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Should radiotherapy be avoided or delivered differently in elderly patients with rectal cancer?

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ABSTRACT

Purpose is to give an overview of treatment possibilities of rectal cancer over time, but also of the real management of rectal cancer especially in relation to age. From literature search representative randomised studies on patients with resectable rectal cancer, comparing only surgery, post- and preoperative radiotherapy with or without chemotherapy, are reviewed. We also reviewed the literature regarding radiotherapy for rectal cancer described in population-based studies.

The overview of the trials showed that preoperative radiotherapy improves local control in relation to no or postoperative radiotherapy. Adding chemotherapy did not significantly improve survival. No relations were seen between age and complications. All population-based studies showed that increasing age is associated with less (neo)adjuvant treatment.

To avoid local recurrence, the best possible treatment, being preoperative RT, should be given to all patients with resectable rectal cancer, irrespective of age.

1. Introduction

In literature there is no clear definition of 'elderly' patients. It is however important to realise that 80% of all patients with rectal cancer is over the age of 60 years, 50% over the age of 70 years and 20% over the age of 80 years. The only treatment modality in rectal cancer for cure is radical (pathological negative tumour margins) surgery. The aim of (neo)adjuvant treatment is the reduction of local recurrences and the improvement of survival. A number of trials assessed the use of either pre- or postoperative radiotherapy (RT). Preoperative RT has the advantage of intact anatomy (vasculature) and good oxygenation of the tumour cells. Well oxygenated tumour cells are more susceptible for irradiation than relative hypoxic cells. Depending on whether a short (e.g. 5×5 Gray (Gy)) or long irradiation course is given, devitalisation or downsizing/downstaging of the tumour can occur. Disadvantages of preoperative RT are that all tumours are irradiated and thus overtreatment may occur for low-staged tumours. Furthermore in case of a long course of preoperative irradiation exact pathological staging is not possible anymore.

The main advantage of postoperative RT is the selection of patients who may benefit of adjuvant treatment on the basis of pathological tumour staging, thus avoiding overtreatment. Disadvantages of postoperative RT are the relative hypoxia in the operated area making tumour cells less susceptible for irradiation and the small bowel that will be in the irradiation fields causing acute and late toxicity.

Although survival is the most important endpoint of any cancer treatment, especially in rectal cancer the avoidance of a local recurrence, causing a very negative impact on the quality of life, is of utmost importance. Meta-analyses[1,2] show that postoperative RT has no impact on survival while preoperative RT is reported to have a significant, be it modest, positive effect. Both post- and preoperative RT reduce

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the local recurrence rate significantly, preoperative RT being more effective than postoperative RT. We give an overview of the treatment possibilities of rectal cancer over time. However, since population-based studies provide insight in the real management of patients with rectal cancer especially in relation to age, this issue will be addressed separately.

2. Methods

In preparation of the national Dutch guidelines for peri-operative RT for rectal cancer, an extensive literature research was performed in (inter)national guideline databases, websites of oncology societies, Medline, Embase, etc., for reviews, controlled randomised trials, etc. in order to establish the role of peri-operative RT with or without chemotherapy (CT) for today's clinical practice. From these results a representative number of reviews and trials over the last two decades is shown to highlight the evolution to the present status of peri-operative RT.

We also reviewed the literature regarding RT for rectal cancer described in population-based studies. For this a computerised search of the literature was performed in Pubmed with the terms population-based, radiotherapy and rectal neoplasms. The reference lists of all identified publications were checked to retrieve other relevant publications, which were not identified by means of the computerised search. With the above mentioned search we identified 22 publications, of which hard copies were obtained. Studies were included if they described, in a population-based setting, RT use or RT use in combination with CT in relation to age. We limited our search to English, German and Dutch language studies.

3. Results

The selected trials are described hereafter in chronological order and are summarised in Table 1. Four of these trials used no age-limitation during the randomization.

