



Propensity score analysis of radical proctectomy versus organ preservation using contact X-ray brachytherapy for rectal cancer

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ABSTRACT

Introduction: Radical proctectomy (RP-TME) with neo adjuvant chemoradiotherapy (nCRT) remains the standard treatment for T2-T3 rectal cancer. Organ preservation (OP) using CRT and a “watch and wait” strategy (W&W) is a field of research. Planned organ preservation can be proposed for early T1-T3 using contact X-ray brachytherapy (CXB). We compared the oncological outcomes of both approaches using a propensity score matched-cohort analysis.

Material and methods: For comparative analyses between patients with nCRT + RP-TME and patients with CXB + CRT, propensity scores were calculated with logistic regression and multiple imputations for missing data. The variables included in the propensity score model were PS status, T-N stage and rectal circumference extension. Patients were matched 1:1 using the *nearest neighbor* method with a 0.1 caliper restriction. The 5-year Cancer Specific survival was the primary end point.

Results: The Accord 12 phase III trial included 584 patients who treated with nCRT + RP-TME. The CXB cohort included 71 patients with a planned OP. To select OP patient candidate, T4, tumor with extension >66% circumference were eliminated and only patients treated with CXB + CRT were analyzed in the CXB cohort resulting in a total of 374 patients. A one to one paired cohort with 36 patients in each group was derived. These two cohorts were well matched for all confounding factors except for age. The 5-year cancer specific rate showed no significant difference between the two groups (89% in Accord 12 vs 82% in CXB; $p = 0.84$). At 5 years, rate of metastasis (15% vs 22%, $p = 0.54$) showed no significant difference. In the CXB group 33/36 patients preserved their rectum.

Conclusion: The organ preservation strategy using CXB boost yielded a 5-year cancer specific survival rate similar to patients treated with RP-TME. In selected early T2-3 rectal adenocarcinoma an organ preservation strategy could be offered as a reasonable option.

Introduction

Organ preservation for rectal cancer is a field of increasing interest [1–5]. As rectal adenocarcinoma is quite resistant to radiotherapy [6] an intra-cavitary brachytherapy approach appears to offer an interesting option to achieve a good therapeutic ratio [7–10]. Contact X-ray brachytherapy (CXB) has been used in early rectal tumors with promising results [11]. The Lyon R96-02 phase III trial, for operable T2 T3

tumors treated using preoperative external beam radiotherapy (EBRT), showed that a CXB boost was able to increase clinical complete response (cCR) and sphincter and also organ preservation [12]. The phase III Opera trial (NCT 02505750) is aimed at improving organ preservation in T2 T3a-b < 5 cm diameter [13]. Presently, after proper early tumor selection, CXB combined with chemo-radiotherapy (CRT), in a planned organ preservation strategy, can achieve long term local control without radical proctectomy (RP-TME) in almost 80% of cases with good bowel

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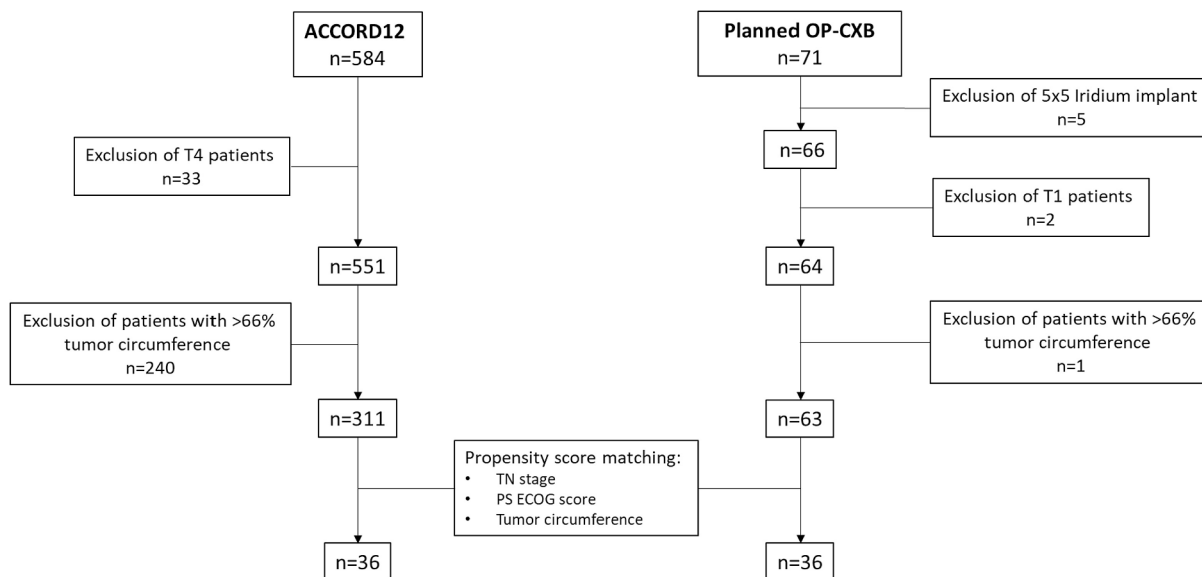


