Rectal Cancer

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Contents

Abstract

Reirradiation combined with chemotherapy for patients developing recurrent rectal cancer after radiation or chemoradiation is feasible and provides high chances for cure and palliation. Nearly one-half of patients with resected disease achieve long-term control of pelvic disease, and up to 65% of them can have long-term (5-year) survival. Even in unresected patients, long-term control can be achieved in about 20% of cases with one out of five patients surviving after 5 years.

Acute and late toxicity are not prohibitive if proper attention is paid to both radiation technique and surgical technique. The use of small radiation fields, exclusion of the bowel and bladder, and the use of hyperfractionated radiation doses up to 40 Gy are recommended.

Since most of treatment failures occur within the radiation treatment field, future studies should investigate methods to further improve local control. In view of the fact that about one-half of surviving patients will develop distant metastases, innovative strategies for reduction of distant metastases should also be explored.

1 Introduction

Reirradiation for rectal cancer can be considered for two patient groups: patients who develop locoregional recurrence after previous pre- or

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postoperative radiation, and patients with newly diagnosed rectal cancer who have received previous pelvic irradiation for other malignancies (e.g. prostate and gynaecological cancers). In this chapter we will focus on the reirradiation of local recurrence.

Locally recurrent rectal cancer (LRRC) is a devastating condition causing severe symptoms, including pelvic pain, bleeding and bowel obstruction in over two-third of patients. These distressful symptoms can cause a loss of quality of life (QoL). LRRC includes recurrence, progression or development of new sites of rectal tumour(s) within the pelvis after previous resection of rectal cancer (Beyond TME Collaborative 2013). Pelvic recurrence includes anastomotic recurrence, as well as recurrence within lymphatics such as residual mesorectal nodes and pelvic sidewall lymph nodes. Also included is inguinal node recurrence and disease manifesting along drain tracts and surgical scars (abdominal or perineal).

Local recurrence may be isolated or combined (local and metastasis). Patient prognosis is generally poor with a median overall survival without treatment of only 3.5–13.0 months (Saito et al. 2003).

The introduction of total mesorectal excision (TME) (Enker et al. 1995; Heald 1995; MacFarlane et al. 1993) together with neoadjuvant radio- and chemotherapy dramatically reduced LRRC rates from 20 to 30 % (Swedish Rectal Cancer Trial 1996; Goldberg et al. 1994) to 6–10 % (Rödel et al. 2015; Gérard et al. 2012). However, due to the high incidence of rectal cancer, still a high absolute number of patients present with recurrent rectal carcinomas. The management strategy in this cohort of patients is complex, with a number of options including surgery, with or without radiotherapy with either curative or palliative intent, with or without chemotherapy. Delay in diagnosis is common, and inequalities exist in referral patterns based on geography, with no clear clinical guidelines (Beyond TME Collaborative 2013).

Surgical excision of LRRC is the most significant measure used to improve survival. Particularly complete surgical resection (R0 resection) remains the only potentially curative treatment with reported 5-year survival rates in selected patients of up to 50 %. However, only 40–50 % of all patients with LRRC can undergo surgery with curative intent, and of those, 30–45 % will have R0 resection. Thus, only 20–30 % of all patients with LRRC have a potentially curative operation (Nielsen et al. 2011). Furthermore, to achieve cure most patients require extended, multivisceral, exenterative surgery, beyond conventional total mesorectal excision planes with high morbidity rates of 40–82 % (Haddock et al. 2011; Nielsen et al. 2012; Harji et al. 2013). Preoperative radiotherapy can provide higher chances of complete resection and local control (Vermaas et al. 2005; Rödel et al. 2000) potentially allowing less extensive surgical resections. In conjunction with fluoropyrimidine-based chemotherapy, preoperative radiotherapy is widely recognized as the most appropriate treatment option in patients with LRRC who have not received prior radiotherapy (Konski et al. 2012).

Although local recurrence rates have decreased, an increasing proportion of patients with LRRC have previously received high-dose pelvic radiotherapy as part of the primary multimodality treatment, either as preoperative short-course radiotherapy (5 × 5 Gy) or as chemoradiotherapy to 45–50 Gy (1.8–2.0 Gy/fraction). The prognosis for patients with LRRC seems to be worse in previously irradiated patients than in those without prior irradiation (Rombouts et al. 2015; van den Brink et al. 2004). Recurrences after neoadjuvant irradiation may represent a selection of patients with very unfavourable tumour characteristics. As an example, more than two-third of patients with LRRC after preoperative radiotherapy have also distant metastases at the time of recurrence as compared to less than half of patients with LRRC after surgery only (van den Brink et al. 2004). It has been observed that patients with LRRC who have received prior neoadjuvant radiotherapy and TME have a higher rate of incomplete resection of the recurrence (Alberda et al. 2014; van den Brink et al. 2004). In addition LRRC in patients treated with radiotherapy for the primary tumour may evolve from radiation-insensitive tumour deposits, rendering reirradiation less effective.

However, several recent observations and trials have demonstrated the safety and efficacy of reirradiation in patients with LRRC who previously underwent irradiation to the pelvis (Mohiuddin et al. 1993, 1997, 2002; Lingareddy et al. 1997; Valentini et al. 1999, 2006; Das et al. 2010; Sun et al. 2012; Koom et al. 2012; Ng et al. 2013; Bosman et al. 2014). Reirradiation might increase the rate of preservation of surrounding organs and radical (R0) resection and provide symptom palliation or long-term local control for inoperable tumours (Guren et al. 2014). However, reirradiation of infield recurrences can also aggravate the late radiation toxicities of adjacent tissue (including small bowel, bladder, etc.) and the complications of surgery. Therefore, the expected benefits in terms of achieving R0 surgery and long-term survival and/or symptom palliation should be weighed against the potential morbidity caused by retreatment.

Because LRRC presents a challenging problem, the international consensus statement by the Beyond TME Collaborative Group (2013) on the management of patients with LRRC clearly identified the need for referral of patients with LRRC to a specialist multidisciplinary team (MDT) for diagnosis, assessment and further management. The subspecialized MDT requires oncological, radiological, surgical and pathological expertise in pelvic exenteration.

2 Diagnosis and Staging of LRRC

Early diagnosis of the recurrence in potential surgical candidates is critical as it increases the likelihood of curative (R0) resection and prevention of dissemination; therefore, different follow-up strategies have been developed (Figueredo et al. 2003; Zitt et al. 2006). The timeframe for recurrence is typically within the first 2 years after resection of the primary tumour (Palmer et al. 2007). However in almost 30 % of patients with locally advanced rectal cancers treated by preoperative chemoradiation, the time to detection of local recurrence (LR) can be longer than 5 years (Coco et al. 2006). Existing nomograms to predict local recurrence can aid the selection of follow-up type and intensity (Valentini et al. 2011; van Gijn et al. 2015).

