Aims of Combined Modality Therapy in Rectal Cancer (M0)

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Abstract

Optimizing the Cost/benefit ratio of treatment: Evidence Based The aim of a cancer treatment is always to achieve the maximum of cure rate with a minimum of toxicity and best quality of life at an acceptable cost for the society. It is always a multifactorial challenge depending on the patient, the tumor, the doctor, and the society cultural and financial backgrounds. The goal is to find the best cost/benefit ratio between all possible strategies in agreement with a well-informed patient. In rectal cancer (M0) surgery is the cornerstone of treatment. Combined modality therapies aim at optimizing the cost/benefit ratio of possible strategies and only randomized trials can bring strong evidence regarding their results and recommendations. *Lessons from randomized trials: quite modest* During the past decades many phase III trials have shown that: (1) neoadjuvant treatment even with "TME" surgery was better than adjuvant, (2) chemoradiotherapy (CRT) was better than RT alone, (3) long course CRT was probably more efficient (in terms of ypCR) than short course (25/5), and (4) capecitabine was as efficient as 5 FU but oxaliplatin was not adding benefit. Overall, the gains of nCRT remain modest and it is mainly a reduction in local relapse not exceeding 5 %, but no benefit in survival and neither in sphincter saving surgery has been proven. *The way forwards organ preservation in case of CCR.* Local

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control: can probably be improved for T4 tumors by RT dose escalation. Survival: can be increased by innovative medical treatment either before or after surgery. Toxicity: may be reduced by a less aggressive treatment in elderly. Conservative treatment: A new field of clinical research is to achieve "organ preservation" (and not only sphincter saving). To modify the surgical approach and preserve the whole rectum, neoadjuvant treatment must achieve safely a *clinical complete response*. As rectal adenocarcinoma is a relatively radioresistant tumor endocavitary irradiation (contact X-Ray) is a promising safe approach and this hypothesis will be addressed by the OPERA randomized trial.

Keywords
Rectal cancer · Multimodality therapy · Organ preservation · Conservative treatment

1 Optimizing the Cost–Benefit Ratio of Treatment According to Evidence-Based Medicine

Since Hippocrates the aim of a curative medical treatment is to achieve the most efficient result against the disease and the less toxic effect for the patient. One the first curative treatments for rectal cancer was introduced by Miles in 1908 using "a radical abdomino-perineal resection" (APR) with an acceptable (although high) operative mortality. Since then surgery has been (and will remain) the cornerstone of the treatment of rectal cancer. The modern era of rectal surgery started with the introduction of the so-called "TME surgery" removing the mesorectum along the "holly plane" with sharp dissection under vision control (Heald and Ryall 1986). To improve local control and survival radiotherapy and chemotherapy have been used in association with surgery. Due to the many confounding factors, the results of such combined treatments can be evaluated only using randomized control trial. The ultimate aim is to reach 100 % cure with 0 % toxicity. Most of the new treatments aiming at better local control or survival use radiation dose escalation or more efficient multidrug medical treatments. The main limiting factor to this intensification is the induced toxicity. It is the merit of the "TME surgery" to be at the same time able to achieve a better local control by reducing the breaching of the rectal fascia and a lower toxicity by sparing the latero-pelvic nerves. It is probably the advantage of the laparoscopic approach to reach similar results by reducing further the operative health constraint for the patient (Panis et al. 2011). May be one of the most significant progress in the past decades impacting survival was the dramatic reduction in the rate of operative mortality. Intensive care, improved anesthesia, reduction of radiation toxicity with smaller irradiated volume, and better surgical bleeding and infection control have reduced the 60 days postoperative mortality from 10 % to close to 1 %. Only in elderly, frail patients surgery is remaining a significant trauma (Rutten et al. 2008).

When analyzing the benefits of the various combined multimodality treatments associated to surgery it is crucial to take into consideration the two aspects of the balance (benefit vs. cost) and to include in the cost all the sustainable aspects relevant to the patient, the healthcare system, and the society. Most probably in this subtle equilibrium between benefit and cost, toxicity is the main parameter because it is, since Hippocrates again, the key ethical message of medicine: "Primum non nocere" which in modern language may be assimilated to the "Principe de précaution." In such a complex situation and as the improvements are generally (and unfortunately) small only RCT can bring reliable scientific evidence, which remains the best way leading to changes of practice in the medical community.