Fig. 1. Study Flow Diagram.

Table 1
Demographic and clinical characteristics among the 72 matched patients by treatment group.

	Accord12 (n = 36)	CXB (n = 36)	P value
Gender – no. (%)			0.631
Male	20 (55.6)	23 (63.9)	
Female	16 (44.4)	13 (36.1)	
Age (years)			< 0.001
Median [range]	64 [41–79]	77.5 [39–93]	
Performance status – no. (%)			1
0	19 (52.8)	19 (52.8)	
1	17 (47.2)	17 (47.2)	
Pretreatment T stage – no. (%)			1
cT2	16 (44.4)	16 (44.4)	
cT3	20 (55.6)	20 (55.6)	
Pretreatment N status – no. (%)			1
cN0	26 (72.2)	25 (69.4)	
cN1/cN2	10 (27.8)	11 (30.6)	
Histological grade – no. (%)			0.169
Well differentiated	12 (33.3)	17 (47.2)	
Moderately differentiated	16 (44.4)	11 (30.6)	
Poorly differentiated	1 (2.8)	0 (0)	
Other	2 (5.6)	6 (16.7)	
Unknown	5 (13.9)	2 (5.6)	
Tumor site – no. (%)			1
Low rectum (<=6cm)	27 (75)	27 (75)	
Middle rectum (>6cm)	9 [25]	9 [25]	
Tumor diameter – no. (%)			0.169
< 3 cm	4 (11.1)	10 (27.8)	
>= 3 cm	30 (83.3)	26 (72.2)	
Unknown	2 (5.6)	0 (0)	
Tumor circumference – no. (%)			1
<50	25 (69.4)	26 (72.2)	
>=50	11 (30.6)	10 (27.8)	

function [7]. Given the lack of high evidence that such a conservative strategy is not detrimental to overall survival on account of an increased risk of local recurrence, we aimed to address this question using a matched- treatment analysis comparing oncological outcomes between a cohort of patients treated with planned organ preservation using CXB + CRT and a cohort of patients treated using a similar preoperative CRT and RP-TME within the ACCORD 12 phase III study (NCT 00227747)

Table 2
Treatment characteristics of the 72 matched patients by treatment group (EBRT/CXB).

	Accord12 (n = 36)	CXB (n = 36)	P value
Received radiotherapy dose (Gy) median [min–max]	50 [44–50]	50 [22–50]	0.839
Received X-ray dose – no. (%)	NA		NA
<60		4 (11.1)	
60–79		2 (5.6)	
80–110		28 (77.8)	
>110		2 (5.6)	
Chemotherapy regimen – no. (%)			< 0.001
Capecitabine only	16 (44.4)	27 (75)	
Capecitabine + Oxaliplatin	20 (55.6)	1 (2.8)	
No chemotherapy	0 (0)	8 (22.2)	
Adjuvant chemotherapy receive – no. (%)			0.028
No	28 (77.8)	28 (77.8)	
Yes	6 (16.7)	0 (0)	
Unknown	2 (5.6)	8 (22.2)	

Table 3
Clinical response rate after matching (72patients) in the Accord 12 cohort before radical surgery (3A) and in the CXB cohort 1–2 months after end of irradiation (3B).