Two Scandinavian studies, the Stockholm study[3] and SRCT study,[4–6] comparing surgery versus surgery and a short course of preoperative RT (5×5 Gy in 1 week), showed a significant reduction of the local recurrence rates in favour of the irradiated patients. Due to the large irradiation fields (up to L2) and the irradiation techniques (2 opposing fields) there was an 8% postoperative mortality rate in the irradiated group in the Stockholm trial. This mortality excess disappeared when irradiation was limited to the small pelvis and multiple field technique was used as in the SRCT trial. Cancer specific survival was significantly improved in both trials. Perineal wound healing problems were seen significantly more in the irradiated group especially when the perineum was included in the irradiation fields and an abdominal perineal resection had been performed. Another Scandinavian study,[7,8] the only one in the world until now comparing a short course of preoperative RT with postoperative RT, showed a significant reduction in local recurrence rate in favour of the preoperative short course; survival was not significantly different. However, the patients in the preoperative irradiated group had significantly more perineal wound healing problems (acute toxicity). Small bowel obstructions as well as grade 3 toxicity occurred more often in the postoperative irradiated group (late toxicity). Noteworthy was the fact that 50% of the patients could not start their postoperative treatment within 6 weeks of operation. In 1991 Krook and colleagues[9] published the results of a study comparing postoperative RT alone with postoperative RT and CT. Local recurrence and distant metastases rates were significantly reduced in the combined modality arm; survival was significantly improved in the combined modality arm. Toxicity was comparable between both arms. The Dutch TME trial[10–15] comparing total mesorectal excision (TME) versus a short course of preoperative RT (5×5 Gy in 1 week) followed by TME within one week showed a significantly lower 5-year local recurrence rate for the irradiation arm. Survival was the same. Perineal wound healing disturbances (acute toxicity) and bowel dysfunction (late toxicity) were seen significantly more in the irradiated group. Sauer and colleagues[16] published in 2004 the results of a German study comparing preoperative CT–RT versus postoperative CT–RT. The local recurrence rate was lower for patients treated preoperative with CT–RT; survival was the same. Both acute and late toxicities were significantly increased in the postoperative treated group. Furthermore, ±50% of the patients treated postoperative did not receive full course irradiation or CT. The EORTC 22921 study[17] comparing long course preoperative RT versus preoperative CT–RT versus preoperative RT followed by postoperative CT versus preoperative CT–RT followed by postoperative CT described a significant difference in local recurrence rates in favour of the CT-arms; survival was the same. Similar results were reported from the French FFCD 9203 study[18] comparing preoperative RT versus preoperative CT–RT, both arms followed by adjuvant CT. Bujko and colleagues reported in a randomised trial comparing preoperative short-course RT with preoperative conventionally fractionated CT–RT no differences in survival, local control nor late toxicity.[19]

In contrast with clinical studies, population-based studies are the best way to assess the management of a disease in daily practice. We found 10 population-based studies (described below, summarised in Table 2), all published after 1999, describing the management of patients with rectal cancer in relation to age. Most studies examined the relationship between patient characteristics, among which age, and the use of adjuvant (pre- or postoperative) RT or RT and CT. However, this was not always the only endpoint.

Paszat and colleagues described the use of surgery for rectal cancer and the subsequent risk of permanent colostomy. Patients older than 80 years were less often irradiated after resection without colostomy in relation to younger patients.[20] Schrag and colleagues examined the relationship between patient characteristics and the use of RT with and without CT among patients aged 65 years or older with stage II and III rectal cancer. The chance to receive RT (mostly postoperative) or RT combined with CT was significantly lower for patients older than 69 years of age.[21] Schroen and colleagues identified patient, hospital and surgeon characteristics associated with variation in treatment. The compliance for RT in stage II and III was 73% for patients

Table 1 – Nine randomised studies comparing different treatment modalities in patients with resectable rectal cancer

