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Original Article

Determining the use of preoperative (chemo)radiotherapy in primary rectal cancer according to national and international guidelines

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ABSTRACT

Background: Pre-operative radiotherapy (RT) or chemoradiotherapy (CRT) is frequently used prior to rectal cancer surgery to improve local control and survival. The treatment is administered according to guidelines, but these recommendations vary significantly between countries. Based on the stage distribution and risk factors of rectal cancers as determined by magnetic resonance imaging (MRI) in an unselected Swedish population, the use of RT/CRT according to 15 selected guidelines is described.

Materials and methods: Selected guidelines from different countries and regions were applied to a well-characterized unselected population-based material of 686 primary non-metastatic rectal cancers staged by MRI. The fraction of patients assigned to surgery alone or surgery following pre-treatment with (C)RT was determined according to the respective guideline. RT/CRT administered to rectal cancer patients for other reasons, for example, for organ preservation or palliation, was not considered.

Results: The fraction of patients with a clear recommendation for pre-treatment with (C)RT varied between 38% and 77% according to the different guidelines. In most guidelines, CRT was recommended to all patients who were not operated directly, and, in others, short-course RT was also recommended to patients with intermediate risk tumours. If only non-resectable or difficult to resect tumours were recommended pre-treatment, as stated in many Japanese publications, 9% would receive CRT followed by a delay to surgery.

Conclusions: According to most guidelines, well over 50% of primary non-metastatic rectal cancer patients from a general population, in which screening for colorectal cancer is not practised, are recommended treatment with pre-operative/neo-adjuvant therapy.

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Radiotherapy (RT) or chemoradiotherapy (CRT) has a role in the management of many rectal cancers, but its use varies considerably [1–3]. The most obvious use is to enable radical surgery of a non-resectable tumour. Pre-operative CRT followed by delayed surgery is recommended to downstage/downsize the tumour in such cases [4]. As an alternative, short-course RT (5 × 5 Gy delivered in one week, scRT) has been used in patients who are not considered to tolerate CRT [5–7]. Neo-adjuvant therapy is often given to decrease local recurrence (LR) rates in less advanced cases considered resectable but running a risk of LR. Several randomised trials have shown that these LR rates are reduced by 50–70% with the help of RT [8–10]. Such cases do not require downstaging/downsizing, and surgery could be performed immediately after treatment. The scRT schedule was developed for this purpose [11] and has been extensively used [8–10,12,13]. A frequently recommended alternative is to give CRT with a subsequent delay, since CRT is more efficient than the same long-course RT in reducing local failure rates [14,15]. In this group of patients, two trials have shown that the two alternatives, scRT with immediate surgery or CRT with delayed surgery, result in the same LR rates and survival [16,17]. The application of scRT with delayed surgery has also become popular in this group since it results in downstaging/downsizing [13,18]. The additional treatment (usually CRT) could also be administered post-operatively but is no longer recommended in most guidelines since pre-operative therapy is more efficient and less toxic [19]. Finally, treatment with RT/CRT is increasingly used to limit or avoid surgery, i.e. as a sphincter or organ preservation strategy [20–22]. For this purpose, a prolonged delay after the RT/CRT is required to allow a maximum decrease in the tumour mass, with, if no surgery is aimed at, complete disappearance of the tumour (clinical complete remission, cCR).

The scientific evidence for favourable effects to increase resectability and decrease LR rates is based on large randomised studies, whereas the evidence for more limited surgery or no

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surgery at all is limited. Despite solid documentation, diverse recommendations for the use of pre- or post-operative RT/CRT or RT/CRT alone exist [23], leading to considerable geographical variations [1,2,24–27].

We have recently described the distribution of stages, or categories, according to relevant MRI-parameters in a large unselected population of primary rectal cancers [28]. In this population, it is possible to estimate the proportions of non-metastatic rectal cancer patients who were recommended RT/CRT according to different guidelines, to better understand the wide variability seen across the world and to help estimate radiotherapy resources.