A	
Accord12 (n = 36)	
Tumor response – no. (%)	
Complete response	3 (8.3)
Partial response	23 (63.9)
Stabilisation	6 (16.7)
Unknown	4 (11.1)
B	
CXB (n = 36)	
Clinical best response – no. (%)	
CCR	32 (88.9)
nCCR	3 (8.3)
PR	1 (2.8)

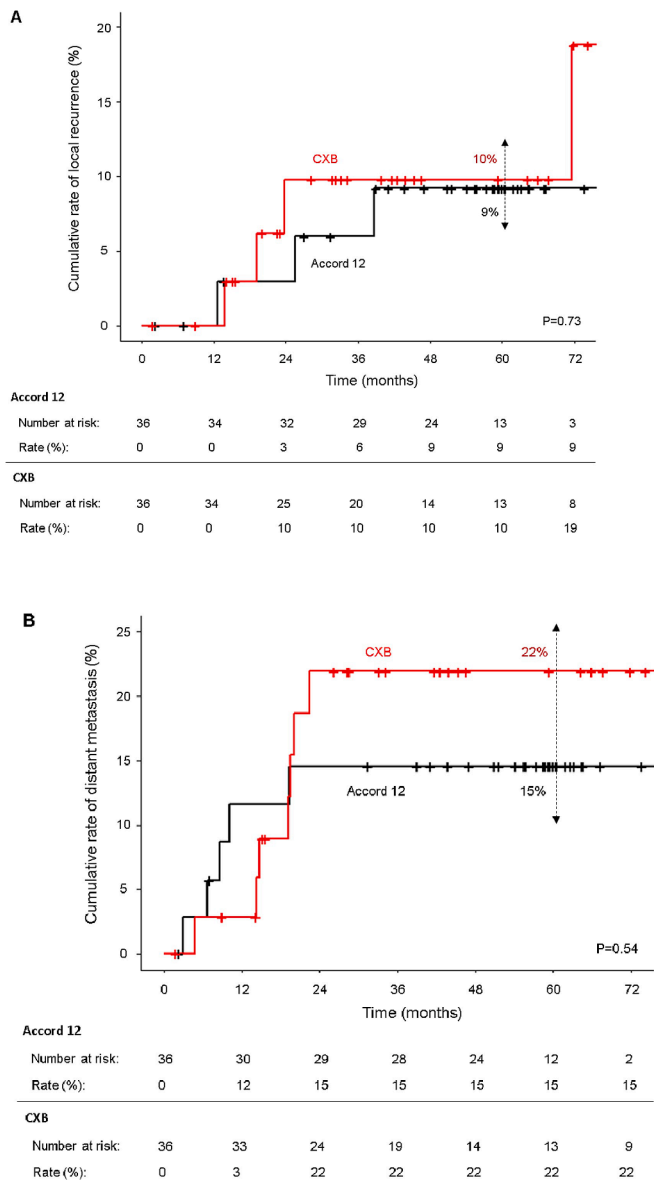


Fig. 2. Cumulative rate of Local recurrence (2A) and Distant metastasis (2B) among the 72 matched patients.

[14,15].

Patients and methods

Study design and participants

We performed a propensity -score matched observational analysis using the anonymous databases of two cohorts of patients treated in France within the same Unicancer working group. This analysis was a real-world observational clinical practice study including patients with adenocarcinoma T1-4 N0-2 M0 of the distal and middle rectum and treated within the framework of the Accord 12 phase III trial [12] or using CXB at the Centre Antoine Lacassagne (CAL) in Nice [16]. This study was approved by the Research board of the CAL.

The Accord 12 trial included 584 operable patients between 2005 and 2008. Between 2002 and 2018, 177 patients received CXB for rectal cancer in Nice and are prospectively registered in the institution’s Contem Data Base [16]. These patients were stratified in four different groups: 1) 42 patients managed first with local excision for polyps or T1N0 adenocarcinoma and treated with adjuvant CXB (±EBRT) for