Regarding the pattern of LRRC in terms of location within the pelvis, in recent years, a subtle change has been observed. In general terms, in the pre-TME years, most recurrences were central, perianastomotic and anterior, whereas since the adoption of combined therapies, lateral and posterior (presacral) forms dominate (Enríquez-Navascués et al. 2011). With conventional surgical techniques, segments of the mesorectum could be left behind, and local recurrences in the remaining part were not uncommon, often being located in the anastomotic region (Palmer et al. 2007). After TME surgery, presacral LRs are the most common type of LR, and due to prior surgery, tumour growth is not confined to a specific compartment lined by fascias, because these fascias have been damaged during the primary surgery (Dresen et al. 2008). Furthermore it has been observed that while preoperative RT helps to prevent LRs at all sites, it is especially effective in preventing anastomotic recurrences (Mohiuddin and Marks 1993).

Many factors affect the risk of local recurrence. The involvement of circumferential resection margin (CRM) is the most important factor (Quirke et al. 1986). The pelvic recurrence rate is also tumour-stage dependent (Sagar and Pemberton 1996). The combination of risk factors is also important: in patients with T1-T2 stage, the incidence of LR is 1 % with a negative CRM but this rises to 12 % for a positive CRM, while for those with T3-T4 tumour, it is 15 % for a negative CRM but 25 % for a positive CRM (Kusters et al. 2010). A poor pathologic response and downstaging to preoperative chemoradiation is also a negative prognostic marker for LR (Rödel et al. 2005). Anatomical site of the tumour is also another critical factor; indeed LR is more likely with tumours in the lower third of the rectum (10–15 %) than in patients with tumours in either the middle third (5–10 %) or upper third (2–5 %) (MacFarlane et al. 1993; Kusters et al. 2010). The risk of LR is also related to the position of the tumour within the circumference of the rectum, being higher for tumours affecting the anterior

side of the rectum than for other locations (Chan et al. 2006). Other factors that can influence the risk of local recurrence are the shape (exophytic versus non-exophytic) of the tumour, the presence or absence of budding, lymphatic, venous or perineural invasion, the presence of obstruction or perforation, the degree of tumour differentiation and the fixity of the tumour (Sagar and Pemberton 1996).

Clinical examination, tumour markers and radiologic modalities such as ultrasonography (US), computed tomography (CT), magnetic resonance (MR) and positron emission tomography (PET) are routinely used in follow-up. CT is the most commonly used modality for identification of pelvic recurrence, but it has poor accuracy in distinguishing between scar tissue and tumour (Grabbe and Winkler 1985), and this becomes even more difficult if radiotherapy has previously been applied (Heriot et al. 2006). Compared with CT, MR can more accurately differentiate recurrent cancer within a presacral scar, based on differences in signal intensity between tumour and fibrosis using T2-weighted sequences or contrast-enhanced imaging techniques (Dicle et al. 1999). Thus high-resolution MR with a sensitivity of 80–90 % and a specificity as high as 100 % (Lambregts et al. 2011) is generally regarded as the optimum modality for imaging the pelvis in patients with suspected LRRC. Differently from fibrosis, which appears hypointense on T2-weighted MR images, recurrent tumours typically display higher signal intensity than that of muscle. Moreover, tumours tend to have contrast enhancement greater than 40 % of the volume of a mass or a typical rim-enhancement pattern after gadolinium contrast material administration (Messiou et al. 2008).

However, benign fibrotic scarring, malignant local tumour recurrence and inflammation can all enhance after the administration of a gadolinium-based contrast agent (Tan et al. 2005). Furthermore, a tumour with significant fibrosis can cause low signal intensity on T2-weighted images. PET is an accurate diagnostic tool and may have advantages over CT and MR in discriminating fibrosis from cancer (Huebner et al. 2000), although false-negative results can occur in small deposits or in mucinous tumours. An increase in serum carcinoembryonic antigen (CEA) level may assist in reaching a diagnosis, although a spuriously high or low result can be confusing (Tan et al. 2009).

Given these limitations, the ideal for diagnosis of LRRC still remains tissue biopsy. Where tissue biopsy is not possible or is negative, serial enlargement of a lesion accompanied by either positive PET-CT or rising CEA level and specialist MDT opinion suggestive of malignancy can be accepted for diagnosis (Beyond TME Collaborative 2013).

The management of patients with LRRC mainly depends on the type and extent of recurrence. Therefore, radiologic assessments are used to determine whether recurrent disease is limited to the pelvis or has metastasized, and to outline the local extent of recurrent disease and its distribution within the pelvis to help surgeons determine the feasibility of resection and plan the optimal surgical approach.

A meta-analysis investigating the value of US, CT, MR and PET in detecting liver metastases demonstrated sensitivity of 63 %, 75 %, 81 % and 97 %, respectively, and high specificity (Floriani et al. 2010). Particularly PET with ^{18}F-fluorodeoxy-glucose has been demonstrated to be highly accurate in the detection of disseminated disease (Ogunbiyi et al. 1997). PET has also been shown to have a high impact on the management of patients with suspected recurrent colorectal cancer (Kalff et al. 2002).

The identification of patients who can potentially achieve a R0 resection is crucial and extremely difficult. Resection margin status is an independent prognostic factor for re-recurrence rate and overall survival in surgically treated, locally recurrent rectal cancer. In the complete resection group, patients with tumour-free resection margins of 0–2 mm have a higher re-recurrence rate and a poorer overall survival than patients with tumour-free resection margins of >2 mm (Alberda et al. 2015). Preoperative imaging and clinical assessment are utilized in an effort to optimize the selection of patients in

whom curative resection is considered possible. Although MR imaging has proved to be the preferred first-choice staging modality for primary rectal cancer, its performance for predicting tumour extent in patients with local recurrence could be impaired by the fibrosis after surgery and adjuvant therapies. In a retrospective analysis of 40 consecutive patients with locally recurrent rectal cancer, Dresen et al. (2010) found that although the positive predictive value of MR imaging was low (53–85 %) especially at the lateral pelvic side walls, MR was highly accurate for the prediction of the absence of tumour invasion into pelvic structures with negative predictive values of 93–100 %. Therefore, preoperative MR imaging in patients with LRRC could be a useful diagnostic tool for the identification of the absence of tumour invasion into pelvic structures.

2.1 Classification of LRRC

Although several classifications have been proposed to assess LRRC resectability (Table 1), at the moment no classification system is universally shared. Such a lack of a standard classification of LRRC strongly impairs the possibility of interpreting results and comparing between different series. Indeed, in addition to assisting decision-making regarding the potential for and the extent of resection, classification has also an important prognostic value.