Patients and methods

All 968 patients with a rectal cancer diagnosed between 2010 and 2016 in two counties (total population 630,000 in 2015) in Sweden were identified via nationwide registries with a near 100% coverage [28]. Since 2007, it is recommended that all patients are staged with MRI of the pelvis and computed tomography (CT) of the thorax and abdomen, discussed at a multidisciplinary team (MDT) meeting [29] and reported to the nationwide Swedish Colorectal Cancer Registry (SRCRC) [30]. Relevant information in the SRCRC was confirmed in the original radiology reports and clinical records from the surgeon, clinical oncologist, radiologist and pathologist participating in the MDT conference. MRI investigations were performed as described [31]. In cases of missing information, the original images were re-evaluated. The UICC TNM-7 classification was used.

Identification of national and international guidelines and referral to prognostic groups

Representative guidelines were identified and used in the estimation of the proportion of patients recommended to treatment with pre-operative (C)RT. In the guidelines, two, three or, recently, more risk groups were identified. If two groups, they were classified as low and high risk (or early and locally advanced, corresponding to stage I and stages II + III, respectively); if three groups, low, intermediate/moderate and high risk (or early, intermediate, locally advanced). Referral to the prognostic groups was based on clinical criteria (described below), endoscopy examination and MRI characteristics (some guidelines permit ERUS). Selected guidelines and criteria used for risk group characterization are described in Supplementary Table 1.

Estimation of percentage of rectal cancers with different risk criteria and treatment allocation

The different guideline criteria were applied to a Swedish material of completely staged non-metastatic rectal cancers ($n = 686$, Fig. 1). As a result, the cohort was divided into subgroups based on stage and other relevant parameters such as tumour height, distance to the mesorectal fascia (MRF) and MRI-identified extramural vascular invasion (mrEMVI) status. Based on these specifics, each tumour was allocated to one subgroup, and each subgroup was then allocated to either direct surgery or to receive presurgical treatment with CRT or scRT according to the different guidelines. If a risk group was recommended to more than one treatment, this was noted. RT/CRT for organ preservation was not considered since this indication has not yet been included in most guidelines. Neither was post-operative treatment considered, even if several guidelines provide recommendations as to when it should be used, if pre-operative therapy was not administered. Patient-related factors were also not considered, even if they are important in daily practice. In most guidelines, the rectum is defined as the distal 15 cm above the anal verge and the proportions irradiated were calculated based upon this definition. The 15-cm long rectum is often divided into three parts, low (0–5 cm), middle (5–10 cm) and high (10–15 cm). Some guidelines only provide recommendations for tumours up to about 10 cm above the anal verge, in these cases the proportions irradiated are also adjusted to comply with this definition.

Statistics

Guideline comparisons were carried out using descriptive statistics in Microsoft Excel (version 16). Data were visualized in pie charts and in a Likert plot created in R (version 3.4.3). For categorical variables, differences between groups were investigated using the Chi-square test of independence. The level of statistical significance was set at $P < 0.05$. Statistical analyses were performed using the IBM®SPSS® statistical software version 24.0.

The study was approved by the research ethics committee of Uppsala University (Dnr 2011/092).

Results

Factors considered in guidelines and distribution of characteristics in the Swedish population

All factors considered of relevance in the different guidelines are presented in Table 1. Of greatest importance when deciding whether pre-operative treatment should be given or not are clinical tumour (cT) and nodal (cN) categories. cT-category is in all but the Norwegian [32] guideline most important, either directly (category cT1-4) or indirectly (UICC/AJCC stage II, cT3-4N0; stage III cTanyN+). In cT4, the separation between cT4a and b is sometimes important [33–35]. A few guidelines take into consideration whether cT4 tumours are (easily) resectable or not [33,34,36,37]. Nodal category (cN0 or cN+) is considered in most, but not all guidelines [32,36], reflecting the inaccuracy of nodal imaging [38]. In two guidelines [33,34], cN1 is handled differently from cN2. Tumour level, extramural distance (EMD, categorized in cT3 as subcategories a–d) and/or distance to the MRF (in low-lying tumours the intersphincteric fascia) expressed in mm (most often <1 mm, designated MRF+, or ≤2 mm, here designated MRF ≤2) are also frequently considered. Two guidelines do not consider EMD/distance to MRF [39,40]; NCCN incorporated distance to MRF in their recommendations in 2018 [41]. In a few guidelines, mrEMVI [33–35,42] and/or lateral node involvement [34,35,43] (LN+, not considered in this investigation) are considered. Tumour differentiation is not considered in any guideline, except in EORTC that considers a mucinous character on MRI as being of possible relevance [33].

