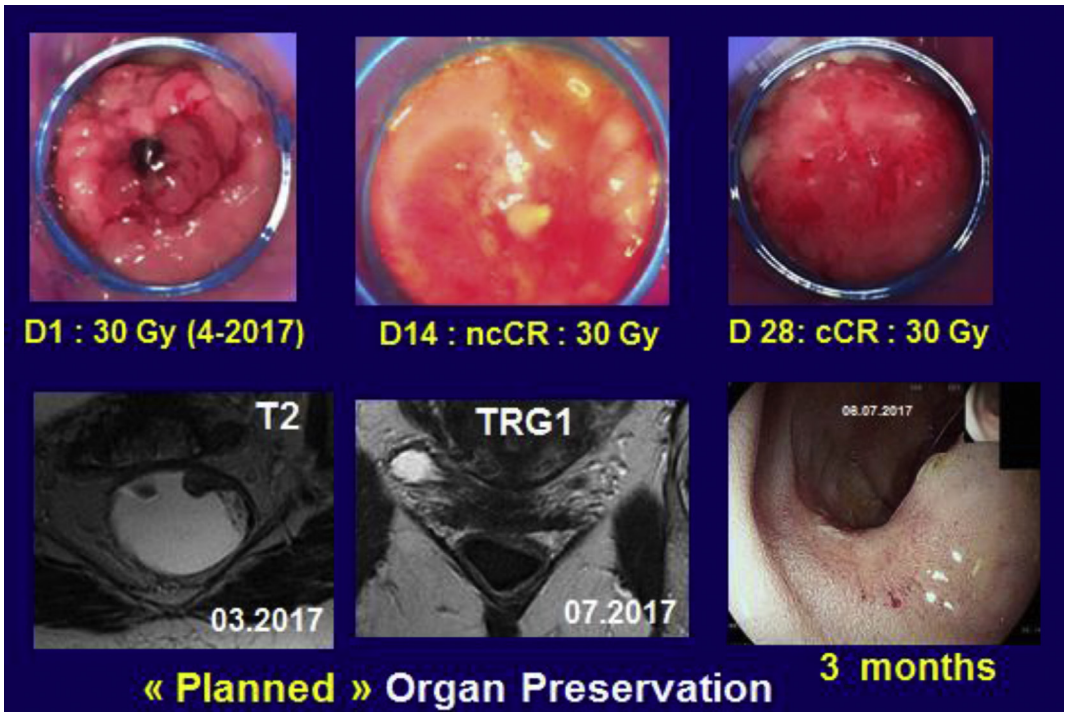
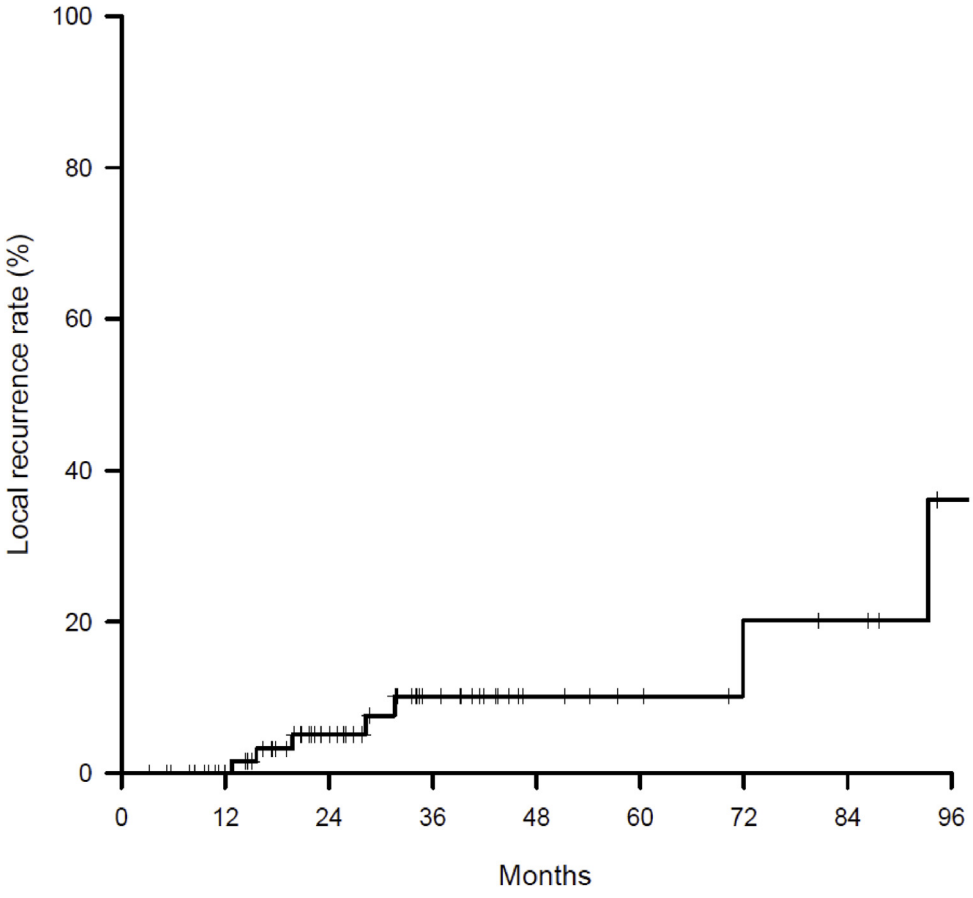