In a recent prospective study by the Royal Marsden Hospital, a new classification is described based on the extent of tumour invasion in each of seven intrapelvic compartments, as seen on preoperative pelvic MR imaging (Georgiou et al. 2013). These correspond to the fascial boundaries and planes of dissection between the pelvic organs, and are described as central (C), posterior (P), inferior (I), anterior above (AA) and anterior below (AB) the peritoneal reflection and lateral (L) and peritoneal reflection (PR). Such a MR-based classification system is particularly promising, since it allows for better understanding of tumour invasion within the pelvis, hence contributing to optimal surgical planning.

3 The Role of Surgery in LRRC

Resectability in recurrent rectal cancer can be defined as the ability to complete a surgical resection with a microscopically clear margin (R0) and acceptable postoperative morbidity and mortality. According to the recent consensus statement by the Beyond TME Collaborative Group (2013), absolute contraindications to resectability include bilateral sciatic nerve involvement and circumferential bone involvement. Benefits of surgery are unclear when the tumour extends through the sciatic notch, or encases the external iliac vessels or involves the sacrum above the S2/3 junction or irresectable distant metastases are present.

There are three broad pelvic site patterns that determine resectability: (i) central recurrence, (ii) sacral recurrence and (iii) lateral recurrence. For central recurrences, if the recurrence does not involve any of the anterior genitourinary structures, an abdominoperineal resection (APR) of the anus and neorectum is occasionally possible. Where there is involvement of the anterior urogenital structures, an extended multivisceral resection is required to achieve a R0 resection. When posterior structures are involved, more extended radical resections are often necessary. Where bony invasion is present, an R0 resection is only possible with a sacral resection. Recurrence involving the lateral pelvic sidewall is associated with the poorest chance of achieving an R0 resection (Moore et al. 2004). Wound healing is frequently impaired after previous chemoradiotherapy, and in selected patients, optimal healing is best achieved using a variety of pedicled flaps.

A summary of outcomes of exenterative surgery for LRRC from contemporary studies has been recently provided by Renehan (2016). R0 resection rates are about 50 % (range 38–62 %) (Ferenschild et al. 2009; Bhangu et al. 2014; Nielsen et al. 2012) with almost half of patients requiring sacrectomy. Less than half of patients remain free from disease at long term, with reported 3-year disease-free survival of 22 % (Nielsen et al. 2012) and 50 % (Bhangu et al. 2014) in two different series.

Table 1 Classifications systems in use for locally recurrent rectal cancer

Study group	Classification	Definitions	
Mayo Clinic (Suzuki et al. 1996)	Symptoms	S0	Asymptomatic
		S1	Symptomatic without pain
		S2	Symptomatic with pain
	Degree and site of fixation	F0	No fixation
		F1	Fixation to 1 point
		F2	Fixation to 2 points
		F3	Fixation to > 2 points
Yamada et al. (2001)	Pattern of pelvic fixation	Localized	Invasion to the adjacent pelvic organs or tissue
		Sacral invasive	Invasion to lower sacrum (S3, S4, S5), coccyx, periosteum
		Lateral invasive	Invasion to sciatic nerve, greater sciatic foramen, lateral pelvic wall, upper sacrum (S1, S2)
Wanebo et al. (1999)	Five stages	TR1	Limited invasion of the muscularis
		TR2	Full-thickness penetration of the muscularispropria
		TR3	Anastomotic recurrences with full-thickness penetration beyond the bowel wall and into the perirectal soft tissue
		TR4	Invasion into adjacent organs without fixation
		TR5	Invasion of the bony ligamentous pelvic including sacrum, pelvic/sidewalls or sacrotuberous/ischial ligaments
Memorial Sloan-Kettering (Moore et al. 2004)	Anatomical region involved	Axial	Anastomotic, mesorectal, perirectal soft tissue, perineum (APER)
		Anterior	Genitourinary tract
		Posterior	Sacrum and presacral fascia
		Lateral	Soft tissues of the pelvic sidewall and the lateral bony pelvis

Leeds	Anatomical region involved	Central	Tumour confined to pelvic organs or connective tissue without contact with or invasion into the bone
		Sacral	Tumour present in the presacral space and abuts on to or invades into sacrum
		Sidewall	Tumour involving the structures on lateral pelvic sidewall, including greater sciatic foramen and sciatic nerve through to piriformis and gluteal region
		Composite	Sacral and sidewall recurrence combined
Royal Marsden Hospital (Georgiou et al. 2013)	MRI; planes of dissection	C	Rectum or neorectum, intraluminal recurrence, perirectal fat or mesorectum, extraluminal recurrence
		PR	Rectovesical pouch or rectouterine pouch of Douglas
		AA PR	Ureters and iliac vessels above the peritoneal reflection, sigmoid colon, small bowel and lateral sidewall fascia
		AB PR	Genitourinary system
		L	Ureters, external and internal iliac vessels, lateral pelvic lymph nodes, sciatic nerve, sciatic notch, S1 and S2 nerve roots, piriformis or obturator internus muscle
		P	Coccyx, presacral fascia, retrosacral space, sacrum up to the upper level of S1
		I	Levator ani muscles, external sphincter complex, perineal scar (APER), ischioanal fossa

Modified from the Beyond TME Collaborative (2013) Consensus
APER abdominoperineal resection, *MRI* magnetic resonance imaging, *C* central, *PR* peritoneal reflection, *AA* anterior above, *AB* anterior below, *L* lateral, *P* posterior, *I* inferior

The morbidity and mortality rate can be as high as 60 % (range 25–60 %) and 8 % (range 0–8 %), respectively.

The complication rate might be higher in patients who undergo multivisceral resection versus those having single organ resection (Gezen et al. 2012).

Morbidity and mortality rate might be higher for more extended surgical procedures. For example, sacrectomy (compared with other operations) was associated with significantly higher mean blood loss, longer duration of surgery and longer length of stay. Cystectomy (compared with no cystectomy) was associated with longer duration of surgery. Perineal flap reconstruction (compared with primary closure or nonflap reconstruction) was associated with a longer mean operating time and a longer mean length of stay (Bhangu et al. 2014).

Unfortunately, only one-third to one-half of LRRCs will be resectable with conventional surgical procedures; the rest will require extended radical resection with removal of surrounding organs, to achieve clean margins. Optimizing patients before multivisceral resection is vital to minimize perioperative morbidity, requires a multispecialist approach and may best be achieved by formal cardiopulmonary testing (Beyond TME Collaborative 2013).

