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ORIGINAL ARTICLE – COLORECTAL CANCER

2010 SSO John Wayne Clinical Research Lecture: Rectal Cancer Outcome Improvements in Europe: Population-Based Outcome Registrations will Conquer the World

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ABSTRACT During the past two decades, rectal cancer treatment has improved considerably in Europe. Clinical trials played a crucial role in improving surgical techniques, (neo)adjuvant treatment schedules, imaging, and pathology. However, there is still a wide variation in outcome after rectal cancer. In most western health care systems, efforts are made to reduce hospital variation by focusing on selective referral and encouraging patients to seek care in high-volume hospitals. On the other hand, the expertise for diagnosis and treatment of common types of cancer should be preferably widespread and easily accessible for all patients. As an alternative to volume-based referral, hospitals and surgeons can improve their results by learning from their own outcome statistics and those from colleagues treating a similar patient group. Several European surgical (colo)rectal audits have led to improvements with a greater impact than any of the adjuvant therapies currently under study. However, differences remain between European countries, which cannot be easily explained. To generate the best care for colorectal cancer in the whole of Europe and to meet political and public demands for transparency, the European CanCer Organisation (ECCO) initiated an international, multidisciplinary, outcome-based quality improvement program: European Registration of Cancer Care (EURECCA). The goal is to create a multidisciplinary European registration structure for patient, tumor, and treatment characteristics linked to outcome registration. Clinical trials will always play a major role in improving rectal cancer treatment. To further improve outcomes and diminish variation, EURECCA will establish the basis for a strong, multidisciplinary, international audit structure that can be used as a template for similar projects worldwide.

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During the past two decades, rectal cancer treatment has improved considerably in Europe. Whereas this counts for most solid malignancies, improvements in diagnosing and treating rectal cancer surpass virtually all others. In the early 1990s, outcome after rectal cancer treatment was poor, with survival and recurrence rates of approximately 45%.[1] Nowadays, survival after rectal cancer is sometimes even higher than after colon cancer.[2,3] Although radiotherapy and chemotherapy are very important in modern multidisciplinary treatment of rectal cancer, surgery remains the inevitable cornerstone for cure. For all the improvement in surgical techniques, (neo)adjuvant treatment schedules, imaging and pathology, clinical trials, and population-based audit registrations played a crucial role.

EARLY SWEDISH TRIALS

During the early 1970s in Sweden, local recurrence after rectal cancer surgery was 38%, and the majority of those patients never developed distant metastases.[4] Although it was known that radiotherapy could reduce local recurrence, a major question remained whether radiotherapy should be given before or after the operation. Between 1980 and 1985, the "Uppsala trial" randomized 471 patients with rectal cancer to preoperative 25 Gy radiotherapy or postoperative 60 Gy radiotherapy. Postoperative radiotherapy had an inferior tolerance compared with preoperative radiotherapy. Besides, 46% of the patients could not start postoperative radiotherapy within 6 weeks after surgery because of complicated postoperative recovery. After a mean follow-up of 6 years, local recurrence in the preoperative radiotherapy group was 12% compared with 21% in

the postoperative radiotherapy group, although there was no difference in survival between the treatment arms.[5]

Simultaneously with the "Upssala trial," the "Stockholm Rectal Cancer Study Group" started the "Stockholm I" trial, which randomized 849 patients with rectal cancer between preoperative 25 Gy radiotherapy versus surgery alone. After a median follow-up of 9 years, local recurrence in the irradiated group was 14% compared with 28% in the surgery alone group. Cancer-specific death was lower in the irradiated group. However, postoperative mortality within 30 days of surgery was increased after radiotherapy, mainly in elderly patients, resulting in an equal overall survival in both arms.[6]

With the objective to reduce postoperative mortality while maintaining the reduction of local recurrences, a new study was initiated with a reduced irradiated volume and exclusion of patients older than 80 years: the Stockholm II trial. Between 1987 and 1993, 557 patients were randomized between 25 Gy radiotherapy followed by surgery within a week or surgery alone. After a median follow-up of 9 years, local recurrence in the irradiated group was 12% versus 25% in the surgery alone group. With the reduced irradiation volume and the exclusion of older patients, there was no significant difference in postoperative mortality. Nevertheless, there was still no difference in overall survival.[7]