Fig. 3. **Illustration of a planned organ preservation with cCR on day 24**. A 47-year-old female patient presenting a 2.5-cm cT2N0 adenocarcinoma in the distal anterior rectum (D1). On day 14 (after CXB: 30 Gy on day 1), the tumour has disappeared, and a small (0.3 cm) superficial ulceration is visible (ncCR). On day 28, after a second dose of 30 Gy on day 14, the rectal wall is supple on DRE, and no tumour can be seen. There is normal rectal mucosa with moderate inflammation (cCR). MRI at the baseline in March 2017 showing a T2/N0. Three months after the start of treatment, MRI showing a normal rectal wall (TRG 1) and sigmoidoscopy in July 2017 with no visible tumour and small inflammatory capillaries. Patient alive and well with local control in November 2018. D, day, cCR, clinical complete response, ncCR, near-clinical complete response, TRG, tumour regression grade; CXB, contact X-ray brachytherapy; DRE, digital rectal examination; MRI, magnetic resonance imaging.

4. Discussion

One important finding of this study is the good early and late tolerance at any age of this high-dose radiotherapy. This is explained mainly by the small volume ($\leq$5 cm^3) irradiated using CXB and also with EBRT protecting the small bowel and anal canal. Owing to tumour selection and high-dose well-targeted irradiation to the tumour, a high rate of cCR or ncCR (>90%) was observed with an acceptable rate of local recurrence (<15%) and organ preservation with good bowel function in the large majority of cases. The very low risk of perirectal lymph node relapse tends to show that CRT can sterilise most small perirectal nodal deposits. Main side-effect was rectal bleeding occurring after 1 year in one-third of cases and was related to radiation-induced telangiectasia. This strategy appears to be reproducible as these results are similar in the three participating centres. All patients were well informed and were treated from the outset with organ preservation intent, based on the experience gained in Lyon during the 1990s using the RT50 ^{TM} (Philips, NL) machine [10,11]. Considering the present data, it appears possible to propose to operable patients, after strict tumour selection, a planned organ preservation treatment as a possible alternative to TME radical surgery (Fig. 3). Such a strategy appears to be highly recommended for frail, elderly patients. One advantage, when treating T2 tumours $\leq$ 3 cm to start using CXB first, is the rapid confirmation on day 28 of the high chance of local control when a cCR (or ncCR) is observed. Long surveillance is mandatory as local recurrences may occur late.

This study comprises many limitations. The cohort of patients is still small and the follow-up short. Selection bias is always possible in a non-randomised cohort series. Use of MRI was heterogeneous, but all patients underwent either MRI and/or ERUS. Treatment was also inhomogeneous. The dose of CXB was adapted to the tumour response, and concurrent chemotherapy was omitted in frail, elderly patients. All patients were treated using CXB with some form of EBRT. The standardisation of clinical tumour response as cCR or ncCR is not yet general practice and is clinician dependent. MRI was not performed for re-evaluation in every patient, and the TRG score may remain controversial. The same is true for bowel function scores.



Time (months)	0	12	24	36	48	60	72	84	96
Number of patients	74	64	44	25	14	11	8	7	3
Number of events	0	0	3	2	0	0	1	0	1
Number of censored	0	10	17	17	11	3	2	1	3
Recurrence rate	0	0	0,05	0,10	0,10	0,10	0,20	0,20	0,37
95% CI lower	0	0	0	0,01	0,01	0,01	0	0	0
95% CI upper	0	0	0,11	0,19	0,19	0,19	0,38	0,38	0,62

Fig. 4. **Local recurrence cumulative rate**. CI, confidence interval.