4 The Role of Reirradiation in LRRC

Neoadjuvant external beam radiation up to a dose of 50.4 Gy with concurrent chemotherapy is the standard of care for patients with LRRC who have not received any radiotherapy, since it has been demonstrated to improve the local control (Vermaas et al. 2005; Dresen et al. 2008). Indeed neoadjuvant long-course chemoradiotherapy has the potential to increase the resectability rate of delayed surgery in LRRC from 29.2 to 64.9 % (Dresen et al. 2008) and, by downstaging the tumour, may theoretically allow for less-extended surgical operations. In general, recurrent rectal cancers are treatment-resistant tumours. In a recent study at the Royal Marsden Hospital, only 9 % of patients with LRRC had a pathologic complete response compared to 17 % of patients with locally advanced primary tumour after long-course chemoradiation (Yu et al. 2014). Recurrent rectal cancer after previous irradiation might be even more radio resistant due to the possible origin from radio-resistant clones. Reirradiation is also challenging, because the surrounding normal tissues may have already received doses near the organ- or endpoint-specific tolerance dose during the primary treatment. Therefore reirradiation has been generally discouraged for the fear of prohibitive normal tissue complications, particularly of the small intestine and bladder. However, there is increasing evidence in clinical studies that reirradiation is tolerable and yields good results. Particularly in a recently published study including a large number of patients with LRRC, reirradiated patients had almost the same R0 resection rate and long-term local disease control as those who received full-course irradiation for the first time. Furthermore, despite more extensive surgical procedures in the reirradiation group, reflecting more advanced disease, no significant difference was noted in the rate of complications between the two treatment groups (Bosman et al. 2014).

Intraoperative radiation therapy might also represent a useful technique for these patients, with the possibility of precisely delivering a large single dose (10–20 Gy) to the surgically defined recurrence site and avoiding the surrounding normal tissues (Gunderson et al. 1996; Mannaerts et al. 2001).

A recent systematic review suggests that only 40 % of unselected consecutive patients with locally recurrent rectal cancer are candidates for intentionally curative treatment (Tanis et al. 2013). Surgical resection should be evaluated in all instances of isolated LRRC. However, in some cases, a resection is not possible, or medical reasons such as concomitant illnesses restrain the surgeon from surgical interventions. In other cases, surgery is performed, but a gross resection is not possible, and macroscopic tumour remains, which requires adjuvant treatment. The remaining patients with isolated LRRC might benefit from image-guided stereotactic radiotherapy,

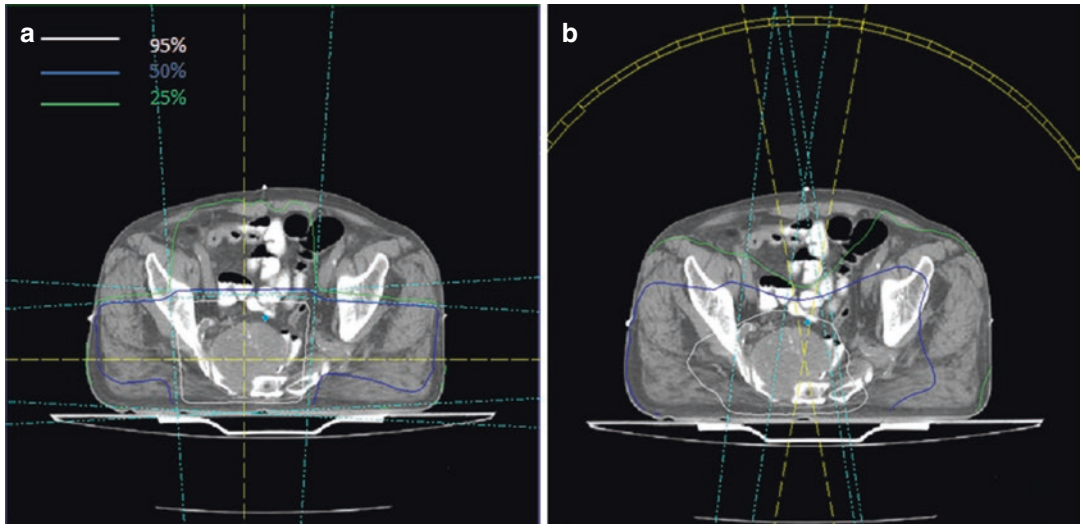

Fig. 1 Dose distribution of three-dimensional conformal radiotherapy (**a**) and volumetric-modulated arc therapy (VMAT) (**b**) for presacral relapse in a previously irradiated rectal cancer patient, showing small bowel sparing with VMAT

brachytherapy or particle beam radiotherapy with the aim of achieving both palliation and long-term local control (Combs et al. 2012).

4.1 Long-Course Reirradiation

The effects of conventional external beam reirradiation in terms of feasibility, toxicity and long-term outcomes in previously irradiated LRRCs were the subject of a recent systematic review (Guren et al. 2014) which included ten publications describing seven patient cohorts/studies for a total of 375 patients (range 13–103) (Mohiuddin et al. 1993, 1997, 2002; Lingareddy et al. 1997; Valentini et al. 1999, 2006; Das et al. 2010; Koom et al. 2012; Sun et al. 2012; Ng et al. 2013). Most studies were retrospectively designed, with highly variable therapies, patient populations and duration of follow-up. Median time since previous RT in different series ranged between 8 and 30 months and was longer than 24 months in most series. Reirradiation for rectal cancer was mostly given with hyperfractionated chemoradiotherapy to total doses of 30–40 Gy, although higher doses have been explored (range 23.4–50.2 Gy). EQD2Gy ($\alpha/\beta = 3$ Gy) of previous irradiation ranged between 43.2 and 51.8 Gy3 with an estimated cumulative EQD2Gy with retreatment ranging between 71.9 and 101.7 Gy3 (Guren et al. 2014).

In older series, reirradiation was generally given by opposed lateral or three fields with a shrinking field technique, encompassing the presacral region or posterior pelvis (as prophylaxis for subclinical disease) and the gross tumour volume plus a margin of 1–4 cm (usually 2 cm) followed by a boost to the gross tumour volume (plus margin) only (Mohiuddin et al. 1993, 1997, 2002; Lingareddy et al. 1997; Valentini et al. 1999). In newer studies, reirradiation was delivered by multiple fields with a three-dimensional conformal or intensity-modulated technique, and the treatment volumes encompassed the gross tumour only with a 2-cm GTV to PTV margin (Valentini et al. 2006; Das et al. 2010; Koom et al. 2012; Sun et al. 2012; Ng et al. 2013).

Figure 1 shows the possibility of small bowel sparing with intensity-modulated techniques.

Disease control and survival outcomes in contemporary clinical trials of reirradiation (Valentini et al. 2006; Das et al. 2010; Koom et al. 2012; Sun et al. 2012; Ng et al. 2013; Milani et al. 2008; Bosman et al. 2014) are reported in Table 2. The proportion of patients who underwent resection after reirradiation varies widely (range 20–100%).