Study	Author	Number of patients	Age limit	Year start trial	Year results	Treatment-arms	Local recurrence rate	Survival
Stockholm study	Stockholm Rectal Cancer Study Group[3]	849	No upper age limit	1980	1990	S versus RT (5 × 5 Gy) + S	4 year: 23% versus 11%, $p \leqslant 0.01$	4 year: 50% versus 60%, $p = 0.05$
Swedish rectal Cancer Trial	Folkesson et al.[4–6]	1168	<80	1987	2005	S versus RT (5 × 5 Gy) + S	13 year: 26% versus 9%, $p \leqslant 0.001$	13 year: 62% versus 72%, $p = 0.03$
Upsala trial	Frykholm et al.[7,8]	471	No upper age limit	1980	1990	S + RT (60 Gy) versus RT (5 × 5 Gy) + S	5 year: 22% versus 13%, $p = 0.02$	5 year: NS
USA	Krook et al.[9]	204	No upper age limit	1980	1991	S + RT (45–50 Gy) versus S + RT (45–50 Gy) + CT	7 year: 25% versus 13.5%, $p = 0.04$	7 year: 48% versus 57%, $p = 0.03$
TME	Kapiteijn et al.[10–15]	1861	No upper age limit	1996	2005	S (TME) versus RT (5 × 5 Gy) + S (TME)	5 year: 11% versus 6%, $p = 0.001$	5 year: NS
Germany	Sauer et al.[16]	823	<75	1994	2004	S + CT + RT (50 Gy) versus CT + RT (50 Gy) + S	5 year: 13% versus 6%, $p = 0.006$	5 year: NS
EORTC 22921	Bosset et al.[17]	1011	<80	1993	2005	RT (45 Gy) + S versus CT + RT (45 Gy) + S versus RT (45 Gy) + S + CT versus CT + RT (45 Gy) + S + CT	5 year: 17% versus 9% versus 10% versus 8%, $p = 0.002$	5 year: NS
FFCD 9203	Gerard et al.[18]	733	<75	1993	2005	RT (45 Gy) + S + CT versus RT (45 Gy) + CT + S + CT	5-year: 16.5% versus 8%, $p = 0.003$	5 year: NS
Poland	Bujko et al.[19]	312	<75	1999	2006	RT (5 × 5 Gy) + S versus RT (50 Gy) + CT + S	NS	NS

RT = radiotherapy, CT = chemotherapy, S = surgery, Gy = Gray, NS = not significant.

younger than 60 years of age and only 25% for patients aged 75 years or older. After adjusting patients aged 60 years or younger received 9.5 times more often a combination of surgery, RT and chemotherapy for stage II and III rectal cancer than patients aged 76 or older.[22] Dharma-Wardene and colleagues also found that elderly patients (⩾75 years) received multimodality therapy less often than younger patients; they also described a risk of death 2.35 higher for patients aged 75 or older receiving surgery only with respect to elderly patients undergoing surgery plus multimodality therapy.[23] In the study of Neugut and colleagues an increasing age was associated with a decreased probability of adjuvant treatment with RT and CT. Combined RT and CT was associated with improved survival for stage III rectal cancer.[24] Ayanian and colleagues found a significantly lower chance to receive RT for patients older than 75 years of age. The lack of clinical efficacy was cited by physicians as the most common reason for not administering radiation therapy to patients with rectal cancer, followed by patient refusal and co-morbidity.[25] Phelip and colleagues described a shift from postoperative RT in 1990 into preoperative RT in 1995, when 72% of all irradiated patients received preoperative RT. Patients aged 75 or older were given adjuvant RT half as often as younger patients, and major geographical differences were observed.[26,27] In the USA an increase was seen in adjuvant RT from 1976 to 2000, with a shift into preoperative RT from 1996; patients who underwent RT were younger than those who did not undergo RT, also in multivariate models.[28] Also in our own region we found a significantly lower use of RT for elderly patients.[29]

4. Discussion

All population-based studies showed that increasing age is associated with less (neo)adjuvant treatment. Also other authors described this phenomenon.[30–32]