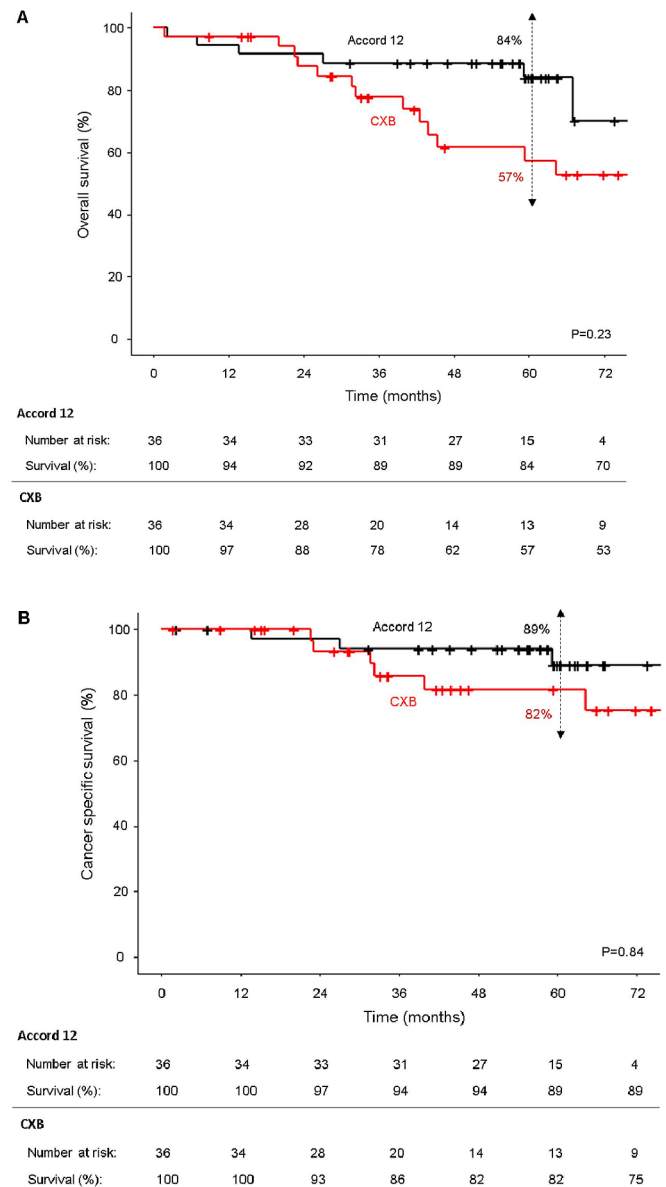


Fig. 3. Overall survival (3A) and Cancer specific survival (3B) among the 72 matched patients.

pejorative pathological features; 2) 71 patients fit or not for surgery presenting T1-2-3 N0-1 M0 tumors treated with a planned organ preservation strategy because the tumor volume was compatible with a reasonable chance of cCR and long term local control using CXB and CRT; 3) 43 patients with distal T3 N0-1-2 M0 > 3 cm diameter treated with CXB + CRT and elective RP-TME in order to increase the chance of sphincter preservation: Lyon R96-02 trial (12–16); 4) a miscellaneous group (21patients) where CXB was used for local recurrence, previous pelvic EBRT, metastatic rectal tumor, various histologies (melanoma, squamous cell carcinoma) or palliative goals. Only the 71 patients treated with planned organ preservation were considered for this analysis.

For this propensity score 33 patients were eliminated from analysis in the Accord 12 cohort: T4 tumors and tumors with circumferential extension >66%. These locally very advanced tumors would not have been candidates for organ preservation due to their large volume. A total of 311 patients from the Accord 12 cohort were analyzed. In the CXB cohort, out of the 71 patients in the planned organ preservation group, in order to ensure similar treatments to the Accord 12 cohort, we

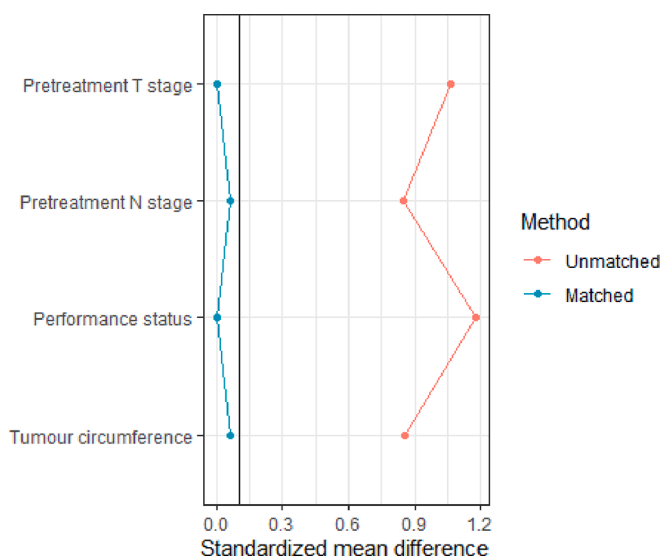


Fig. A1. Propensity score diagram.