2 Recent Results Gained Through Randomized Trials

2.1 Quite Modest Even if Local Recurrence Rate Is Now Below 7 %

Until the end of the twentieth century radical surgery followed by adjuvant chemoradiotherapy (CRT) was the standard treatment for rectal cancer (stage M0) (Conference 1990; Krook et al. 1991; O'Connell et al. 1994) (Table 1). It was the merit of the Swedish and mainly German trials (Folkesson et al. 2005; Pahlman and Glimelius 1990; Frykholm et al. 1993; Sauer et al. 2004, 2012) to demonstrate that neoadjuvant CRT (nCRT) was more efficient and possibly less toxic than adjuvant CRT (Park et al. 2011). As "TME surgery" was introduced in early 2000, it was one of the main conclusion of the Dutch trial to show that even with a "TME surgery" preoperative radiotherapy (short course) was improving local control (Kapiteijn et al. 2001; van Gijn et al. 2011). Other more recent trials demonstrated that nCRT was more efficient for long-term local control than radiotherapy alone (Bosset et al. 2006, 2014; Gerard et al. 2006), that capecitabine was as efficient as Fluorouracile (5FU) (Gerard et al. 2010, 2012; Aschele et al. 2011; Schmoll et al 2013; Roh et al. 2011) that radiation dose escalation using external beam radiotherapy (EBRT) from 45 Gy/5 weeks up to 50 Gy/5w was producing more pathologic sterilization of the tumor (ypCR) without increase in 3-year toxicity, but without other clinical significant benefits (Gerard et al. 2012) and that oxaliplatine was not to be given concurrently with EBRT and Capecitabine (or 5FU) (Schmoll et al. 2013; Roh et al. 2011). As local control is at the present time close to 95 % in T2-3 M0 tumors the only way to improve survival is to find an efficient (and not too toxic) medical treatment. First-line chemotherapy has been proven possible without compromising nRT and surgery (Fernandez-Martos et al. 2010; Chua et al. 2010). With increasing knowledge about the molecular abnormalities driving cell growth, immune reaction, and tumor proliferation various molecular targeted drugs (MTD) have been tested. So far the results have not been totally convincing using as neoadjuvant

Table 1 Overview of some of the main messages and conclusion derived from recent randomized control trials

Study	Regimen	5-year local recurrence (%)	5-year overall survival (%)	Sphincter preservation (%)	Comments
Krook et al. (1991) (1980–1986) $n = 204$	Postoperative radiotherapy (45 Gy) versus postoperative concurrent chemoradiotherapy (45 Gy and 5-FU)	25 versus 13.5 ($P = 0.03$)	48 versus 58	50 versus 50	Postoperative concurrent chemoradiotherapy improves local control and survival; becomes standard treatment
Pahlman and Glimelius (1990), Frykholm et al. (1993) (1987–1990) $n = 908$	Surgery alone versus preoperative radiotherapy (25 Gy in 5 fractions)	25 versus 8 ($P = 0.001$)	55 versus 63 ($P = 0.008$)	44 versus 40	Postoperative death in experimental arm was reduced from 15 to 4 % by reducing the radiation volume ($P = 0.001$)
Marsh et al. (1994) (1982–1986) $n = 284$	Surgery alone versus preoperative radiotherapy (20 Gy in 4 fractions) small field (10 × 10 cm)	36.5 versus 12.8 ($P = 0.0001$)	50 versus 56	48 versus 46	4 MV linear accelerator and small fields in the posterior pelvis reduce local recurrence without toxicity
Kapiteijn et al. (Pettersson et al. 2010) (1996–1999) $n = 1{,}861$	Total mesorectal excision versus preoperative radiotherapy (25 Gy in 5 fractions)	11 versus 6 ($P = 0.001$)	63 versus 64	67 versus 65	Short course preoperative radiotherapy improves local control even with total mesorectal excision surgery
Lyon R96–02 (Gerard et al. 2004; Ortholan et al. 2012) (1996–2001) $n = 88$	Preoperative radiotherapy versus preoperative radiotherapy and CBX (85 Gy in 3 fractions)	11 versus 8	67 versus 67	44 versus 76 ($P = 0.004$)	Safe high-dose RT escalation with CBX enables improved sphincter and rectal preservation
CAO/ARO/AIO (Sauer et al. 2004, 2012) (1995–2002) $n = 823$	Postoperative concurrent chemoradiotherapy (45 Gy in 25 fractions and 5-FU) versus preoperative concurrent chemoradiotherapy (45 Gy in 25 fractions and 5-FU)	13 versus 6 ($P = 0.006$)	74 versus 76	71 versus 69	*Preoperative concurrent chemoradiotherapy* superior in terms of local control and early toxicity; *becomes standard treatment*