Table 2 Disease control and survival outcome in contemporary clinical trials of long-course reirradiation

Author, publication year and study design (inclusion period)	Patient n°	Previous radiation dose Gy, median value (range)	Reirradiation median total dose (range)/ fractionation	Technique	Concurrent chemotherapy	Tumour resection n (%)	Local control	Distant metastases-free survival	Median survival months	Overall survival
Bosman et al. (2014), retrospective (1994–2013)	135	15–55 Gy	30.6/1.8 or 30/2 Gy + IOERT boost 10 (R0), 12.5 (R1) or 15 (R2) Gy at the 90 % isodose	3-field or 3DCRT	Yes (86.7 %)	135/135 (100 %) 75/135 (55.7 %)	45.9 % (5-year)	56.6 % (5-year)	–	34.1 % (5-year)
Ng et al. (2013), retrospective (1997–2008)	56	50.4 Gy (21–64)	39.6 (20–39.6)/1.8 Gy	3DCRT or IMRT	5-FU	11/56 (20 %) R0:8/11 (72 %)	–	–	All, 19 Resected, 39 Unresected, 15	–
Sun et al. (2012), prospective (2004–2008)	72	<50 Gy (not reported)	30–36/1.2 Gy bid; nonresectable: redraw GTV, total 51.6–56.4 Gy	3DCRT	Capecitabine	18/72 (25 %) R0:16/18 (88 %)	–	–	All, 32	All, 45.1 % (3-year)
Koom et al. (2012), retrospective (2000–2007)	22	54 Gy (45–59.4 Gy)	50.2 Gy (30–66)/1.8–3 Gy	3DCRT or IMRT	Yes	5/22 (23 %)	All, 32 % (2-year)	–	All, 21	All, 50 % (2-year)
Das et al. (2010), retrospective (2001–2005)	50	47 Gy (25–70)	39Gy (if retreatment interval ≥ 1 year) or 30 (if retreatment interval < 1 year)/1.5 Gy bid +/− IORT, 5–10	3-field	Capecitabine	18/50 (36 %) R0:7/18 (38.8 %)	All, 33 % (3-year) Resected, 47 % Unresected, 21 %	–	All, 26 Resected, 60 Unresected, 16	All, 39 % (3-year) Resected, 66 % Unresected, 27 %

Milani et al. (2008), retrospective (2000–2005)	24	50.4 Gy (38.0 – 59.4 Gy)	39.6 Gy (30.0– 45.0 Gy)/1.8 Gy	3–5 field	5-FU + hyperthermia	0 %	–	–	–	–
Valentini et al. (2006), prospective (1997–2001)	59	50.4 (30–55)	30 Gy (+boost 10.8 Gy)/1.2 Gy bid	3DCRT	5-FU	30/59 (51 %) R0:21/30 (70 %)	All, 38.8 % (actuarial 5- year) Resected (R0), 69.0 %	42 % (actuarial 5 years)	All, 42	All, 39.3 % (5-year)
									Resected, 44	Resected (R0), 65.0 %
									Unresected, 14	Unresected (or partial tumour removal), 22.3 %

Differences in resection rates can be mainly explained by the fact that patients with unresectable disease or intraoperatively detected distant disease were not excluded from the initial study population in some studies. Furthermore, as previously said, the lack of a standard classification of LRRC negatively affects the possibility of comparing results between different series. Although pathological complete responses were rarely described, R0 resection was obtained in more than 70 % of operated patients in almost all series (range 39–89 %).

Median survival for all patients with LRRC ranged between 19 and 42 months. Unresected patients had median survival time of 14–16 months, whereas patients who underwent surgical removal of tumour had median survival of 39–60 months. Nearly one-half of patients, with resected LRRC treated with multimodality approach including reirradiation, achieved long-term control of pelvic disease, and up to 65 % of them had long-term (5-year) survival. Even in unresected patients, after preoperative long-course chemo-reirradiation, long-term control can be achieved in about 20 % of cases with a significant proportion of long-term (5-year) survivors (up to 22 %). About 50 % of patients developed distant metastases during follow-up (Valentini et al. 2006; Bosman et al. 2014).

Reirradiation is highly effective for palliation. Eighty-three to 94 % of reirradiated patients experienced partial pain relief, rectal bleeding completely resolved in 100 % of patients and rectal mass was palliated in more than 80 % of patients with a median duration of symptom relief of 9, 10 and 8 months, respectively, for each symptom (Guren et al. 2014).

Probably due to more conformal treatment and reduced volumes, there was a trend towards less acute and late toxicity in recent studies as compared to older trials (Guren et al. 2014). In modern series (Table 3), treatment break or termination due to toxicity infrequently occurred (less than 5 %). The most commonly observed grade 3–4 acute toxicities were diarrhoea (5–10 %) and skin reactions (5 %). The most frequently reported late toxicities were gastrointestinal and urinary complications such as small bowel obstruction or stricture in up to 14 % of patients, fistula, chronic diarrhoea, cystitis and impaired wound healing. In the series by Koom et al., a high rate (27 %) of ureter stricture was also reported.

A great proportion of late toxic events after multimodality treatment of LRRC is likely a consequence of surgery or local disease growth within the pelvis. It has already been said that the morbidity of surgery for LRRC can be as high as 60 %. Das and co-workers (2010) observed a trend towards a higher rate of grade 3–4 late toxicity in patients who had surgery than in patients who did not have surgery after reirradiation. More than half LRRCs re-recur or progress locally after treatment. In the series of Mohiuddin et al. (2002), small bowel obstruction without disease recurrence was seen in only 4 out of 15 (26.6 %) patients. Similarly in the series of Das et al. (2010), half of patients with small bowel obstruction also showed peritoneal carcinomatosis.

4.1.1 Prognostic Factors for Disease Control and Survival Outcomes After Long-Course Reirradiation

Several factors have been evaluated as potential prognostic determinants after reirradiation for LRRC. Response to chemo-reirradiation gives a better chance of achieving a R0 resection (Valentini et al. 2006).

A better local control was observed when R0 surgery was performed (Bosman et al. 2014; Valentini et al. 2006), when reirradiation doses higher than 30 Gy (Haddock et al. 2001) or 50 Gy_{10} (Koom et al. 2012) were delivered, or the interval between the primary treatment and recurrence was longer than 24 months (Valentini et al. 2006).

A better overall survival was observed in patients with good performance status (Karnofsky index $\geq$70), less-advanced stage of primary tumour (Mohiuddin et al. 2002), when the LRRC was completely resected (Bosman et al. 2014; Ng et al. 2013; Das et al. 2010; Valentini et al. 2006; Mohiuddin et al. 2002), when the interval between the primary treatment and recurrence was longer than 24 (Das et al. 2010) or 36 months (Bosman et al. 2014) or a reirradiation dose higher than 30 Gy was delivered (Mohiuddin et al. 2002).