The distribution of the 686 completely staged non-metastatic rectal cancers in the Swedish material according to these criteria is shown in Table 2. The number of cases in each cTN category is shown in Fig. 1. For reasons of comparison, the distribution of characteristics is also shown in primarily metastatic patients, revealing significantly more advanced tumours ($P < 0.001$) (Supplementary Table 2). The distance to the MRF, of importance in many guidelines, in cT2 and cT3a-d is demonstrated in Table 3.

Pre-operative RT/CRT according to MRI characteristics in different guidelines

The fraction of patients recommended to undergo surgery directly versus receive pre-operative treatment is shown in Fig. 2. The guideline recommendations and pie charts with brief comments to explain the differences between guidelines are presented in Supplementary Table 1 and Supplementary Fig. 1. The fraction with unambiguous pre-treatment recommendations var-

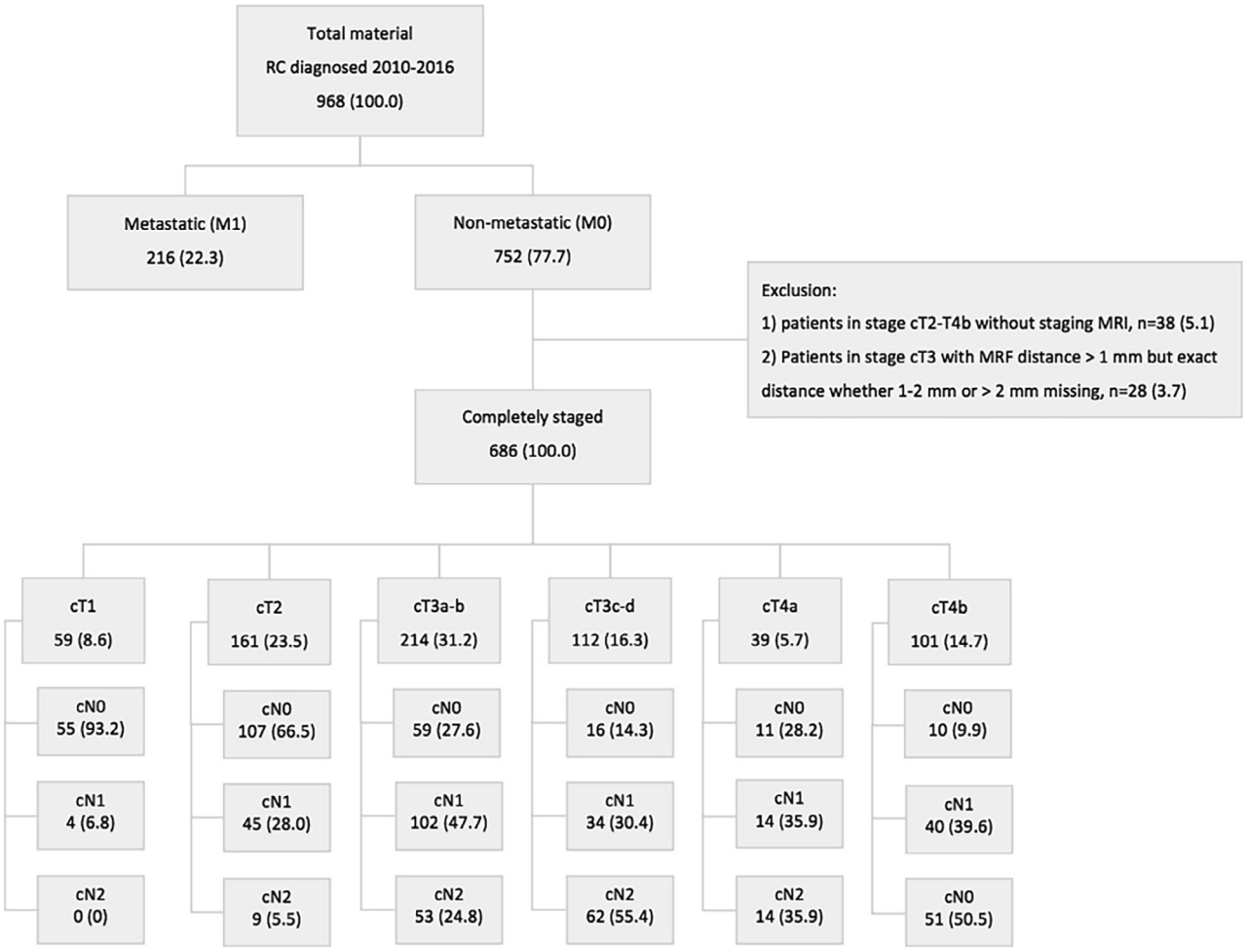

Fig. 1. Flow chart of study cohort selection from the total cohort of 968 rectal cancer patients diagnosed between 2010 and 2016 in two Swedish counties with clinical tumour and nodal category distribution shown. Numbers of patients (%) are shown.

Table 1
Factors considered in guidelines for preoperative rectal cancer radiotherapy/chemoradiotherapy.

Guideline	cT category	cN category	Rectal third[1]	EMD (cT3)	MRF distance (cT3)	mrEMVI	LN	cT4 subcategory	Resectability (cT4)