(continued)

Table 1 (continued)

Study	Regimen	5-year local recurrence (%)	5-year overall survival (%)	Sphincter preservation (%)	Comments
FFCD 9203 (Géard 2006) (1993–2003) $n = 762$	Preoperative radiotherapy (45 Gy in 25 fractions) versus preoperative concurrent chemoradiotherapy (45 Gy in 25 fractions and 5-FU)	16 versus 8	67 versus 67	50 versus 50	Properative concurrent chemoradiotherapy is superior to radiotherapy alone in terms of local control
MRC CRO7 (Sebag 2009) (1998–2005) $n = 1{,}350$	Preoperative radiotherapy (25 Gy in 5 fractions) versus selective postoperative concurrent chemoradiotherapy (45 Gy and 5–FU)	10.6 versus 4.4	70 versus 68	63 versus 65	Confirmation of Kapiteijn et al. (Pettersson et al. 2010) with minimal radiation toxicity; local control improved with preoperative radiotherapy versus postoperative concurrent chemoradiotherapy
ACCORD 12 (Gerard et al. 2003) (2005–2008) $n = 598$	Preoperative concurrent chemoradiotherapy (45 Gy and capecitabine) versus preoperative concurrent chemoradiotherapy (50 Gy and capecitabine and oxaliplatin)	6.1 versus 4.7[§]	85 versus 83[§]	74 versus 76	A sterilized operative specimen was observed in 13 % of cases in first arm and 19 % in second Local relapse at 3 years <5 % with 50 Gy radiotherapy
STAR 01 (Aschele 2011) (2003–2008) $n = 747$	Preoperative concurrent chemoradiotherapy (50.4 Gy in 28 fractions and 5-FU) versus preoperative concurrent chemoradiotherapy (50.4 Gy in 28 fractions and oxaliplatin)	NR	NR	79 versus 81	A sterilized operative specimen was observed in 16 % of cases in both arms. Oxaliplatin associated with higher early grade 3 toxic events and does not increase tumor sterilization

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Table 1 (continued)

Study	Regimen	5-year local recurrence (%)	5-year overall survival (%)	Sphincter preservation (%)	Comments
KOREA (Park et al. 2011) $N = 220$	Preoperative versus postoperative chemoradiotherapy (CAP50)	4 % versus 6 %	77 % versus 73 %	80 % versus 72 %	Despite more ypCR in preop group no significant difference in sphincter preservation. Post op less toxic than preop
		(4 year)	(3y DFS)	(NS)	
CAO/ARO04 (Rodel et al. 2012) 1236 pts	Preop RT (46 Gy + 5Fu ± oxaliplatin)	NR	NR	88 % (no different)	FU+ oxalipt give a higher reate of ypCR without excessive toxicity. Waiting for endpoints 3y DFS
PETTAC6 (Schmoll et al. 2013) $N = 1094$	Néoadjuvant and adjuvant treatment using capecitabine + oxaliplatin versus capecitabine alone	NR	NR	68 % (no difference)	Oxaliplatin does not increase tumor response or local control or survival but gives more toxicity
NSABP R04 (Roh et al. 2011) $N = 1608$	2 × 2 format 5FU versus capecitabine with or without oxaliplatin néoadjuvants	NR	NR	62 % (no difference)	Capecitabine is equivalent to 5FU. Oxaliplatin no benefit more early toxicity

treatment either anti EGFR MDT (Dewdney et al. 2012) or anti-VEGF concurrently with radiotherapy. Such MDT can provide sometimes increased toxicity (Crane et al. 2003) or decreased radiosensitivity (Machiels et al. 2007; Willett et al. 2009).