Interestingly, similar results have recently been published in British centres using the same Papillon 50™ system [19–21]. Also, the main limitation to a wider use of CXB is the lack of experience in rigid rectoscopy among radiation oncologists and the limited number of CXB machines.

Some discussion is called for regarding organ preservation. The definition of cCR and the choice of tools necessary for optimal evaluation remain controversial. For many experts, DRE and endoscopy are the most reliable examinations [22]. Imaging forms part of this evaluation, and MRI is the key method. However, there is also controversy regarding image interpretation and the role of DWI [15,16,23]. For distal rectum T2 tumours, ERUS is considered by some experts to be superior to MRI for distinguishing among T1, T2 or T3a. An international validated consensus on such examinations and definitions would be of interest. After cCR or ncCR, the role of local excision remains controversial. In America and northern Europe, the recommendation in case of cCR is to rely on close surveillance [3,5]. In southern Europe, the consensus is in favour of routine local excision to increase the chances of local control and/or, depending on the ypT

score, to advise TME radical surgery [24,25]. The high surgical morbidity of TME salvage surgery performed after nCRT and local excision has been well demonstrated by the GRECCAR 2 trial [24]. The debate will be difficult to settle without a randomised trial. One must remember that rectal adenocarcinoma is a quite radioresistant tumour and that, even with a high radiation dose and optimal medical combined treatment, tumour sterilisation will remain a challenge. A strong radiobiology principle is that tumour volume is a key parameter of radiosensitivity [26] and that tumours $\geq$ 5 cm (or 40 cm^3) are difficult to sterilise and control without surgery [27,28]. At the present time, in operable patients, selecting 'early tumour' for planned organ preservation could be a good clinical option. The classification used in the European and French guidelines [1,29] dividing T3 into T3a-b and T3c-d appears relevant, and MRI and ERUS are crucial for this type of stratification. Tumour diameter should be measured accurately. As shown in this study, maximum tumour diameter could offer a simple criterion as tumours $\leq$ 3 cm in diameter achieve a high rate of cCR when using CXB first. Combining 'early tumour' selection with CXB treatment provides an opportunity to achieve cCR and long-term local control above 85%. In this situation, it appears possible to inform an operable patient that radical TME surgery could be avoided and that organ preservation can be planned, as for squamous cell anal carcinoma. This selective approach is quite different from the standard watch-and-wait neoadjuvant CRT for locally advanced tumours advising if cCR a so called 'opportunistic' organ preservation. The worldwide reference is the Habr-Gama experience with a CRT extended protocol and optimal results in T2 tumours [27]. Different strategies are being tested in phase III trials to increase the chances of cCR and organ preservation in rectal T2-3 tumours. The European OPERA trial (NCT 02505750) is testing the role of a CXB boost. Other trials are testing dose escalation using Iridium HDR (Morpheus: NCT 03051464) or chemotherapy intensification (GRECCAR 12: NCT 02514278). The STAR-TREC (NCT 02945566) trial is randomising immediate TME surgery versus conservative approach after neoadjuvant treatment to assess a possible detrimental effect of conservative treatment on survival with an increased risk of local relapse and distant metastases.

In conclusion, organ preservation is a field of active clinical research in rectal cancer with many pending questions. Strict selection of early T2 T3 tumours and safe radiation dose escalation using CXB could be an interesting option in operable patients to successfully implement a planned organ-saving approach of this type.

Contributors

J.-P.G., N.B. and R.C. designed the study, provided study patients and treatments and analysed and interpreted the data. K.B., C.D., L.E., J.G., E.B., G.B. and E.F. provided study patients and/or treatments. J.G. and R.S. assembled the data and participated in statistical analysis. J.-P.G. wrote the report. All authors contributed to data interpretation and approved the manuscript.

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Conflict of interest statement

J.-P.G. is a medical advisor to Ariane Medical Systems (UK) manufacturers of the Papillon 50™ machine. Other authors have no conflict of interest.