ASTRO	1–2,3,4	0,1,2	–	–	±2 mm	–	–	–	–
Australia	1–2,3,4	0, +	–	a, b–d	–	–	–	–	–
Belgium	1–2,3,4	0, +	Low, mid, high	–	±2 mm	–	–	–	–
Canada	1–2,3,4	0, +	–	–	–	–	–	–	–
Denmark	1–2,3,4	–	Low, mid, high	–	±5 mm	–	–	–	+
EORTC	1–2,3,4	0,1,2	Low–mid, high	ab < 4 mm, cd	±2 mm	+	–	+	+
ESMO	1–2,3,4	0,1,2	Low, mid, high	ab, cd	±1 mm (MRF+)	+	+	+	+
France	1–2,3,4	0, +	Low–mid, high	–	±2 mm	–	–	–	+
Greece	1–2,3,4	0, +	Low-mid, high	ab, cd	±1 mm (MRF+)	–	–	–	–
Holland	1–2,3,4	0,1,2	–	ab, cd	±1 mm (MRF+)	–	+	–	–
Japan	1–2,3,4	0, +	–	–	–	–	–	+	+
NCCN	1–2,3,4	0, +	–	–	–*	–	–	–	–
Norway	Any T	–	–	–	±2 mm	–	–	–	–
Sweden	1–2,3,4	0,1,2	Low, mid, high	ab, cd	±1 mm (MRF+)	+	+	+	+
UK (NICE)	1–2,3,4	0, +	–	a, b–d	±1 mm (MRF+)	+	–	–	–

Abbreviations: cTN: clinical T and N-category; EMD: extramural depth of invasion categorized as a: <1mm; b: 1–5 mm; c: 5–15 mm and d: >15 mm; LN: lateral nodes; MRF: mesorectal fascia; MRF distance, i.e. distance to the MRF in mm (±2 mm, designated in the text as MRF ≥2 or ± 1 mm, designated MRF+); mrEMVI: MRI-identified extramural vascular invasion; ASTRO = American Society for Radiation oncology; ESMO = European Society for Medical Oncology; ESTRO = European Society for Radiotherapy and Oncology; NICE = National Institute for Health and Care Excellence; NCCN = National Comprehensive Cancer Network.

* Included in the 2018 version 3.