2.2 Does Neoadjuvant Treatment Reduce the Rate of Permanent Stoma? Surprisingly NO

One of the most common medical beliefs is that preoperative treatment especially nCRT with long interval will "downsize" the tumor (T2-T3-T4) and increase the chance of a conservative treatment, namely sphincter saving surgery (SSS) using either low anterior resection (LAR) or inter sphincteric resection (ISR) (Rullier et al. 2013). In fact, conservative treatment of rectal cancer is a very complex situation with the interaction of many multifactorial parameters related to the tumor, the patient, the surgeon, and the general culture of a specific country or area. Here, more than everywhere else, only randomized trials can give strong evidence regarding the benefit of any preoperative treatment in terms of conservative treatment. Two literature reviews have analyzed this question (Bujko et al. 2006; Gerard et al. 2012). Both authors came to the same conclusion: for T2-3 (4) rectal cancers the rate of permanent stoma (for distal and middle rectum) have dramatically decreased during the past decades from 70 to 25 % (and sometimes 10 %), but this increase in sphincter preservation was due to technical surgical innovation and new concepts regarding the distal margin to be respected (from 5 to 2 even 1 cm) (Pahlman et al. 2013). In none of the randomized trials the group using the experimental treatment showed a significant increase in the rate of SSS despite often an increase in sterilization (ypCR) of the operative specimen (Fig. 1). A recent randomized trial performed in South Korea (Park et al. 2011) compared (as in the German CAO/ARO trial) postoperative CRT with nCRT. Despite a highly significant difference in the rate of ypCR (0 vs. 20 %) there was a non-significant increase in the rate of sphinter saving surgery (62 vs. 70 %). In a Nordic trial (Braendengen et al. 2008; Braendengen et al. 2011) nCRT when compared to short course RT with immediate surgery for T4 tumor was able to increase R0 surgery, local control, and sphincter preservation.

2.3 The Clinical Complete Response Hypothesis

The Lyon R96-2 trial using sphincter preservation as the main endpoint was the only trial showing a benefit of the neoadjuvant treatment to improve the rate of conservative treatment (Table 2). The addition of a boost using contact Brachytherapy X Ray 50 kV (CBX) 90 Gy in 3 fractions to EBRT increased the SSS rate from 44 to 76 % without increase in toxicity and preservation of a good bowel function (Gerard et al. 2004). Two points were of interest in this trial: first the rate of clinical complete response (CCR) was increased in the CBX boost group from 2 to 29 % and this finding may explain why the surgeons were more in favor of a

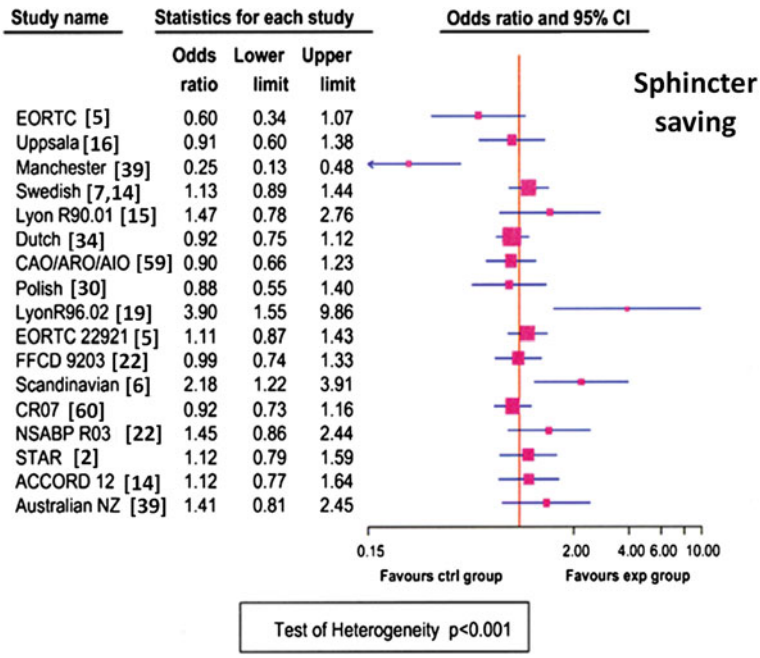

Fig. 1 Forest plot summarizing the results of recent randomized trials about sphincter preservation and showing the lack of benefit of neo adjuvant treatment (with the exception of the Lyon R 96-2 trial)

conservative approach in the boost group. When the surgeon see only a partial response he does not modify his surgical initial decision, but when he cannot see or palpate anymore a lesion he may reappraise his decision and perform a more conservative technique (Ortholan et al. 2006). Second, not only Anterior Resection was more frequent in the boost group, but also most of all "organ preservation" as 10 patients out of 45 in the CBX group were able to preserve the whole rectum after CCR using either a local excision or only a careful surveillance (Watch and wait). These data has been updated after 10 years of follow-up and the gain in stoma-free rate was maintained on the long-term without detrimental effect on local control or survival (Ortholan et al. 2012).