eliminated 2 patients with T1 tumors treated with CXB alone, 3 patients treated with short course EBRT regimen (5x5 Gy) and 2 patients with interstitial iridium brachytherapy [7]. Another patient with circumferential extension >66% was eliminated. Patients treated using local excision after CXB + CRT were retained in the analysis. A total of 63 patients were included. Among these 374 patients (311 + 63) a propensity score was performed to match the following variables: PS score (age could not be matched), T and N classification, circumferential extension. A total of 72 comparable patients were analyzed in two cohorts of 36 patients in each group (Fig. 1).

These two cohorts (Accord12: 311 and CXB: 63) displayed important points of similarity. In both cases the prime investigator was the same (JPG). The staging was performed for all patients with the same clinical approach always using DRE, endoscopy, MRI and/or EUS for local staging and CT-scan for distant metastases. The screening used the same TNM UICC classification. The site of the tumor was the same (distal and middle rectum). The definition of endpoints was similar for post-treatment clinical and pathological response, for local recurrence and for most clinical outcomes. Data collection used similar case report forms for tumor classification, tumor response assessment and clinical outcome. Quality control of the data base for the Accord 12 cohort was performed within the data management of this randomized trial while for the CXB cohort the data based was prospectively controlled and included in the IWWD database [17].

Procedures-treatments

In the Accord 12 cohort, patients were treated using two neoadjuvant chemo-radiotherapy regimens: CAP 45 (EBRT 45 Gy/25 fractions/ 5 weeks + capecitabine 800 mg/m² BID on radiation day) and CAPOX 50 (EBRT 50 Gy/25 fractions/5 weeks + same capecitabine + oxaliplatin 50 mg/m² once weekly). A radical proctectomy (RP-TME) was performed in all patients after an interval of 5 (±1) weeks. The primary endpoint of this trial was complete sterilization of the operative specimen. Clinical response, local recurrence, distant metastases, survival and toxicity were secondary endpoints. Definition of cCR was no tumor felt on DRE, no tumor seen on endoscopy and no tumor or only moderate fibrosis when MRI was performed. A ncCR was the presence of a small residual ulcer with smooth edge or minor induration on DRE and non-suspicious MRI as in cCR. Partial response was obvious visible or palpable residual tumor. All the results have been published with a 5 years follow-up [14,15].

In the CXB organ preservation cohort, like in the OPERA trial [13],

patients were treated with a combination of CXB (80–110 Gy in 3–4 fractions) and CRT, usually the CAP 50 regimen (or EBRT alone: 45–50 Gy/5 weeks). CXB was given first in tumors ≤3 cm in diameter and in T3 > 3 cm in diameter CRT was the initial treatment. A local excision was performed in some individuals after irradiation. Results of this cohort have been published [7–18]. Treatments are presented in Table 1. In both cohorts EBRT irradiation was delivered into a “small pelvic volume” not exceeding 1 L with the upper limit of the CTV kept below S1/S2 junction for tumors of the midrectum and below S2/S3 for distal tumors. A 3D conformal technique or IMRT technique was used with 6–20 mV X-ray beam energy.

Response assessment was done using validated criteria [1,4,11,12]. MRI using TRG score has been routine since 2012. In the Accord 12 cohort clinical response was assessed before surgery and in the CXB cohort between one or two months after end of irradiation. Definition of cCR was: no visible or palpable tumor. ncCR (non-suspicious residual ulcer, induration or mucositis) was considered and managed as cCR. During the first three years, patients with conservative management underwent surveillance every 3–4 months using DRE, endoscopy and MRI. Local recurrence was any relapse after (n)cCR in the rectal wall (regrowth), mesorectum or posterior pelvis.