[1] Rectal thirds: low (0–5 cm distance from the anal verge is referred to as low, 6–10 cm as mid and 11–15 as high.

Table 2
Study cohort characteristics.

Characteristics		Study cohort (n = 686)
Age groups	<65	202 (29.4)
	65–79	348 (50.7)
	>80	136 (19.8)
Sex	Male	393 (57.3)
	Female	293 (42.7)
cT category	cT1	59 (8.6)
	cT2	161 (23.5)
	cT3	326 (47.5)
	cT3a	76 (11.1)
	cT3b	138 (20.1)
	cT3c	88 (12.8)
	cT3d	24 (3.5)
	cT4	140 (20.4)
	cT4a	39 (5.7)
	cT4b	101 (14.7)
cN category	cN0	258 (37.6)
	cN1	239 (34.8)
	cN2	189 (27.6)
cT4 resectability	Easy	77 (55.0)
	Difficult	63 (45.0)
Clinical TNM stage	Stage I	162 (23.6)
	Stage II	96 (14.0)
	Stage III	428 (62.4)
mrEMVI	mrEMVI−	469 (68.4)
	mrEMVI+	176 (25.7)
	Missing	41 (6.0)

Results are given as numbers, n (%). cT and cN stand for clinical category tumour and node, respectively. mrEMVI means MRI-identified extramural vascular invasion.

ied from 38% to 77%. If treatment was to be given only to "non-resectable" (or difficult to resect, for definition, see Supplementary Table 1) tumours, 9% of patients would be recommended CRT (Table 2, Fig. 2, Supplementary Fig. 1). CRT was most often recommended, whereas scRT is recommended for 0–46% of patients. In several guidelines [39,41,44,45], scRT is an alternative to CRT in between 7– and 56% of fit patients without CRT contra-indications.

Traditionally, stages II-III have been considered locally advanced, requiring pre- or post-operative RT/CRT. Several guidelines consider CRT adequate treatment for tumours of these stages, which constitute 77% of all non-metastatic rectal cancers (Table 2) [39–41]. Most European guidelines, however, do not consider that all stage II + III tumours are at risk of LR, thus decreasing the proportions irradiated. In some guidelines [33,37], only low and mid-rectal cancers are considered for RT/CRT, whereas high cancers are recommended to be treated as colon cancers, with the exception of "non-resectable" cT4 cancers, that should be treated with CRT.

cT1-2

Most guidelines consider cT1-2 tumours (stage I) as early, with such a low risk of recurrence that pre-operative therapy is unnecessary. Many guidelines [37,39,41,42,44,46–48], however, consider RT/CRT indicated in all patients with cN+. Thus, patients with cT1-2N+-tumours should be irradiated. Node positivity is infrequent in cT1 (12%) but present in 21% in cT2. Furthermore, the Norwegian guidelines [32] consider CRT indicated in all tumours with a distance to the presumed surgical plane (MRF or intersphincteric fascia) less or equal to 2 mm (MRF $\leq$2), irrespective of T-category.

cT3

In cT3, approximately half of the guidelines consider the EMD or distance to MRF (if MRF+, EMD is not important) to be most important [34,35,46], whereas the remainder consider MRF $\leq$2 (or MRF $\leq$5 in Denmark) as most discriminatory [33,36,48]. Using the former, the recommended border for RT/CRT is between cT3ab and cT3cd in tumours >5 cm from the anal verge [34,35,46], whereas two guidelines [39,42] only consider cT3a to indicate low risk (if staging/surgery is of a good quality). In the ESTRO consensus document, the EMD should be <4 (not 5) mm in cT3b [33]. Since cT3 tumours constitute the most common category (about 50%) and cT3b is the most common subgroup within cT3, the variability in the recommendations of cT3 tumours greatly influences how often RT/CRT is recommended (from 100% down to about 50%). Tumours characterized by cT3 MRF+ make up about 38% of the cT3 tumours and about 10% grow within 1–2 mm. Low cT3 tumours are more likely to be MRF+ compared with mid and high tumours, but an increase in MRF+ tumours was observed in more advanced cT3 subcategories at all levels (from 12% to 35% in cT3a to 50–69% in cT3d, Table 3). At least 30% of the MRF− cT3 tumours are recommended RT/CRT due to node positivity. Moreover, mrEMVI+ is of relevance whether RT/CRT should be given or not in one guideline [42], whereas three guidelines [33–35] consider mrEMVI relevant in the decision to give scRT or CRT.