2.4 How to Increase Safely the Rate of CCR to Perform More Conservative Treatment

There are mainly three ways to increase the CCR rate:

(1) Increase the *interval* between the end of the neoadjuvant treatment and the surgery: the Lyon R 90-1 trial compared an interval of 2 versus 6 weeks. An increase in ypCR was observed (2 vs. 13 % p: 0.005), but it did not translate in

Table 2 Lyon R96-02 randomized trial 1996–2001 (Géard 2004; Ortholan et al. 2012)

Inclusion criteria		T2-T3 <½ circumference ≤6 cm from anal verge (distal rectum) Operable patient-any age >18	
Randomization		A- Preoperative EBRT alone (39 Gy/13 F/3 W)	
		B- Preoperative same EBRT + boost CBX (90 Gy/3F) Boost usually given before EBRT. Surgery TME: 5 weeks after end EBRT. No chemoradiotherapy	
Endpoint		Sphincter preservation	
		Hypothesis: A: 40 % B: 70 %	
1996–2001		88 patients included	
		EBRT (43 pts)	CBX + EBRT (45 points)
Med age		67	69
T2		12	10
T3		29	33
CCR		1 (2 %)	11 (29 %)
APE		24	11
Sph. Savint Tt		19 (44 %)	34 (76 %) p = 0.004
Watch and Wait Loc Excision	Organ preserved	0 0 — 0	7 3 — 10
Distant meta 3 y		11	9
10 year ov. Surv		56 %	55 %
10 year loc rec		5 (15 %)	4 (10 %)
10 year stoma free		27 %	61 % p < 0.001

At 10 years, 9 patients with organ preserved with no local recurrence, good anorectal function for all. Rectal bleeding G2 during the first 3 years. *CCR* Clinical Complete Response, *APE* Abdomino-Perineal Excision

a better SSS rate (Francois et al. 1999; Glehen et al. 2003). In Sao Paulo, Habr Gama has been for many years a strong advocate of a conservative treatment in case of CCR after nCRT. By increasing the interval before evaluation of the response from 5 to 12 weeks habr gama was able to increase the rate of CCR from 30 to 55 % (Habr-Gama et al. 2009; Habr-Gama et al. 2014). In the stockholm trial after short course an interval of 5 weeks (compared to immediate surgery) increased the ypCR without difference in toxicity, but without increase in SSS (Pettersson et al. 2010, 2012). It is probably after 2 to 3 months after the end of the nCRT that the optimal tumor response can be seen (Sloothaak et al. 2013; Wang et al. 2005).

(2) Concurrent use of one or two *chemotherapy* with radiotherapy: The FFCD 9203 and EORTC 22921 trials have shown that the addition of 5FU to preoperative irradiation is increasing ypCR and most of all local control in T3-4

rectal cancer, but without gain in SSS (Bosset et al. 2006; Gerard et al. 2006). The addition of oxaliplatin to 5FU or Capecitabine is not adding any benefit to the patient and may increase the risk of diarrhea (Gerard et al. 2010; Aschele et al. 2011; Schmoll et al. 2013).