Table 3 Toxicity in contemporary clinical trials of long-course reirradiation

Author, publication year, and study design (inclusion period)	Grade 3–4 acute toxicity (%)	Treatment break or termination (toxicity)	Follow-up time, months median (range)	Incidence of grade ≥ 3 late complication (%)						Surgical mortality (%)
				Small bowel obstructions	Fistula	Abscess	Wound dehiscence	Ureter	Bladder/urethra	
Bosman et al. (2014), retrospective (1994–2013)	Diarrhoea 5 Neutropenic sepsis 1	–		–	9.9[a]	15.9[a]	9.9[a]	–	10[a]	4.6
Ng et al. (2013), retrospective (1997–2008)	Skin 5 Gastrointestinal 9 Mucositis 2	Termination 4 %	15 (1–108)	1.7[b]	1.7[b]	3.5[b]	1.7[b]	–	3.5[b]	0
Sun et al. (2012), prospective (2004–2008)	Diarrhoea 10 Granulocytopenia 8	Termination 4 %	24 (10–57)	1.4	–	–	–	–	5.6	0
Koom et al. (2012), retrospective (2000–2007)	Diarrhoea 9	–		14	5	–	–	27	14	0
Das et al. (2010), retrospective (2001–2005)	Nausea/vomiting 4	–	25 (0–71)	4	4	4	4	4	–	0
Milani et al. (2008), retrospective (2000–2005)	Gastrointestinal 12.5	0	–	–	–	–	–	–	–	–
Valentini et al. (2006), prospective (1997–2001)	Gastrointestinal 5	Break 10 % Termination 3 %	36 (9–69)	3	–	–	–	–	4	2.6

[a]Thirty-day surgical complications
[b]Resected patients

4.1.2 Reirradiation Tolerance of the Pelvic Organs to Long-Course Reirradiation

Escalating the dose of reirradiation might improve the chance of local control and survival (Haddock et al. 2001; Mohiuddin et al. 2002; Koom et al. 2012). However, it is still unclear what the optimal dose of reirradiation is, since the tolerance of pelvic organs to reirradiation is poorly understood.

In the series of Bosman et al., there were no significant differences of incidence of acute toxicity between patients who were previously irradiated versus those who were not. This finding is in accordance with many clinical studies that have shown an almost complete recovery of acute responding tissue within a few months from irradiation (Langendijk et al. 2006; Würschmidt et al. 2008).

Much lesser is known about the reirradiation tolerance for late effects. The risk of late complications may depend on prior radiation dose. Das et al. (2010) observed a significantly higher incidence of late toxicity in patients who had received a radiation dose of ≥54 Gy than in those who had received a lower dose. The interval from the previous radiotherapy course might also have an impact. Long-term complications were reduced significantly in patients whose interval to reirradiation was longer than 24 months in the series of Mohiuddin et al. (2002).

Tumour location can be a predicting factor for toxicity risk too. In the series by Koom et al. (2012), patients with an axial or anterior tumour location had a significantly higher rate of grade 3 or 4 late toxicities than patients with a lateral or posterior tumour location (64 vs. 9 %).

Many of the published studies have employed hyperfractionated regimens in an attempt to minimize potential late toxicity. Mohiuddin et al. (2002) evaluated long-term results of reirradiation in 103 patients with recurrent rectal carcinoma. Patients were treated with either 1.8 Gy fractions daily or 1.2 Gy fractions twice daily, with a median dose of 34.8 Gy. Long-term complications were significantly reduced in patients receiving hyperfractionated radiation.

Reported late complications of long-course reirradiation occurred to the small bowel, urethra (incontinence, stenosis), bladder (cystitis), ureter (stricture, leakage) and skin (ulceration, fibrosis, delayed wound healing). Thus all these organs should be considered at risk of injury.

The most frequently reported late toxicity in clinical trials of pelvic reirradiation is small bowel obstruction or stricture. Despite hyperfractionation, early studies of reirradiation reported small bowel obstruction in nearly 15 % of patients (Mohiuddin et al. 1997, 2002; Lingareddy et al. 1997). Among older series only in the study by Das et al. (2010), the incidence of small bowel obstruction was particularly low (4 %), maybe because special efforts were made to limit the volume of small bowel in the field, and most patients were treated in a prone position with a belly board device for bowel displacement. The incidence of small bowel obstruction was also low (less than 4 %) in modern series where smaller radiation volumes defined on simulation CT and more conformal techniques were used (Bosman et al. 2014; Ng et al. 2013; Sun et al. 2012; Das et al. 2010; Valentini et al. 2006). Among contemporary studies, the highest incidence of late bowel obstruction (14 %) was reported by Koom et al., particularly in patients with an axial or anterior recurrent tumour, even if reirradiation was delivered to limited volumes with 3DCRT or IMRT. Differently from other modern series, in the study by Koom et al., hyperfractionation was not used; on the contrary, many patients received moderate hypofractionation (up to 3 Gy per fraction).

Fistula formation has been reported to have an incidence of 4 % after reirradiation. Similarly to bowel obstruction, fistula formation is often associated with disease persistence or recurrence (all patients in the series of Mohiuddin et al. 2002).

In the series published by Sun et al., the dose allowed for the small bowel located in the radiation field was 10 Gy for less than 50 % volume (Sun et al. 2012). No specific dose constraints for the small bowel were used in the other series. Therefore, in order to minimize the risk of late injury to the small bowel, it seems reasonable to recommend any efforts to limit the volume of the small bowel in the field and to use hyperfractionated schedule whenever the small bowel cannot be completely excluded.

Intraoperative technical problems or poor healing of surgical wound is among the major concerns discouraging preoperative reirradiation. In the series of Mohiuddin et al. (2002), although wound healing was slower, surgical morbidity was not dissimilar to patients treated without preoperative reirradiation, and there was no mortality. In contrast to previously published data that indicated significantly higher postoperative morbidity rates after preoperative radiotherapy, wound-healing complications or other complications after multimodality treatment were comparable to previously described results of surgery for nonirradiated recurrent rectal cancer (Bosman et al. 2014, Haddock et al. 2001).

4.2 Reirradiation with Intraoperative Radiotherapy (IORT)

IORT is a treatment modality that allows the delivery of high dose to the tumour bed while moving out from the radiation field the radiosensitive bowel and bladder. IORT can be given by three different techniques: electrons (IOERT), high-dose rate (HDR) brachytherapy and low-dose rate (LDR) brachytherapy using iodine 125 seeds.

Studies on IORT have now been published for nearly 30 years; however, still the effect of IORT in rectal cancer treatment is not clear, with some authors who have reported higher overall survival and lower LR rate with IORT in locally advanced/recurrent rectal cancer (Eble et al. 1998; Gunderson et al. 1997; Mannaerts et al. 2001), while others did not confirm such results (Dresen et al. 2008; Ferenschild et al. 2006; Masaki et al. 2008; Dubois et al. 2011).

IOERT 15–20 Gy to the 90 % isodose was used as the sole reirradiation modality in 43 patients with LRRC by Roeder et al., but results were disappointing in patients with incomplete resection with 5-year local control and overall survival rate of 19 % and 11 %, respectively (Roeder et al. 2012).