cT4

Most guidelines recommend CRT for the majority of patients with a cT4 tumour. A few guidelines [33–35] discriminate between cT4a and cT4b when it comes to whether RT/CRT should be given or not. Four guidelines [33,34,36,37] discriminate between whether the growth towards another organ or structure means that the tumour is difficult (inextirpable, e.g. to sacrum, lateral pelvic side walls, base of the bladder, prostate or the pelvic floor) or

Table 3
Distance to mesorectal fascia/intersphincteric fascia (MRF) in relation to rectal third (low, mid, high) in cT2,3a-d tumours.

	cT2	cT3a	cT3b	cT3c	cT3d	Total cT3	P-value[a]
Tumour level 0–5 cm (low)	48	20	35	23	2	80	0.296
MRF+ (0–1 mm)[b]	23 (48)	8 (40)	20 (57)	15 (65)	1 (50)	44 (55)	
1–2 mm	13 (27)	10 (50)	8 (23)	4 (17)	0	22 (28)	
>2 mm	12 (25)	2 (10)	7 (20)	4 (17)	1 (50)	14 (17)	
Tumour level 6–10 cm (mid)	67	32	56	43	16	147	<0.001
MRF+ (0–1 mm)[b]	1 (2)	7 (22)	15 (27)	22 (51)	11 (69)	55 (37)	
1–2 mm	18 (27)	5 (16)	4 (7)	4 (9)	2 (13)	15 (10)	
>2 mm	48 (72)	20 (63)	37 (66)	17 (40)	3 (19)	77 (52)	
Tumour level 11–15 cm (high)	46	24	47	22	6	99	<0.001
MRF+ (0–1 mm)[b]	0	3 (13)	10 (21)	12 (55)	4 (67)	29 (29)	
1–2 mm	0	0	3 (6)	3 (14)	1 (17)	7 (7)	
>2 mm	46 (100)	21 (87)	34 (72)	7 (32)	1 (17)	63 (64)	

Results are given as numbers, n (%). cT3 subgroups were compared in the statistical analyses.
[a] Chi^2 test of independence
[b] MRF+ was defined as primary tumour outgrowth or lymph node metastasis within a distance of <1 mm from the mesorectal fascia/intersphincteric fascia. Tumours with a distance $\leq$2 mm are in the text designated as MRF $\leq$2.