Between 1987 and 1990, the Swedish Rectal Cancer Trial randomized 1,168 patients younger than aged 80 years with resectable rectal cancer to undergo preoperative 25 Gy radiotherapy followed by surgery within 1 week or to have surgery alone. After 5 years, the local recurrence ratio in the irradiated group was 11% compared with 27% in the surgery alone group. In contrast to the earlier trials, preoperative radiotherapy improved survival in the Swedish Rectal Cancer Trial: the overall 5-year survival rate was 58% in the irradiated group and 48% in the surgery alone group ($p = 0.004$).[8]

TOTAL MESORECTAL EXCISION ERA

In 1979, Heald stated that mesorectal tissue should be removed together with the tumor to reduce local recurrence.[9] Together with Enker he popularized the total mesorectal excision (TME) technique: a complete and sharp excision of the mesorectum under direct vision, with preservation of the hypogastric plexus.[10] During the late 1990s, both TME pioneers convinced the surgical world with 5-year local recurrence rates <10% in patients with rectal cancer who were operated on with the TME technique without (neo)adjuvant therapy.

Because all studies showing positive effects of radiotherapy were performed with conventional surgery on top of the fact that TME surgery alone came with low local recurrence rates, the Dutch Colorectal Cancer Group conducted a trial to study the effects of preoperative radiotherapy in combination with TME surgery: The TME Trial.[11] The new surgical technique was implemented in a structured way. All participating surgeons were trained in the TME technique by workshops and videotapes. At least five procedures of each participating surgeon were supervised by an instructor surgeon. Pathologists were trained to examine the specimens according to the protocol of Quirke et al. regarding the circumferential resection margin (CRM), lymph nodes, and dissection plane.[12]

Between 1996 and 1999, 1,861 patients were randomized for the TME trial. Five-year local recurrence rate were 5.6% with and 10.9% without preoperative radiotherapy and a 5-year overall survival of 64% in both groups.[13] Ten-year follow-up data of the TME trial will be published in the near future.

The transition from conventional surgery to a quality-controlled multidisciplinary treatment regimen was not limited to the trial population. In the Netherlands, survival improved for all rectal cancer patients treated in the Comprehensive Cancer Centres South and West. Before the TME trial (1990–1995), 5-year overall survival after rectal cancer was 56%, during the trial (1996–1999) it was 62%, and after the TME trial (2000–2002) 65%.[14] This means that the traditional survival backlog of rectal cancer compared with colon cancer has been completely nullified, proving the lasting positive effects that standardization and quality assurance in surgical oncology can have.[3]

In some countries, chemoradiotherapy was preferred as a standard therapy for rectal cancer instead of only radiotherapy. The German Rectal Cancer Study Group compared preoperative chemoradiotherapy with postoperative chemoradiotherapy for patients with locally advanced rectal cancer, operated with TME surgery. Between 1995 and 2002, 421 patients were included. Five-year local recurrence was 6% in the group assigned to preoperative chemoradiotherapy compared with 13% in the postoperative chemoradiotherapy group. There also was reduced toxicity in the preoperative chemoradiotherapy group but no survival advantage.[15]

The Polish Rectal Cancer Trial investigated whether preoperative chemoradiation offered an advantage in sphincter preservation compared with preoperative short-term radiation for patients with resectable T3-T4 rectal cancer operated with TME surgery. Between 1999 and 2002, 316 patients were included. Despite significant downsizing in the chemoradiation group, there was no difference in sphincter preservation, local control, late toxicity, or survival.[16,17]

Because irradiating all patients with rectal cancer possibly overtreats certain patient groups, the MRC CR07/NCIC-CTG C016 trial compared 25 Gy preoperative

radiotherapy with selective postoperative chemoradiotherapy restricted to patients with an involved circumferential margin. After 3 years, local recurrence was 4.4% in the group treated with preoperative radiotherapy compared with 10.6% in the selective postoperative chemoradiotherapy group. There was no difference in overall survival.[18]

ADJUVANT CHEMOTHERAPY FOR RECTAL CANCER

In contrast to colon cancer, there is not much evidence that adjuvant chemotherapy improves survival for patients with rectal cancer. The only study that showed an improved survival after chemotherapy is the Japanese "National Surgical Adjuvant Study of Colorectal Cancer." Two hundred seventy six patients with a completely resected stage III rectal cancer were randomized between 1 year of uracil-tegafur or no adjuvant treatment. Three-year overall survival was 91% in the uracil group compared with 81% in the surgery-alone group ($p = 0.005$).[19] However, there are many differences between the treatment given in this trial and in Europe. Selective lateral pelvic lymphadenectomy is only standardly performed in Japan in contrast to radiotherapy, which is standard in Europe but not in Japan. Furthermore, uracil is no longer the regimen of first choice.