(3) *Radiation dose escalation* is probably the most efficient way so far. In Toronto the dose escalation from 40 to 45 until 50 Gy was associated with a progressive increase of ypCR from 10 to 19 % (Wiltshire et al. 2006). In the ACCORD 12 trial a biological dose escalation of 15 % (from 45 to 50 Gy with the same protraction time of 5 weeks) increased the ypCR from 13 to 19 % (Gerard et al. 2010). The main limitation of such dose escalation, even with modern RT technique as IMRT or Proton therapy is the tolerance of the normal pelvic tissues and OAR (Gerard et al. 2004, 2003). The most efficient way to escalate the RT dose with regards to the "Toxicity/Benefit" ratio is using endocavitary irradiation, which can concentrate the dose to the primary tumor without arming too severely the surrounding OAR. With HDR Iridium combined with EBRT it is possible to achieve in T3 tumors a CCR rate of 70 % (Vuong et al. 2007). The randomized trial performed in Danemark (Jakobsen et al. 2006, 2012) despite an increase in ypCR in the group treated with Ir HDR did not show an increase in SSS and lead to more toxicity. Same findings in a phase III trial in Pakistan (Tunio et al. 2010). On the other hand as previously reported a safe dose escalation using CBX 50 kV was able to significantly increase CCR, sphincter saving, and most of all organ preservation. Unfortunately, this trial performed in a single institution in a limited number of patient has not influenced clinical practices (Gerard et al. 2004; Ortholan et al. 2012).

3 Aim of the Ongoing and Upcoming Randomized Trials

The most relevant and standard endpoint of CRT is overall survival, but in practice this endpoint is seldom used because it requires to include more than 1,000 patients and a very long follow-up. Disease Free Survival at 3 years is often the main endpoint of trial aiming at increasing survival. Other endpoints as ypCR, TRS (tumor regression score) (Taylor et al. 2011; Patel et al. 2011; Nougaret et al. 2013), R0 surgery may be used, but none can be considered as a robust surrogate endpoint of overall survival (Methy et al. 2010). Toxicity, rate of organ preservation, quality of life, and bowel or sexual functions are always major endpoints (Table 3). From a pragmatic point of view neo or adjuvant treatments are aiming at improved four clinical objectives:

(1) *Local Control* In T2 T3 tumors it will be difficult to demonstrate a further improvement over 95 % local control. In T4 following the trial of Braendegen (Braendengen et al. 2008, 2011), the GRECCAR 4 trial (EUDRACT N° 1234556…) is comparing a standard radiation dose of 50 Gy combined with capecitabine to 60 Gy dose in a reduced boost volume. Different techniques of

Table 3 Ongoing or up coming randomized control trials in operable T2-3-4 Nx M0 rectal cancer

Study	Inclusion criteria	Regimen	Endpoint	N° pt
RAPIDO	T3 c-d	• Cap50 + TME	3y DFS	600
Sweden ongoing	T4	• 5 × 5-chemo (folfox) TME	60–70 %	
	Nx			
PRODIGE23	T3-T4	• Cap 50 + TME	3y DFS	500
France NCT	Nx	• Folfirinox-cap 50	65–75 %	
01804790		+TME		
Ongoing				
Aristotle	T3-T4	• Cap45 TME	3y DFS	600
UK	Nx	• Capiri 45 TME	60–70 %	
Ongoing				
GRECCAR4	T3-T4	First-line chemo	R0 resection	250
France		Folfirinox poor response	85 → 95 %	
Ongoing		• Cap50-TME		
N1048		• Cap60-TME		
GRECCAR4	T3-T4	First-line chemo folfirinox	RO resection	250
France ongoing		Good response	95 versus 95 %	
		• CAP50-TME		
		• TME		
PRODIGE X	T3-T4	• CAP50-TME	Toxicity - Q.L	250
France up coming	Age >70 years	• 5 × 5-TME		
OPERA	T2 T3a-b	CAP45	Organ preserved 5–25 %	236
European		• EBRT boost 5.4 Gy		
up coming		• CBX boost 90 Gy/3F		
NCCTG	T3	• Folfox + TME	• R0	1060
N1048 (US)		if response >20 %	• Survival	
		• nCRT		
BACCHUS (UK) up coming	T3	±6 cycles bevacizumab with FOLFOX or FOLFOXIRI preop		
COPERNICUS (UK) up coming	T3	Firs line chemo + 5 × 5		

(continued)

Table 3 (continued)

Study	Inclusion criteria	Regimen	Endpoint	N° pt
Poland NCT00738790	T2-T3a	Preop 5 × 5 versus CRT 6 weeks local excision	Local control pCR	200
GRECCAR7 NCT01648894	T3-4	CRT and interval 7 weeks versus 11 weeks: TME	Pathological response	250
Rectum 51B UZB NCT01224392	T3-4	CRT versus RT with simultaneous integrated TBODSV	pCR	
Rectum TEM spain NCT01308190	T2T3	CRT TEM versus TME	Local control	

radiotherapy are tested to increase the tumor dose without increasing toxicity. Proton therapy if financially available is a promising technology (Thariat et al. 2013) to be used for rectal adenocarcinoma, which require dose above 90 Gy for 80–90 % rate of ypCR (Appelt et al. 2013).