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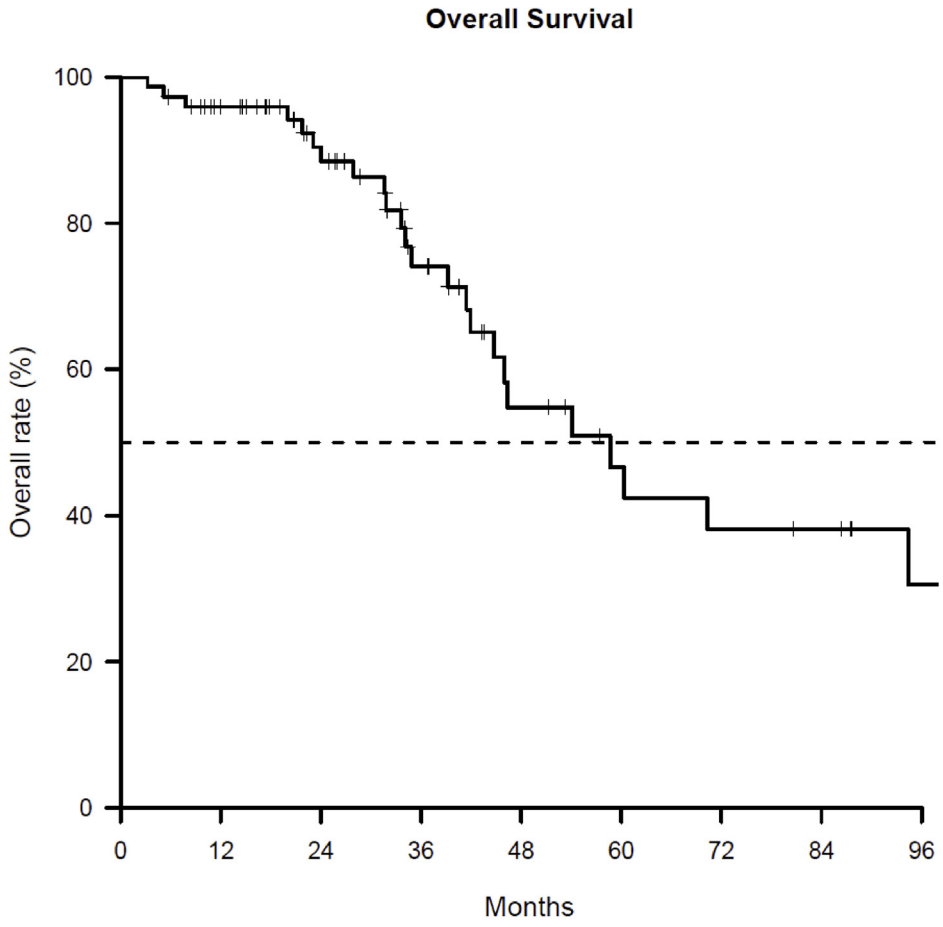
Research in context