Outcomes

The primary endpoint of this propensity score study was five-year cancer specific survival rate defined as the length of time between date of treatment start or randomization and date of death due to cancer. Patients who were still alive at time of analysis or dead from causes other than cancer were censored at time of last news. As the cause of cancer death in rectal cancer is mainly metastatic spread we estimated the rate of distant metastasis and the rate of local recurrence.

Statistical analysis

We compared patients and tumor characteristics at baseline using the Wilcoxon test for continuous variables and Chi2 or Fisher test for categorical variables.

After first selection for organ preservation criteria we analyzed a total of 374 patients (Accord 12: 311; CXB: 63)

To address the imbalance of confounding variables between these two selected cohorts (374 patients) and to minimize these differences and their impact on clinical outcomes, a 1:1 ratio propensity score was performed with a 0.1 caliper restriction (Austin PC). The variables included in the propensity score model were T-N classification, PS ECOG score and circumferential rectal extension. After matching, the standardized mean differences (SMD) were under 10% for all variables included in the propensity score (Appendix Fig 4).

We constructed Kaplan-Meier curves for all time-to-event endpoints taking zero as the randomization date for the Accord 12 cohort and date of first treatment for the CXB cohort, and estimated survival rates with corresponding 95% confidence interval (CI). Difference between groups was assessed using the Log-rank test. The Cox proportional hazards model was used to calculate hazard ratios and 95% CI.

A two-sided p value of less than or equal to 0.05 was considered as statistically significant. All analyses were performed using R.3.6.1 software on Windows®.

Results

Between 2005 and 2008, 584 patients were included in the Accord 12 trial in 56 French institutions and 311 met the inclusion criteria (for planned organ preservation) and constituted the final study Accord 12 group. At the CAL Nice between 2002 and 2017 a total of 177 patients received CXB. Among them 71 were treated with a planned organ preservation strategy. After elimination of 8 patients to have treatment and tumor classification similar to the Accord 12 group, 63 were

retained in (Fig. 1) (Table 1).

Patient demographic and clinical characteristics of these 374 patients are presented in Table 2. Patients in the CXB group were older and had more comorbidities.

Among the 311 patients in the Accord 12 group, cCR was observed before surgery at week 5 (± 1) after the end of CRT in 15/311 (5%) (Appendix Table 2). With a median follow-up time of 61 months the 5-year overall and cancer specific survival rates were 83% [95% CI: 79–87] and 86% [95% CI: 82–91] (Appendix Fig. 1). The 5-year cumulative rate of local recurrence and distant metastases were respectively 6% [95% CI: 3–9] and 23% [95% CI: 18–28] (Appendix Fig. 2). After a median follow-up of 54 months, the 63 patients in the CXB group had a 5-year overall and cancer specific survival of 50% [95% CI: 37–68] and 80% [95% CI: 68–95] (Appendix Fig. 1) respectively, and a 5-year cumulative rate of local recurrence and distant metastases of 18% [95% CI: 6–28] and 24% [95% CI: 11–35] (Appendix Fig. 2).

We derived one-to-one paired cohorts (36 patients in each group) for RP-TME (Accord 12 group) versus organ preservation (CXB group). These cohorts were well-matched for their confounders -i.e. T and N classification, PS score and circumferential extension (Table 3). After matching, differences remained for age. We compared these 72 included patients with those who were excluded from the matched analysis (275 in Accord 12 and 27 in CXB) (Appendix Table 1), and noted that the matched CXBs (36) were representative of the whole CXB cohort (63).

A clinical response assessment was possible at 5 weeks after the end of CRT in 32 patients in the matched Accord 12 group with cCR in 3/32 (9%) and in the matched CXB group a (n)cCR, 1 or 2 months after end of irradiation, was seen in 35/36 (97%) (Appendix Table 3).

Out of these 35 patients with cCR, local recurrence was seen in 4 patients, in one case occurring after 5 years and in 3 cases (always intramural) before 3 years. Out of the 36 CXB patients, 3 underwent a RP-TME during the first 5 years (8%). The 5-year cumulative rate of local recurrence was not significantly different between the Accord 12 and CXB groups with respectively 9% [95% CI: 0–19] vs 10% [95% CI: 0–20] and with a Hazard ratio (HR): 1.3 [95% CI: 0.28–6; $p = 0.73$] (Fig. 2) and similarly for the 5-year distant metastases rate at, respectively, 15% [95% CI: 2–26] vs 22% [95% CI: 6–35]; HR: 1.4 [95% CI: 0.45–4.5; $p = 0.54$] (Fig. 2).