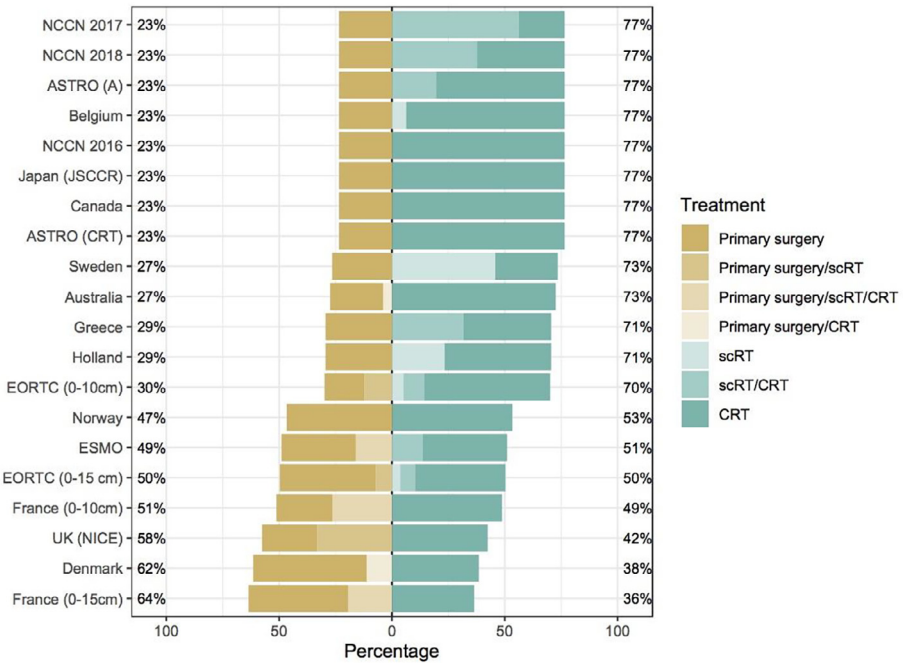

Fig. 2. Proportions of patients recommended different therapies according to selected national and international guidelines. The guidelines are ranked according to the proportions recommended to be irradiated. Prior to 2017, the National Comprehensive Cancer Network (NCCN) recommended all patients considered for radiation to receive CRT (NCCN 2016), whereas in 2017 several patients could, as an alternative, receive scRT (NCCN 2017). In the 2018 guidelines, fewer patients could receive scRT (NCCN 2018). ASTRO (CRT), American Society for Radiation Oncology consensus recommendations, means that CRT is always appropriate when radiation is indicated, ASTRO (A) means that scRT may be appropriate as an alternative to CRT in certain situations. EORTC, European Organisation for Research and Treatment of Cancer; ESMO, European Society for Medical Oncology; JSCCR, Japanese Society for Cancer of the Colon and Rectum. (0–10 cm) means that RT/CRT are only recommended for the distal 10 cm; (0–15 cm) gives the proportions for the entire rectum, assuming that no patients with tumours 10–15 cm from the anal verge are irradiated unless the tumour is difficult to resect (some cT4b) (relates to EORTC and France). Uncertainty about the fraction receiving CRT exists for the Danish guidelines since we did not record whether a mid cT3NX tumour that did not grow within 2 mm from MRF grew within 5 mm from MRF; thus, the fraction to be irradiated is between 38% and 50%. For further details of guideline recommendations, see Supplementary Fig. 1 and Supplementary Table 1.

easy to resect (vagina, uterus, small bowel loops or peritoneum only). If difficult, CRT is recommended whereas if easy, scRT with immediate surgery is an option. N+ is common in cT4, also influencing whether RT/CRT should be given. Of the cT4 tumours (20% of all M0-tumours), between 100% down to about 75% are recommended pre-treatment.

Discussion

Based on the distribution of MRI stages in an unselected, population-based and contemporary cohort [28], between 38% and 77% of primary non-metastasized rectal cancer patients are recommended pre-operative treatment using scRT or CRT according to several current national and co-operative group guidelines [32,33,35–37,39–44,47,48]. Recently reported fractions of irradiated tumours in population registries have been in this range [2,3,25,49,24,50,51] or lower [24,52]. When these proportions (<1 year after diagnosis) have been compared with evidence-based estimates, a discrepancy of up to 30% has been reported [3,53]. A great variability in the use of RT/CRT between hospitals has also been noticed [2,3,25]. The fractions reported as irradiated are not directly comparable since some studies also included stage IV patients, and re-irradiations (not considered in this study). Contra-indications to RT/CRT exist (previous irradiation to the pelvis, severe co-morbidities) and patients may refuse the proposed additional therapy, thereby decreasing its use. If on the other hand, reasons to give RT/CRT also include attempts to preserve the sphincters or the organ [20–22], not considered in the present study, more patients will be irradiated. A major reason for fewer than recommended irradiated tumours is in all probability due to doctors balancing gains versus negative consequences differently. Several studies have also propagated for fewer patients to be irradiated than recommended, due to the negative effects of RT/CRT [54,55]. Many guidelines include a discussion about this intricate balance to be discussed with individual patients.