The EORTC 22921 trial evaluated preoperative and/or postoperative fluorouracil-based chemotherapy as an addition to preoperative radiotherapy for the treatment of patients with T3/T4 rectal cancer; 1,011 patients were enrolled in the trial. After a median follow-up of 5 years, chemotherapy showed significant benefits on local recurrence rates. However, it had no effect on survival, regardless if it was given preoperatively, postoperatively, or both.[20] Whereas patients were enrolled between 1993 and 2003, TME surgery was only recommended since the beginning of 1999.

To evaluate the effect of postoperative chemotherapy for patients with stage II and III rectal cancer who are treated with standardized TME surgery, the Dutch Colorectal Cancer Group initiated the PROCTOR (Preoperative Radiotherapy and / Or adjuvant Chemotherapy combined with TME-surgery in Operable Rectal cancer) trial in 2000. In 2004, the trial was succeeded by the SCRIPT (Simply Capecitabine in Rectal Cancer after Irradiation Plus TME) trial. While still open for accrual, an interim analysis of the SCRIPT and PROCTOR trials will be published in the near future.

QUALITY ASSURANCE AND SURGICAL AUDIT REGISTRATIONS IN EUROPE

In Europe, 5-year relative survival for colorectal cancer varies between 32% and 64%.[21] In most western health care systems, efforts are made to reduce hospital variation by focussing on selective referral and encouraging patients to seek care in high-volume hospitals. Such a strategy of treating a larger proportion of patients in specialized centers can evidently improve outcomes for complex surgical procedures, such as esophagectomies and pancreatectomies.[22] However, the expertise for diagnosis and treatment of common types of cancer should be preferably widespread and easily accessible for all patients. Besides, one must keep in mind that there will always be low-volume providers that perform very well just as there are high-volume providers with unacceptable outcomes.

As an alternative to volume-based referral, hospitals and surgeons can improve their results by learning from their own outcome statistics and those from colleagues treating a similar patient group. Surgical audit is a quality instrument that collects detailed clinical data from different health care providers, which can be adjusted for baseline risk and subsequently fed back to individual hospitals or surgeons. In this way, "best practices" can be identified, communicated, and broadly adopted. After casemix adjustments, a fair judgement can be made on the quality of cancer treatments. Hospitals and surgeons can be faced with their own results compared with those of colleagues treating the same patient category. Another important advantage is the fact that audit registries include the entire patient population, which makes it possible to perform research on patient groups that are usually excluded from clinical trials (e.g., elderly, high comorbidity).

Between 1993 and 2009, eight surgical (colo)rectal audits were set up in Europe. The Norwegian Rectal Cancer Project included more than 99% of the Norwegian patients with rectal cancer. After 4 years the proportion of TME surgery increased from 78% to 92% and the local recurrence rate decreased from 28% to 7%.[23] Moreover, the audit showed to be very cost effective with every saved life being less then €700.[24]

In the Swedish Rectal Cancer Registry, postoperative mortality decreased to <2.5% and the local recurrence rate decreased to <10%. Survival improved dramatically: patients with rectal cancer had an even better 5-year survival rate than those with colon cancer.[2]

The Danish Colorectal Cancer Database also had satisfying results. Since 1994, 93% of all patients with colorectal cancer were included. After 5 years of auditing, 5-year survival increased from 42% to 63% for women and from 37% to 55% for men.[25]

For the National Bowel Cancer Audit Programme (NBOCAP), 95% of trusts in England and Wales submit data. Within 5 years, 30-day mortality decreased from 7% to 4.5%.[26]

In 2000, the "International Quality Assurance in Colorectal Carcinoma" was initiated in Magdeburg, Germany.