The 5-year cancer specific survival rate for all 72 patients was 86% [95% CI: 77–96] with no significant difference between the Accord 12 group: 89% [95% CI: 78–100] and the CXB group: 82% [95% CI: 68–98]; HR: 1.1 [95% CI: 0.34–3.8; $p = 0.84$] (Fig. 3). Five-year overall survival rate was better in the RT-TME group 84% [95% CI: 72–99] vs 57% [95% CI: 41–80]; HR: 1.7 [95% CI: 0.7–4.2; $p = 0.23$] (Fig. 3).

Discussion

In this matched cohort of 36 patients, presenting T2-3 $\leq 66\%$ circumference N0-1 rectal adenocarcinoma managed by planned organ preservation using CXB boost, a total of 35 patients (97%) achieved (n) cCR and 33 (92%) were able to preserve their rectum without significant loss of oncological safety over 5 years follow-up. At 5 years the cumulative rates of local recurrence and distant metastases were respectively 10% and 22%. As median age was different between the CXB cohort and the matched Accord 12 cohort, cancer specific 5-year survival was taken as the main endpoint and showed no difference between the two cohorts (82% and 89%, $p = 0.84$) [25].

This study has limitations. The small number of patients is the major limitation. Tumor response in Accord 12 trial was evaluated earlier than in CXB group with no definition for nCR. Adjuvant chemotherapy was never given in CXB cohort (Appendix Table 4). Difference in age was impossible to eliminate between the two groups. In both studies the first patients were included (2002–2005) a long time ago in a period where MRI was not fully standardized. This could have influenced the response assessment. The CXB cohort is a single center study.

A propensity score was published by Renehan comparing the

oncological outcomes of 109 patients (median follow-up 33 months) treated after cCR using a W&W approach with a matched group of 109 patients receiving preoperative chemoradiotherapy followed by RP-TME. Local recurrence was noted in 34% in the W&W group whereas the 3-year non-regrowth disease-free survival showed no significant difference (88% in W&W vs 78% in the RT-TME group; $p = 0.043$). Similarly no difference was noted in 3-year overall survival (96% in W&W vs 87% in RP-TME; $p = 0.024$). The conclusion was that avoiding colostomy was possible without loss of oncological safety [3].

Wang recently published another propensity score analysis comparing 188 patients all achieving cCR after nCRT. One group (94) underwent a W&W strategy and the other (94) a RP-TME. In the W&W group there were 14 local recurrences and 9 distant metastases and in the RP-TME group, there were 1 local recurrence and 11 metastases. The 3-year non-regrowth disease-free survival was 98%, identical between the two groups, thus suggesting that the W&W strategy was safe [19].

One difference must be highlighted between our study and the two previous studies. In these two latter, patients were included in the W&W group only if they were in cCR after preoperative CRT whatever the initial stage. Conversely in the present study, patients were included in the CXB group before any treatment if deemed good candidate for “planned” organ preservation based on small tumor volume selection. When considering cCR patients alone we are usually unaware of the initial number of patients undergoing neoadjuvant CRT and the overall benefit of this “opportunistic” W&W strategy may remain uncertain [20].

In observational studies reporting W&W strategies the local recurrence rate varies between 5% and 60% and the metastases rate between 6% and 30% being more elevated in cases of local recurrence [21]. In elderly and comorbid patients the competing effects of oncological and surgical risk may argue in favor of a W&W approach as a safe alternative [23].

Estimation of conditional survival using the large IWWD (International Watch and Wait Database) in 768 patients has suggested that after sustained cCR for 3 years the risk of late local recurrence does not exceed 5% [22].

Smith compared 136 patients with RP-TME and ypCR after nCRt and 113 patients with cCR and W&W. At 5 years overall survival was 73% in W&W vs 94% in ypCR with a higher rate of distant metastasis in W&W [21]. In the OPRA study a NOM was possible in up to 60% of patients with no 3-year Disease-Free-Survival difference when compared with historical series [4].