The fear that elderly patients do not tolerate radical pelvic RT as well as young patients is not substantiated in the study by Pignon and colleagues;[33] they conclude that age per se is not a limiting factor. Also doctors or patients' preference, co-morbidity or frailty, socio-economic factors or fear for toxicity may play a role. Shahir and colleagues described an almost twofold higher complication risk within one year after diagnosis for patients who underwent surgery and RT, and for patients aged 70 years or older, but no association was made between age and RT.[34]

Increased postoperative mortality, mainly among elderly patients, was described in two studies, in which a short course of preoperative RT was given in large irradiated pelvic fields.[2,3,35] All other randomised studies we described, used other RT techniques with smaller tissue volumes. In these studies no relations were seen between age and complications, so it is tempting to believe that a large irradiated volume may be deleterious in the older age group.

At this moment staging (by imaging), preoperative treatment and TME-surgery are cornerstones in the treatment of rectal cancer. The choice however between a short preoperative RT course or a long preoperative CT–RT course is made difficult by lack of exact definitions of 'early', 'mobile', 'resectable' and 'locally advanced' rectal cancer. Due

Table 2 – Population-based studies describing radiotherapy or radiotherapy and chemotherapy for resectable rectal cancer in relation to age

Author, study period	Purpose	Number of patients	Stage and age inclusion	Percentage RT	Multivariate analyses
Paszat et al.,[19] 1982–1994	To describe the use of surgery and RT for newly diagnosed rectal cancer patients and the subsequent risk of permanent colostomy	18,695	All stages, all ages	1982: 5%, 1994: 22%	Odds for RT after resection without colostomy: (ref = 60–69), 70–79 = 0.6, 80+ = 0.2 (all sign)
Schrag et al.,[20] 1992–1996	To examine the relationship between patient characteristics and the use of RT with and without CT among patients aged 65 and older with stage II and III rectal cancer	1670	II and III, >65	Total: 57%; 65–69: 73%, 70–74: 66%, 75–79: 52%, 80–84: 39%, 85+: 21%	Odds for RT: (ref = 65–69), 70–74 = 0.7, 75–79 = 0.4, 80–84 = 0.2, 85+ = 0.1 (all sign)
Schroen et al.,[21] 1994–1996	To assess the use of surgical procedures and adjuvant therapy in the initial treatment of rectal cancer and to identify patient, hospital and surgeon characteristics associated with variation in treatment	637	All stages, all ages	Total: 37%. stage I: 14%, stage II: 53%, stage III: 63%, stage IV: 30%	Odds for S, RT, CT in stage II and III: (ref = >76), 70–75: 4.2, 60–69: 4, <59 = 9.5 (all sign)
Dharma-Wardene et al.,[22] 1991–1998	To describe relationship between age and treatment, to compare risk of death in elderly (⩾75 years) receiving optimal (S + RT + CT) regimen with those who received surgery only, and to compare 5-year survival for each treatment group	1979, random subsample of 259	All stages, all ages	Total: 59%	Univariate: elderly (= >75) less often multimodality treatment ($p = 0.0001$)
Neugat et al.,[23] 1992–1996	To investigate the use of treatment with CT and RT among patients over 65 years with surgically resected stage II or III rectal cancer	1807	II and III, >65	Total: 48%. 65–69: 66%; 70–74: 55%; 75–79: 47%; 80–84: 34%; 85+: 17%	Odds for RT + CT: (ref = 65–69), stage II: 75–79 = 0.4, 80–84 = 0.3, 85 + = 0.07. Stage III: 70–74 = 0.4, 75–79 = 0.25, 80–84 = 0.1, 85 + = 0.04 (all sign, p-trend = < 0.01)
Ayanian et al.,[24] 1996–1997	To estimate underreporting of adjuvant therapies in routinely collected registry data, assess rates of adjuvant therapy and factors associated with use, and ascertain why eligible patients were not treated	1956	II and III, >18	<55: 82%, 55–64: 76%, 65–74: 68%, 75–84: 47%, 85+: 14%	Odds for RT: (ref = 65–74), 75–84 = 0.3. 85 + = 0.1. Odds for RT + CT: <55 = 2.7, 75–84 = 0.3, >85 = 0.1 (all sign)
Phelip et al.,[26] 1995	To determine whether diagnostic and therapeutic management practices for rectal cancer vary in different geographic regions	683	All stages, all ages	Total: 47%	Odds for RT: (ref = <75), >75 = 0.47 (sign)
Phelip et al.,[25] 1990 and 1995	To evaluate how the results of a consensus conference (1994) were taken into account	1990: 402, 1995: 543	All stages, all ages	1990: 42%, 1995: 47%	Odds for preop RT: (ref = <75), >75 = 0.67 (sign)
Baxter et al.,[27] 1976–2000	To evaluate US trends in adjuvant RT over 25-year, timing of RT and factors affecting RT	45,000	All stages, > 18	Total: 32%; 1976: 12%, 2000: 42%	Odds for RT in stage II and III: (ref = >70), 65–70 = 3, <60 = 5 (all sign)
Vulto et al.,[28] 1995–2002	To study the influence of age (and co-morbidity) on primary RT	3058	I–III, >50		Odds for RT: (ref = 50–64), 65–79 = 0.7, 80 + = 0.4 (all sign)