In the absence of a sufficiently detailed description of the frequency of relevant MRI-defined characteristics, including T and N categories in unselected population-based materials, with the exception of [28], the fractions to be recommended RT/CRT reported here are open to criticism. They firstly rely on the representability of the Swedish population and secondly on the reliability of the MRI evaluations. The sub-population in Central Sweden is representative of the entire Swedish population (similar distributions of cT (including cT3ab vs cd) and cN (N0 vs N1-2) categories and presence of EMVI). It is also our belief that the Swedish population is representative of those in many other countries. The populations in most Western countries are similar in many respects, including the organization of the health care systems, although important differences exist. The distribution reported from Sweden is comparable with that in two nationwide registry-based studies from The Netherlands [46] and from Norway [49], where also more than 90% were staged with MRI, but since those studies only included patients with a major resection for their rectal cancer, other patients with early tumours not resected, patients with very advanced, but still non-metastatic tumours, and those with severe co-morbidities who often also presented with advanced tumours, were excluded. The reliability of the MRI investigations is of a high international standard since several centres participated in multinational rectal cancer imaging [56] and treatment studies, where imaging was central to the selection of patients [57]. For reasons discussed previously [28], we, therefore, believe that the findings are relevant for, at least, countries in Western Europe.

The accuracy of MRI staging is not perfect, but considered sufficient by the guidelines for deciding the risk for local (and systemic) recurrence and, thus, used at MDT conferences to decide whether pre-treatment should be administered or not [58–62]. The overall performance of the evaluations in Sweden was in line with that reported in a similar study in patients treated with upfront surgery or scRT with immediate surgery, i.e. in patients with predominantly early or intermediate tumours [63]. Considering the moderate accuracy of MRI in the prediction of pathological outcome, many of the detailed recommendations in different guidelines could be questioned. The difficulties in separating cT2 tumours from early cT3a(b) is one issue, being particularly difficult in low rectal cancers at or below the levator muscles. The difficulties of using MRI for staging otherwise in particular relate to the inclusion of node positivity as a sole criterion for RT/CRT, even in cT2 tumours [33–35,37,39,40,42,44,46–48,64]. Two guidelines have omitted the evaluation of nodal status in their recommendations [32,36]. Four guidelines [33,34,43,44] give different recommendations for cN1 and 2; the remaining only consider N-positivity. Two guidelines [34,43,46] have introduced stricter recommendations as to what should be considered a positive node, with increased specificity [46]. New European guidelines along these lines have also been suggested [65].

All evaluated guidelines are said to be based on systematic literature review and the strength of the evidence is often stated and graded, typically from A to D according to GRADE [66]. Several guidelines also define the way the recommendations were reached, sometimes after consensus discussions [33,35,40,44,67,68]. The diversity of recommendations indicates that many factors other than clinical trial results appear to be of importance.

The purpose of this study is not to present the advantages or disadvantages with any recommendation since the appropriate use of RT/CRT to decrease LR rates is unknown; the different recommendations illustrate this uncertainty. The different recommendations have a probable impact on LR rates, but not on overall survival (OS). In a modelling study based on a large US database of rectal cancers with an intermediate risk of recurrence, the elimination of pre-operative radiation, only providing combination chemotherapy, would, however, result in poorer survival [54]. The marked differences in recommendations between Sweden and Norway resulted in different LR rates when the fractions irradiated differed but merging together when the fractions became more similar; however, there was no difference in OS at any time [24].

In summary, 38–77% of newly diagnosed non-metastatic rectal cancers are presently recommended RT/CRT prior to surgery according to guidelines, when strictly applied to a non-selected population-based patient material. Many researchers appear to consider these fractions as too high. One important reason for this opinion is that the patients seen at a hospital are not representative of the population. Alternatively, the guidelines are not appropriate and must be modified. However, even guidelines claiming to be restrictive in the use of RT/CRT, in order to avoid additional toxicity, mean that at least 38% of patients are recommended this therapy. If only difficult-to-resect tumours (less than half of cT4), requiring downstaging/sizing unless mutilating surgery must be performed, are irradiated, 9% will be pre-treated.

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Declaration of interest

No conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.03.036.

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