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Rectal cancer treatment strategy

Two countries – Two treatment strategies for rectal cancer

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ABSTRACT

Background and purpose: Trials in rectal cancer have shown that radiotherapy (RT) decreases local recurrence rates, whereas the effects on survival are uncertain. Swedish and Norwegian oncologists have had different treatment recommendations. The aim was to evaluate local recurrence rates and survival in the two countries.

Patients and methods: Between 1995 and 2012 rectal cancer patients registered in Sweden and Norway were analyzed, presenting population-based "real world" data.

Results: Totally 29,029 Swedish and 15,456 Norwegian patients were analyzed. Resection for cure was performed in two-thirds of the patients. RT was given to 49% of Swedish patients, mainly short-course RT and to 26% of Norwegian patients, predominantly chemoradiotherapy (CRT). In Sweden, the proportion irradiated was stable whereas in Norway, an increase from 10% to 40% was seen. Local 5-year recurrence rates were initially higher in Norway (12%) than in Sweden (8%), whereas they were equally low (4%) during the latter time. No survival differences were seen, however, survival improved with time in both countries.

Conclusions: Two entirely different approaches to preoperative therapy resulted in similar survival with initially higher local recurrence rates in Norway, but similarly low rates in later years. This raises questions about optimal RT rates and regimens.

Treatment for rectal cancer has changed dramatically over the past decades, in particular with new surgical principles and increased use of radiotherapy (RT). Several randomized studies have reported diminished local recurrence rates by 50–60% after preoperative RT [1–4]. Many countries adopted this combined treatment strategy, but there were also indications that surgery following the embryological planes, performing a total mesorectal excision (TME) without RT, could result in low local recurrence rates [5].

In Sweden, RT had been introduced before the "TME era". Large trials showed that when indication for RT was present, it should be given preoperatively, and short-term morbidity was acceptable provided optimal radiation techniques available at the time were used [3,4,6,7]. Moreover, a survival benefit was found in the Swedish Rectal Cancer trial [3]. In Norway, RT was given postoperatively to selected patients [8], and preoperative therapy was rarely used. During the early 1990s, national training programs in the TME-technique were held in both countries [9,10]. In Sweden, RT continued to be used preoperatively, predominantly as a short-course regimen (5 gray (Gy) ×5 during one week). Preoperative therapy was implemented also in Norway, but long-course chemoradiotherapy (CRT) was used (50 Gy in 5 weeks with concomitant 5-fluorouracil or capecitabine and delayed surgery), at first only to the most advanced cases (fixed T4 tumors), later also to patients with threatened circumferential resection margins. Thus, the two neighboring countries chose different treatment strategies.

A quality registration for rectal cancer started in the mid-1990s in both countries. Subsequently, two national population-based registries exist, one where preoperative RT was given to many patients (Sweden) [11] and one where few patients were irradiated initially, followed by an increase in the use of preoperative CRT (Norway) [10,12]. The aim was to compare the results of the two treatment strategies for rectal cancer on a national basis to explore the potential impact of preoperative RT/CRT on local recurrence and survival.

Materials and methods

Patients

The Norwegian Rectal Cancer Registry was established in 1993, and the Swedish Rectal Cancer Registry in 1995. Between 1995 and

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2012 totally 29,029 patients in Sweden and 15,456 patients in Norway were registered (Table 1). These numbers correspond to an annual incidence of 18.8 per 100,000 inhabitants in Sweden and 19.5 in Norway. The corresponding age-standardized rates (World 1960) are 8.8 and 10.6, respectively.

Surgery, staging and adjuvant chemotherapy

The majority of surgeons had adopted the TME-technique in both countries prior to 1995, with rather abrupt improvement of outcomes [9,10,13]. The loco-regional staging was initially done by digital rectal palpation and rigid rectoscopy, but since 2004 by magnetic resonance imaging (MRI) of the pelvis [12,14,15]. Staging for metastases was also similar between the countries, initially with pulmonary X-ray and ultrasonography of the liver, later with computed tomography of the chest and abdomen. Adjuvant chemotherapy has not been recommended, but has been used at some hospitals in Sweden [16], less in Norway.

Radiation therapy

In Sweden, preoperative short-course RT followed by surgery within a week has been recommended for resectable tumors at risk of local failure, initially based upon clinical evaluation but since 2004 upon MRI characteristics. These tumors are presently designated intermediate risk tumors. Locally advanced, non-resectable tumors, about 10–15% of the population, were treated with long-course RT (2 Gy fractions to 50 Gy), initially alone, within a Nordic randomized trial concomitant with 5-fluorouracil [17], or after 2007 with CRT. Some patients (n = 840) participated in the Stockholm III trial randomizing between short-course RT with immediate or delayed surgery and long-course RT [18,19].