Similarly, in other series where IOERT was used as a boost after external beam reirradiation (Bosman et al. 2014; Pacelli et al. 2010), resection margin remained the strongest prognostic factor for LC and OS with R1 having worse outcomes than R0 resection. This finding means that IOERT does not thoroughly compensate for an incomplete resection. Although many series with IORT reported encouraging results of local control for patients with R0 resection, for this subset of patients, the added value of IORT remains still unclear (Roeder et al. 2012).

In the series of Pacelli et al. (2010), no differences were observed with and without IOERT in the incidence of complications despite patients in the IOERT group had more advanced disease, suggesting that IOERT itself had not increased the risks associated with surgery.

Data on late toxicity are scarce. Peripheral neuropathy seems to be the main dose-limiting toxicity of IORT.

Eight percent of patients in the series of Roeder et al. (2012) complained of peripheral neuropathy including severe chronic pain. Neuropathy was found in 11 % of the patients receiving IOERT doses of ≥15 Gy compared to 6 % in patients with <15 Gy, but this difference was not statistically significant. The incidence and severity of neuropathy were related to IOERT dose also in the series by Haddock et al. (2011), and the authors suggest that limiting the IOERT dose to 12.5 Gy may result in decreased peripheral nerve toxicity.

The risk of peripheral nerves damage seems to be lower with intraoperative LDR brachytherapy probably due to the continuous low-dose rate irradiation delivered by the ^{125}I seeds (Martinez-Monge et al. 1998).

Goes et al. (1997) reported on 30 patients who, after undergoing laparotomy and either radical or debulking surgical resection, were treated with brachytherapy involving the temporary or permanent implant of seeds of iridium-192 or iodine-125. Local control was 37 % in patients with gross residual disease, and 66 % with microscopic residual disease. These results suggest that intraoperative ^{125}I or ^{103}Pd seed implantation might improve local control, even in patients with noncuratively resected recurrent rectal carcinoma after surgery and EBRT.

Further studies are needed to assess the value of IORT for reirradiation. While IOERT may be not as effective to eradicate the residual disease after an incomplete resection, it could be more effective against a smaller amount of residual cancer cells, for example, it could be considered in patients with R0 resection but close resection margins that carry a higher risk of local recurrence (Alberda et al. 2015). Intraoperative implantation of iodine 125 seeds for LDR has been poorly investigated but might be a promising alternative in patients with incomplete resection.

4.3 Reirradiation with Stereotactic Radiotherapy

To date surgical resection remains the standard therapy for LRRC, with continuous advances in the surgical techniques. However, in some cases, resection is not possible or cannot be performed safely for medical reasons such as comorbidities. In patients who cannot undergo surgery due to medical or technical reasons, long-course chemo-reirradiation is very effective for symptom palliation but offers only a poor chance of long-term tumour control. Highly conformal treatment planning by the use of IMRT or volumetric-modulated arc therapy (VMAT) combined with daily image guidance that allows for tight safety margins can reduce incidental exposure of normal tissue to high irradiation doses, and thus potentially allowing for delivering of hypofractionated irradiation with high-dose per fraction. This is the concept of stereotactic radiation therapy (SRT). A short duration of treatment can be very convenient for the patient as retreatment often takes place in a palliative setting. Furthermore, since different mechanisms such as vascular damage in addition to DNA strand breaks and/or chromosome aberrations may be involved in response of tumours to high dose per fraction (Song et al. 2015), SRT might overcome the radioresistance of radio-recurrent tumours.

Preliminary results suggest that this approach may be a desirable option in patients with LRRC eligible for reirradiation (Defoe et al. 2011; Dewas et al. 2011; Abusaris et al. 2012; Dagoglu et al. 2015). Particularly in small series, OS and local control rates were comparable with those achieved in series of multimodality approach including surgery, whereas incidence of severe toxicity was remarkable lower (Table 4).

Due to limited experience with SRT for reirradiation in LRRC tumours, neither selection criteria for this approach nor total and fractional dose prescription and dosimetric constraints for the organs at risk can yet been clearly established.

Tumour volume varied widely among series ranging from 6.7 to 1114 cc. Defoe et al. (2011) only included presacral tumour recurrences, Dewas et al. (2011) treated lateral pelvic recurrences only, whereas Abusaris et al. (2012) and Dagoglu et al. (2015) also considered for SRT anterior and lateral recurrences.

A wide range of total and fractional dose was used. The local control in patients treated with a dose of more than 60 Gy_3 was significant better than in patients treated with lower stereotactic reirradiation dose in the series by Abusaris et al. (2012), although the differences in overall survival were not significant.

Also the reirradiation dose to the organs at risk varied widely. In the study by Abusaris et al. (2012), the cumulative maximum dose allowed for the rectum and bowel was 110 Gy_3 where a maximum volume of 10 cc bowel or rectum was allowed to receive a higher dose. The cumulative maximum dose allowed for the bladder was 120 Gy_3, where 10 cc of the bladder was allowed to get a higher dose. Even if the constraints were exceeded in some patients, no acute or late severe toxicity was observed in this study. Applying the principle of ALARA (as low as reasonably achievable) radiation dose to volumes of normal tissues as done by Dagoglu et al. (2015) seems therefore a reasonable approach in clinical trials of SRT for reirradiation of LRRC. All structures that could develop a late damage should be considered as organs at risk when calculating the treatment plan. In series of SRT reirradiation, late toxicity

Table 4 Disease control and survival outcome in clinical trials of stereotactic reirradiation

Author, publication year and study design (inclusion period)	Patient n°	Tumour volume cc median (range)	Previous radiation dose Gy, median value (range)	Reirradiation median total dose (range)/ fractionation	Technique	Median follow-up months (range)	Local control	Overall survival	Pain relief	Grade 3–4 toxicity
Dagoglu et al. (2015), retrospective (2006–2012)	18	90 (36.8–1029.4)	50.4 (25–100.4)	25 (24–40)/5 (3–6) to median isodose 78 % (69–86 %)	CyberKnife	38 (6–86)	68.7 % (2-year)	65.9 % (2-year)	[c]	16.6 % 1 small bowel perforation, 1 neuropathy, 1 hydronephrosis
Abusaris et al. (2012), retrospective (2005–2009)	22[a]	PTV 154 (6.7–1114.5).	EQD2 31–83 Gy10)	34 (8–60)/in 1–10 fractions to 70–85 % isodose	CyberKnife	15 (2–52)	53 % (2-year)	37 % (2-year)	95 % (at least partial relief)	0
Defoe et al. (2011), retrospective (2003–2008)	14[b]	52.5 (19–110)	50.4 (20–81)	36 Gy in 3 fractions, 2–3 times per week or single SBRT dose (12, 16 or 18 Gy) to the 80 % isodose	CyberKnife	16.5 (6–69)	68.2 % (2-year)	78.8 % (2-year)	57.1 % (complete relief)	0
Dewas et al. (2011), retrospective (2007–2010)	16[c]	Not reported	45 Gy (20–75 Gy)	36 Gy in 6 fractions over 3 weeks to the 80 % isodose	CyberKnife	10.6 (1.9–20.5).	51.4 % (1-year)	46 % (1-year)	50 % (partial relief)	0

[a]13 LRRC
[b]Presacral tumours only
[c]Lateral tumour only, 4 LRRC

occurred at the level of the small bowel (perforation), nerves (neuropathy with weakness and dumbness of the lower limb and pelvic pain) and ureter (ureteric fibrosis causing hydronephrosis) (Dagoglu et al. 2015).