RT = radiotherapy, CT = chemotherapy, S = surgery, ref = reference category, sign = significant.

to the overlap of tumour stages between these groups there is a risk of under- or overtreatment. We consider T4 tumours and tumours with a margin less than 2 mm to the perirectal fascia on MRI as 'locally advanced'. In recent years, the value of MRI for reliable prediction of the circumferential resection margin has been established. In single institution studies it was demonstrated that it allows accurate assessment of the circumferential resection margin and by that the choice for optimal therapy. A recent publication of the Mercury study confirmed the reliability of MRI in a multicenter setting. Therefore, MRI should now be considered as standard of care in the preoperative work-up for rectal cancer patients.[36] N2 tumours can be considered as 'locally advanced' also, but the problem is the clinical determination of the N2 status. The issue of sphincter-saving surgery after long preoperative chemo-radiotherapy has not been solved yet.

Given the lack of improvement of survival in trials using long course preoperative CT–RT the question remains whether CT should be added to reduce the local recurrence rate considering the results of the short course preoperative RT trials. We believe that, when no downsizing/-staging is needed, 5×5 Gy followed by TME within one week of completion of RT is the treatment of choice. If the tumour is located more than 10 cm above the anal verge omission of RT may be considered. In case of locally advanced tumours a long course of preoperative CT–RT followed by operation approximately 6 weeks later (in order to achieve downsizing/-staging) is necessary. Depending on the patient' status a short course of preoperative RT like 13×3 Gy with operation 6–8 weeks later (Lyon R90-01 trial) [37] or even 5×5 Gy followed by surgery after more than 4 weeks can be considered (Bujko[19] or ongoing Stockholm-III trial). As pointed out by Rutten and colleagues in 'Rectal cancer treatment in the elderly' (this EJC issue[38]) future studies may focus on delayed TME surgery after a short course of preoperative RT, in order to reduce the hazard of double trauma by RT and surgery. For more locally advanced tumours the role of local excision after preoperative treatment or even chemoradiotherapy alone and omitting surgery in order to reduce the risk of surgical trauma may be explored.[38,39]

5. Conclusion

Preoperative (chemo)-radiotherapy improves local control in rectal cancer. No differences were seen in toxicity between young and elderly patients when modern RT techniques with small tissue volumes are used. To avoid local recurrence, the best possible treatment should be given to all patients with resectable rectal cancer, irrespective of age: a short preoperative RT course for patients with a primary resectable tumour, a long course of preoperative CT–RT for patients with locally advanced tumours. Exceptions should be made only for patients who are unable to fulfil the combination treatment because of patients' condition.

Conflicts of interest statement

None declared.

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