In Norway, initially selected patients with involved margins (<1 mm) or perforation had postoperative CRT [8], but gradually, preoperative CRT was preferred [20], initially as part of the Nordic randomized trial [17], subsequently according to guidelines. Norwegian guidelines initially recommended preoperative CRT only for T4 or fixed tumors, but later also for tumors near ($\leqslant$3 mm) the mesorectal fascia on MRI. Short-course radiotherapy with delayed surgery has been recommended in later years to elderly or comorbid patients [21].

Table 1
Characteristics of patients included in the Swedish and Norwegian quality registries.

	Sweden *N* (%)	Norway *N* (%)
All patients	29,029	15,456
Males	16,903 (58.2)	8899 (57.6)
Females	12,126 (41.8)	6557 (42.4)
Median age (years)	72	71
Radiotherapy (RT)	14,212 (49.0)	3984 (25.8)
Synchronous metastases (M1)	5521 (19.0)	3211 (20.8)
Metastases-free (M0) clinical stage I–III	23,508 (81.0)	12,245 (79.2)
RT (% of M0)	12,398 (52.7)	3222 (26.3)
Local excision	1333 (4.6)	460 (3.0)
Not resected	2851 (9.8)	1182 (7.6)
RT (% of not resected)	544 (19.1)	273 (23.1)
Resected (AR, HA, APE)	19,324 (66.6)	10,603 (68.6)
R2 resection (% of resected)	783 (4.1)	182 (1.7)
Radically resected (stage I–III)	18,541 (63.9)	10,421 (67.4)
Males	10,848 (58.5)	6062 (58.2)
Females	7693 (41.5)	4359 (41.8)
Median age	70	70
Anterior resection	10,480 (56.5)	6124 (58.8)
Hartmann	2106 (11.4)	792 (7.6)
Abdomino-perineal excision	5936 (32.0)	2850 (27.3)
Other or unknown	19 (0.1)	657 (6.3)
RT (% of radically resected)	11,345 (61.2)	2853 (27.4)
Preoperative RT	11,342 (61.2)	2508 (24.1)
Postoperative RT	7 (0.0)	345 (3.3)

The present guidelines in the two countries are given in Supplementary Table 1.

Registry data

The registries have high validity of data [11,22,23]. Most variables were comparable, however, metastatic disease was registered as synchronous if present at diagnosis or surgery in Sweden, and within four months of diagnosis in Norway. The registration of radical surgery also differed; in Sweden, surgery was initially considered radical if reported by both the surgeon and pathologist, whereas after 2003 in Sweden and during the entire time period in Norway, the surgeon reported non-radical surgery (R2) and the pathologist reported free (R0) or involved (R1) resection margins.

For simplicity, (C)RT has been analyzed with 'yes or no' since these variables were registered throughout the whole time period, with more detailed information in later years. In addition, randomized trials have not shown any difference in local recurrence rates or survival when comparing preoperative 5×5 Gy with CRT in patients with intermediate rectal cancer [2,24–26].

Pathological T and N stages are impossible to compare directly. In patients who were operated immediately after RT, the pathologic stage would be designated pT and pN. However, in patients who underwent short-course RT or CRT with delayed surgery, tumor down-staging can occur and the designation would be ypT and ypN.

Recurrence or metastases are reported by the clinician, and all pathology reports for biopsies and surgical specimens are registered. In addition, all hospitals receive queries for occurrence of local recurrence or metastatic disease; in Sweden after 1, 3 and 5 years, in Norway yearly until 5 years [12].

Ethics

According to Swedish laws, quality registries are accepted provided that information about the registration is given at places where the patients can read it (out-patient units or hospital wards), and that they can decline such registration. This is, however, exceptional. This study has been approved by the research ethics committee, Uppsala, Sweden. In Norway, registration in the national cancer registry and the quality registries is mandatory. No separate ethical approval was needed since this study was based on de-identified registry data.

Statistical methods and analytical strategy

Since all data are population-based, and the total patient numbers differ between countries, percentages are shown. Categorical variables were compared using the chi-square test. Overall survival was estimated using the Kaplan–Meier method. Local recurrence and distant metastases rates were estimated using the Aalen-Johansen estimator, taking into account competing risk of death. Relative survival was estimated using the Ederer II estimator as the ratio of observed survival in the study groups compared to expected survival in the general population, matched for age, sex, and time. An estimation of the number of cancer-deaths and non-cancer deaths in radically resected patients was done [27]. Follow-up started at the date of surgery; if not resected, from the date of diagnosis. Ideally, follow-up should have started when treatment decision was made (today usually in a multidisciplinary team (MDT) conference), but this date was not registered.

Of greatest interest when exploring the impact of different preoperative strategies would be to analyze patients where radical surgery was intended, whether the tumor was upfront considered resectable or non-resectable, i.e. patients planned for major radical