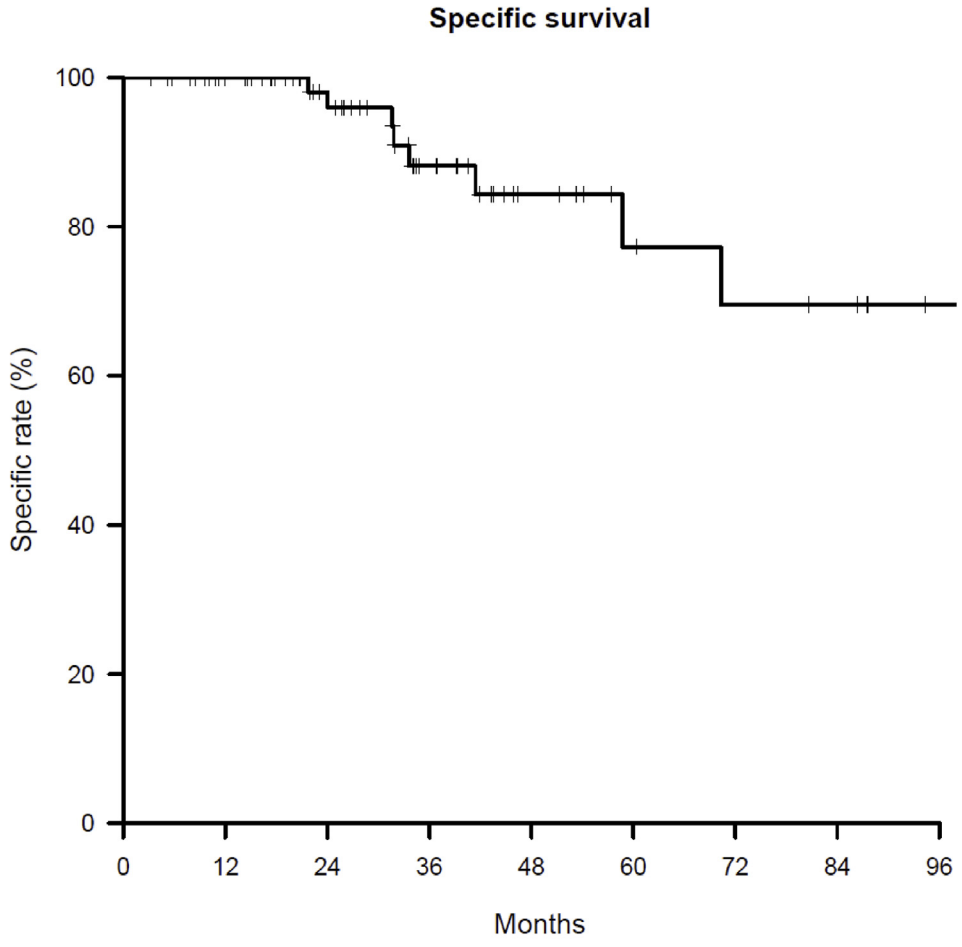
Rectal preservation for T2-3 rectal adenocarcinoma is presently an active field of clinical research. As such, tumours are quite radioresistant when using external beam radiotherapy (±chemotherapy) alone; endoluminal irradiation using contact X-ray brachytherapy (CXB) 50 kV is an attractive approach to increase the radiation dose safely. The Lyon R 96-02 phase III trial has demonstrated, with a long follow-up (10 years), that CXB was able to significantly increase the rate of clinical complete response and sphincter and organ preservation in fit patients. This is the first multicentre study performed by French radiation oncologists with long experience of CXB, treating with organ preservation intent a prospective cohort of T2T3 tumours. Data obtained appear to be of interest in the field of organ preservation and should be consolidated by the ongoing European OPERA phase III trial testing the relevance of such a CXB boost. Other ongoing trials such as GRECCAR 2 and 12, STAR-TREC and Morpheus are addressing similar end-points with different treatment strategies.

Appendix-1



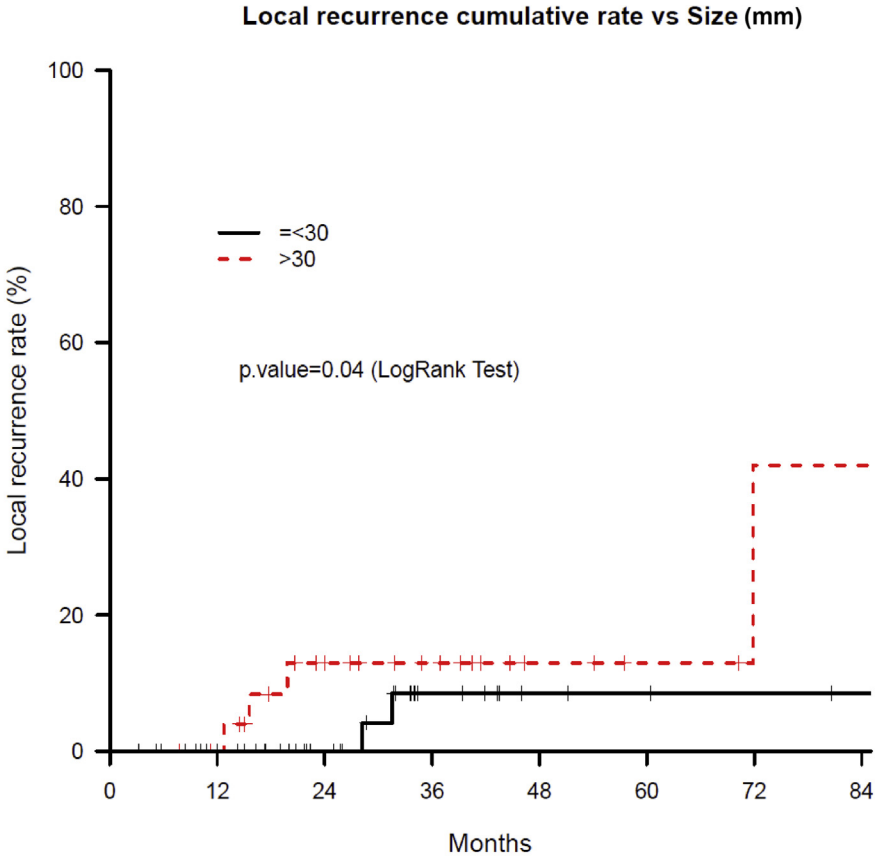
time	0	12	24	36	48	60	72	84	96
n.risk	74	64	47	28	16	11	9	8	4
n.event	0	3	3	7	6	2	2	0	1
n.censor	0	7	14	12	6	3	0	1	3
surv	1	0,959	0,904	0,741	0,548	0,466	0,382	0,382	0,305
upper	1	1	0,981	0,879	0,738	0,677	0,608	0,608	0,578
lower	1	0,915	0,832	0,625	0,407	0,321	0,24	0,24	0,161