Socha et al. made a systematic review of literature to estimate the additional risk of distant metastasis attributable to omission of radical surgery and increased local recurrence rate. After reviewing 17 studies including 1387 patients treated using a W&W strategy they concluded that this additional risk was low with a maximum risk at 5 years of 6.5% (risk between 0 and 6.5%) [24].

In a randomized trial [5] including T2-T3 ≤ 4 cm diameter, Rullier compared after neoadjuvant CRT in good responder a conservative treatment using local excision vs RP-TME. At 5 years there was no difference on survival (85%) between the two groups and organ preservation was possible in 37% of cases in the local excision group.

An overview of all these studies tends to show that the additional risk of distant metastasis after W&W strategy remains low. A higher level of evidence for the oncological safety of the W&W approach is unlikely in a near future in the absence of a phase III trial comparing RP-TME to W&W strategy. With more time and more data, W&W could become a standard (after cCR in selected early T2T3) as happened 30 years ago, without any phase III trial, for the radiosensitive squamous cell carcinoma of the anus. In order to optimize this approach, a more detailed tumor staging is needed at baseline (e.g., T3 abcd, tumor diameter and circumferential extension, tumor type: exophytic or fungating).

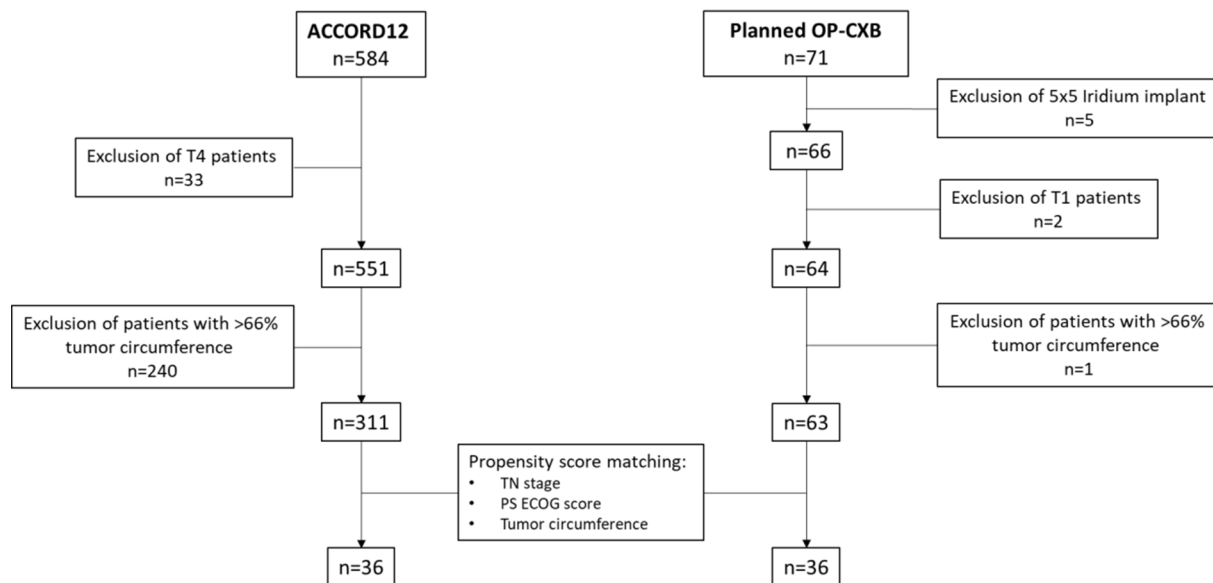
Conclusion

This study shed additional light on the difficult question of the oncological safety of the W&W strategy. It suggests that, if a proper selection of patients presenting small volume tumors is performed and a high dose of irradiation using endocavitary boost is given, the risk of a detrimental oncological event is low and that the toxicity/benefit ratio of this planned organ preservation appears reasonable especially in frail patients. These findings can inform the decision-making process at the initial stage and support organ preservation as a good option to be discussed within MDT and with informed patients.

Appendix

Fig. A1

The standardized mean differences were calculated for all variables included in the propensity score before and after matching to assess the effect of pairing on imbalance. A 10% standardized difference was considered as the limit of a correct balance.



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