(2) *Survival* As none of the medical regimens tested in RCT has so far been able to increase survival (in opposition with colon cancers), various trials are testing different drugs combination and strategy to try to reduce the rate of distant metastases without detrimental effect on the local control and the overall toxicity rates. The Swedish RAPIDO trial is using a first-line chemotherapy with a short course (5 × 5 gy) versus a standard long course CRT in T3c-d T4 M0 tumors. The French Prodige 23 is comparing in T3T4 M0 a standard "Cap 50" regimen versus the same regimen preceded by four cycles of first-line chemotherapy using a Folfirinox regimen. The British Aristotle RCT is comparing Cap 45 versus the same treatment with the addition of concurrent irinotecan. With the growing development of targeted treatment toward specific molecular pathways some RCT intend to select patients according to some specific mutations and to use an adapted MTD.

(3) *Toxicity and constraint reduction* in the French ACCORD 12 trial it was observed that in patients over 70 years of age the rate of treatment interruption, surgery not performed and postoperative toxicity was significantly increased using Capox 50 (or Cap 50) when compared to younger patients (Francois et al. 2014). A new Prodige randomized trial is upcoming who will test the hypothesis that after 70 years of age a short course radiotherapy (5 × 5 Gy in a small posterior pelvic volume) with delayed surgery will be better tolerated than the Standard Cap 50 and will lead to more patients able to undergo with reduced toxicity a TME surgery. No randomized trial has ever proved that in "goodT3 tumors" a surgery alone was as efficient as CRT (or 5 × 5 Gy) to achieve an optimal local control. Some institutions with a highly dedicated colorectal team tend to expect that TME alone can be proposed for these "good T3 tumors". In Greccar 4 these patients staged with MRI are treated with a first-line chemotherapy using a Folfirinox regimen. In case of "good response"

judged on MRI the patients are randomized between a standard Cap 50 nCRT or a TME without any a nCRT. So far no RCT is comparing the standard nCRT strategy versus TME surgery first-line. In MSKCC New York, following a phase II study using first-line Folfox and Bevacizumab with a 25 % ypCR in T3 tumors (Schrag et al. 2014) an upcoming phase III trial is testing the hypothesis that combined first-line chemotherapy and MTD may replace n CRT. It is not sure that replacing the toxicity of radiotherapy by the toxicity (cardio-vascular) of this new approach will benefit the patient.

Following all recent trials capecitabine (oral) is replacing 5FU (iv), which is for the patients a benefit in terms of simplicity and toxic risk.

(4) *Conservative treatment* This is possibly one of the most promising hypothesis. How to increase not so much Sphincter Saving using AR or ISR (Rullier et al. 2013), but organ preservation after CCR? The upcoming European trial OPERA (Organ Preservation for Early Rectal Adenocarcinoma) will include T2 T3a-b and after Cap 45 will compare a boost using EBRT (5.4 Gy) versus a boost using CBX (90 Gy). The hypothesis is that taking advantage of an increase in CCR in the CBX group the organ preservation rate will increase from 5 to 25 %. One still controversial question in case of CCR is to decide between local excision as proposed by Lezocche (Lezoche et al. 2012) or Garcia-Aguilar et al.(2012) (Sauer et al. 2004) and the GRECCAR group (Rullier et al. 2013) or close surveillance (Habr-Gama et al. 2014; Perez et al. 2013; Maas et al. 2011).

4 Conclusion

Important improvements have been made in the past decade in the treatment of rectal cancers and its overall prognosis is now slightly better than colon cancer. Chemotherapy and new molecular targeted drugs should be able to improve survival in the future. Robust prognostic and predictive markers will be necessary to tailor and optimize these "targeted" treatments for each individual patients. The growing development of colorectal screening will lead to the discovery of more early rectal cancers. In these patients and especially when elderly and frail, organ preservation (as for squamous cell carcinoma of the anal canal) should be an important step forward to better quality of life. Only well-conducted randomized control trials will bring strong enough evidence to influence and modify the clinical and surgical practices.

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