Appendix-2



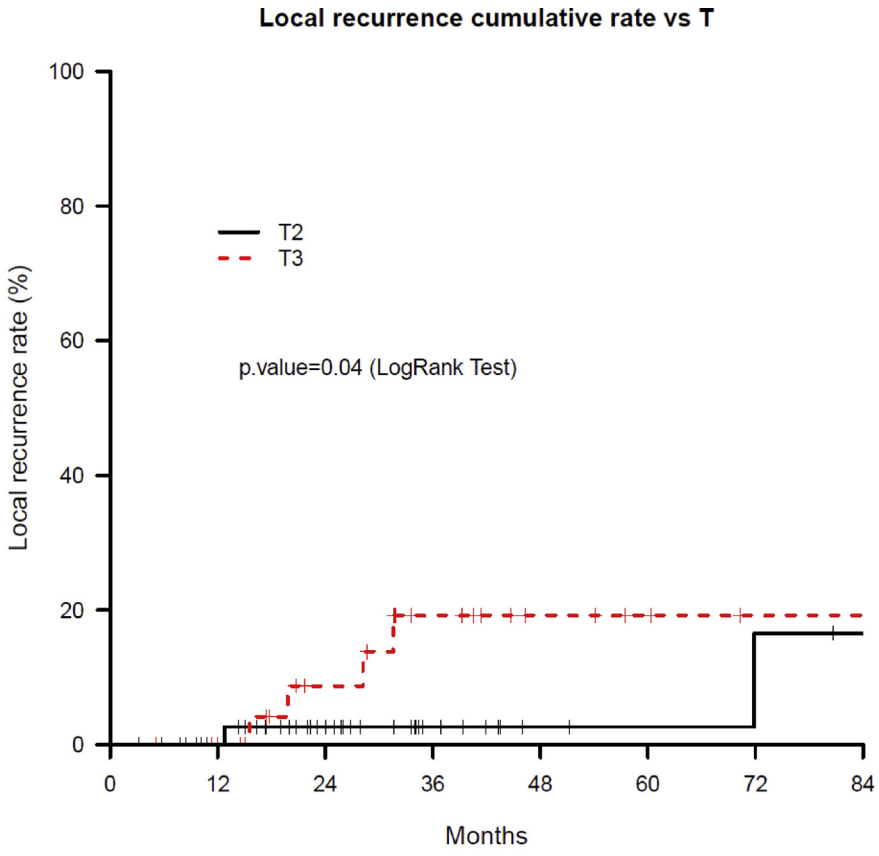
time	0	12	24	36	48	60	72	84	96
n.risk	74	64	47	28	16	11	9	8	4
n.event	0	0	1	4	1	1	1	0	0
n.censor	0	10	16	15	11	4	1	1	4
surv	1	1	0,98	0,881	0,843	0,773	0,696	0,696	0,696
upper	1	1	1	0,986	0,972	0,965	0,942	0,942	0,942
lower	1	1	0,943	0,788	0,732	0,619	0,514	0,514	0,514