All published series of SRT reirradiation for LRRC used the CyberKnife technology. Patient positioning and image guidance was performed with registration to the patient's spine and pelvic bones (Dewas et al. 2011) or real-time fiducial tracking (Dagoglu et al. 2015; Abusaris et al. 2012; Defoe et al. 2011). However, it is well known that the position of the organs at risk, particularly the small bowel and the bladder, can change during treatment delivery, thus potentially moving into the high-dose region. While two-dimensional localization systems cannot detect such inter- and intra-fractional movements, volumetric onboard image guidance systems such as onboard CT or MR potentially can, thus allowing a further minimization of the risk of severe injury.

4.4 Reirradiation with Brachytherapy

Interstitial brachytherapy might be an alternative in the treatment of LRRC in patients who cannot or choose not to undergo radical surgical resection. Particularly, percutaneous image-guided seed implantation, which can be performed without surgery or general anaesthesia, has attracted increasing attention. Indeed in contrast to EBRT and IORT, it has the advantage of delivering low-dose-rate radiation, which allows continuous DNA repair of sublethal damage to occur in the normal tissues while ensuring protracted cancer cell killing, and thus resulting in a wider therapeutic index. Another advantage of interstitial brachytherapy is the relatively rapid dose fall-off. These benefits allow higher cumulative doses to be delivered, which may provide better tumour control. However, there are few reports on CT-guided implantation of radioactive seeds in the treatment of localized pelvic recurrences (Table 5) (Wang et al. 2010, 2011; Bishop et al. 2015).

In all these reports, patients were selected based on the technical feasibility of performing brachytherapy, the size of the recurrent lesions and the proximity of the lesions to critical organs. Particularly in the series of Bishop et al., patients with less infiltrative and smaller lesions were selected over time, after initial results for patients with larger tumours were unsatisfactory.

Interestingly in the series of Wang et al. (2010), three patients had ever received radiotherapy twice.

In such selected populations of patients, CT-guided interstitial brachytherapy led to durable local control and long-term survival. Treatment was also well tolerated and symptomatic palliation was common.

4.5 Reirradiation with Particle Therapy

Particle therapy using protons (^{1}H) or carbon ions (^{12}C) offers physical and biological advantages compared to photon radiotherapy. With particle therapy the dose can be precisely applied while avoiding normal tissue irradiation due to the high local-dose deposition within the Bragg peak. Moreover, ions offer an increased relative biological effectiveness (RBE), which for ^{12}C in particular, can be calculated between 2 and 5 depending on the cell line as well as the endpoint analysed, due to an increased induction of clustered DNA double-strand breaks within the irradiated cells, which are difficult to repair by the cells' intrinsic repair mechanisms. This higher relative biological effectiveness (RBE) can translate into improved clinical results (Combs et al. 2012).

Preliminary results of the phase I/II German trial PANDORA using carbon ions for reirradiation of LRRC were recently published. Ninety-nine patients treated with ^{12}C reirradiation at the Heidelberg Ion-Beam Therapy Center (HIT) between 2010 and 2013 were included in this preliminary analysis. All patients had a history of surgery and pelvic radiotherapy of at least 50.4 Gy. Median dose was 36 Gy [relative biologic efficacy (RBE)] [range 36–51 Gy (RBE)],

Table 5 Disease control and survival outcome in clinical trials of interstitial LDR brachytherapy

Author, publication year and study design (inclusion period)	Patient n°	Tumour volume cc median (range)	Previous radiation dose Gy, median value (range)	Reirradiation median total dose (range)/ fractionation	Technique	Median follow-up months (range)	Local control (2-year)	Overall survival (2-year)	Pain relief	Grade 3–4 toxicity
Bishop et al. (2015), retrospective (2000–2012)	20	n.r.	90 (72–149)	80 Gy at a 1-cm margin or 120 Gy to 100 % of the GTV	CT-guided percutaneous seeds implantation (^{198}Au or ^{125}I)	23 (13–132)	60 %	62 %	69 %	1 patient ureteral stricture
Wang et al. (2011), retrospective (2006–2009)	20	Volume implanted 68.9 (26.9–97.3)	70 % of patients, 60 Gy (50–70)	Median minimal peripheral dose 120 Gy (range 100–160)	CT-guided percutaneous seeds implantation (^{125}I)	22 (3–34)	15 %	25 %	85 %	1 patient ureteral stricture
Wang et al. (2011), retrospective (2006–2009)	15	n.r.	n.r.	Median minimal peripheral dose 150 Gy (range 110–165)	CT-guided percutaneous seeds implantation (^{125}I or ^{103}Pd)	8 (4–50)	8.1 %	10.7 %	53.8 %	1 cutaneous fistula (tumour invasion of the perineal skin)

n.r. not reported

and median planning target volume was 456 ml (range 75–1,597 ml). After a median follow-up of 7.8 months, three patients (16 %) died, four patients (21 %) experienced local progression after RT and three patients (16 %) were diagnosed with distant metastases. No grade 3 or higher toxicities were observed.

Conclusions

For patients with isolated LRRC or primary locally advanced rectal cancer after previous pelvic irradiation, the complete surgical removal (R0 resection) of the tumour is the most important measure to achieve long-term local control of the disease and survival. Preoperative long-course chemo-reirradiation can improve the chance of R0 resection without adding unacceptable morbidity if proper caution is paid to both radiation and surgical techniques. The use of small radiation fields, exclusion of the bowel and bladder and the use of hyperfractionated radiation doses up to 40 Gy are recommended.

Although intraoperative delivery of reirradiation doses lower than 15 Gy is feasible, the added value of IORT is still unclear.

In patients who cannot undergo surgery due to medical or technical reasons, long-course chemo-reirradiation is very effective for symptom palliation but offers only a poor chance of long-term tumour control. Patients with small isolated LRRC who cannot undergo surgery due to medical or technical reason might benefit from image-guided stereotactic reirradiation with the aim of achieving both palliation and long-term local control. Percutaneous image-guided seed implantation for LDR interstitial brachytherapy can be also considered in this subset of patients, especially for LRRC that is very close to critical normal structures.

Particle therapy, due to its physical and biological characteristics, might offer a chance of cure in nonsurgical candidates with large isolated LRRC. However, the optimal dose applicable in this clinical situation as well as efficacy as reirradiation still has to be determined.

Since distant metastases are a major problem in surviving patients, the role of anticancer drugs in reducing distant recurrences should also be explored.

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