Appendix-3



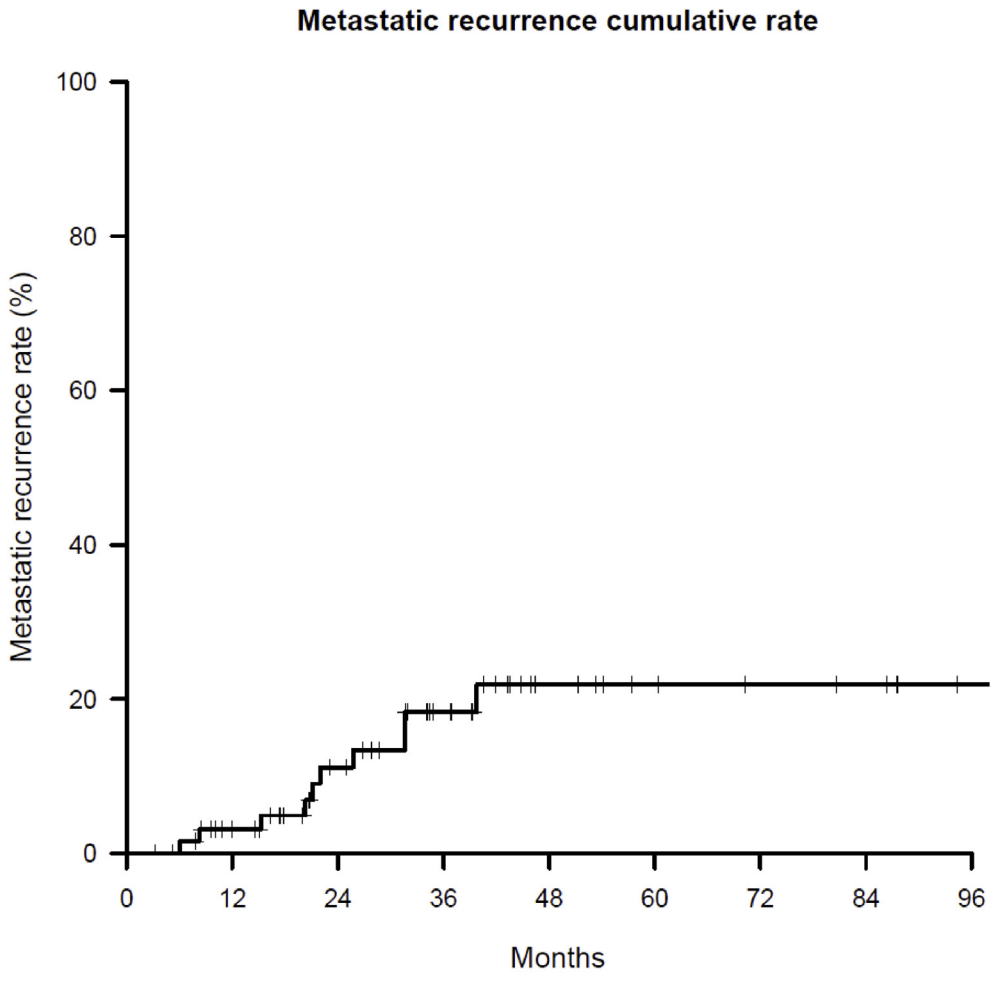
	≤30					>30				
Time (months)	0	24	36	60	84	0	24	36	60	84
Number of patients	47	27	13	7	5	27	17	12	4	2
Number of events	0	0	2	0	0	0	3	0	0	1
Number of censored	0	20	12	6	2	0	7	5	8	1
Recurrence rate	0	0	0,09	0,09	0,09	0	0,13	0,13	0,13	0,42
95% CI lower	0	0	0	0	0	0	0	0	0	0
95% CI upper	0	0	0,20	0,20	0,20	0	0,25	0,25	0,25	0,75

Appendix-4



	T2					T3				
Time (months)	0	24	36	60	84	0	24	36	60	84
Number of patients	45	26	14	7	5	29	18	11	4	2
Number of events	0	1	0	0	1	0	2	2	0	0
Number of censored	0	18	12	7	1	0	9	5	7	2
Recurrence rate	0	0,03	0,03	0,03	0,17	0	0,09	0,20	0,20	0,20
95% CI upper	0	0	0	0	0	0	0	0,01	0,01	0,01
95% CI lower	0	0,08	0,08	0,08	0,39	0	0,20	0,35	0,35	0,35

Appendix-5



Time (months)	0	12	24	36	48	60
Number of patients	67	57	41	27	15	11
Number of events	0	2	4	3	1	0
Number of censored	0	8	12	11	11	4
Recurrence rate	0	0,04	0,12	0,19	0,22	0,22
95% CI upper	0	0	0,02	0,07	0,08	0,08
95% CI lower	0	0,07	0,2	0,29	0,34	0,34

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