Between 2000 and 2008, 372 hospitals from Germany and Poland included 57,429 patients. The percentage of abdominoperineal excisions was significantly reduced from 26.1% in 2000 to 21.3% in 2008.[27]

The Belgian Project on Cancer of the Rectum (PROCARE) standardized and implemented national guidelines and started a prospective registration in 2006. Besides registering crude outcome data after rectal cancer treatment, extensive efforts and resources are used to train surgeons, pathologists, and radiologists in the latest standards of rectal cancer treatment.[28]

The Spanish TME project audit registration includes >3,000 patients so far. First reports show a 30-day mortality of 3.1% and an anastomotic leakage rate of 8.2%.[29]

The Dutch Surgical Colorectal Audit (DSCA) reached a 100% national coverage within a year with more than 11,000 patients included since 2009. In a recently published first annual report, important findings were discovered, such as the high percentage urgent and acute surgery, even for many patients who had already visited a surgeon in an outpatient setting. Given the fact that for rectal cancer, mortality after elective surgery is only 2.4% compared with 9.5% after acute surgery, it seems obvious that many lives can be saved when these "unnecessary urgent" patients are reduced.[30]

EURECCA: AN INTERNATIONAL, MULTIDISCIPLINARY, OUTCOME-BASED QUALITY IMPROVEMENT PROJECT OF THE EUROPEAN CANCER ORGANISATION

Although all national audits contributed to improved results, differences remain between European countries that cannot be easily explained. Considering the results, there are differences in mortality, complications, recurrence, and survival. Moreover, there are substantial differences in (neo)adjuvant treatment regimens. Whereas in Sweden and the Netherlands most patients with rectal cancer receive preoperative radiotherapy, in Norway it is a minority (4% between 1993 and 1997).[24] Nevertheless, local recurrence rates in Norway equal the rates in Sweden and the Netherlands.[23] To generate the best care for colorectal cancer in the whole of Europe and to meet political and public demands for transparency, a deep and broad insight in treatment outcomes is needed. A European audit registration can realize transparency, benchmarking, and feedback across nation's borders and can rapidly lead to less variation and improved outcomes around the continent. Urged by these arguments, the European CanCer Organisation (ECCO) initiated an international, multidisciplinary, outcome-based quality improvement program: European Registration of Cancer Care (EURECCA). The goal is to create a multidisciplinary European registration structure for patient, tumor, and treatment characteristics linked to outcome registration (morbidity, mortality, locoregional control, and survival). The registration will be used for benchmarking and internal feedback among participants and enhance further improvements in quality and efficiency of cancer care. All eight audit registries described in this article have given their full commitment to participate in the EURECCA framework. Key partners are the European CanCer Organisation, the European Society of Surgical Oncology, the European Society for Therapeutic Radiology and Oncologists, the European Organisation of Research and Treatment of Cancer, and the national audit structures. The EURECCA project has a strong clinical research component complemented by the provision of practical tools for care providers all aiming at the optimization of the delivery of surgery, radiotherapy, and chemotherapy in colorectal cancer. Among the main scopes of research is the definition of the "core quality treatment standards," which, by way of recommendations, will be systematically disseminated to optimize current treatment patterns and offer patients the maximum quality treatment locally available with strategies to limit undesirable effects.

CONCLUSIONS AND FUTURE

Clinical trials contributed with a great extend to the treatment improvements for rectal cancer. They showed that preoperative radiotherapy is more effective in reducing local recurrence than postoperative radiotherapy, also in combination with TME surgery. However, only one trial for which conventional surgery was used showed a survival improvement so far. Until now, there is little evidence for adjuvant chemotherapy for rectal cancer treatment. Finally, trials demonstrated that preoperative chemoradiotherapy is favorable compared with postoperative and that preoperative chemoradiotherapy has no advantage over short course preoperative radiotherapy when no downsizing is needed. If downsizing is needed, the standard treatment at present is chemoradiotherapy; the Dutch TME trial showed that short-course 25 Gy radiotherapy followed by surgery within 1 week does not shrink the tumor.[31] A trial that examines the possible downsizing effects of short-course 25 Gy radiotherapy in combination with delayed surgery is the Swedish "Stockholm III" trial. Control groups are patients treated with short-course radiotherapy followed by surgery within 1 week and patients treated with chemoradiotherapy followed by delayed surgery. Accrual started in 1998 and according to a recently published interim analysis, compliance was acceptable and severe acute toxicity was low. Based on the interim analysis, it seems that short-course radiotherapy with delayed surgery has a

downstaging effect as opposed to short-course radiotherapy without delayed surgery.[32]

A possible explanation for the better results of preoperative therapy opposed to postoperative therapy might be the fact that due to various reasons compliance is much lower for postoperative therapy. Utilizing the better compliance of preoperative therapy, final adjustments are made on the protocol of a new trial: The Dutch Swedish Rectal Cancer Trial. The goal of this trial will be to evaluate the combination of short course radiation therapy combined with preoperative chemotherapy in patients with rectal cancer with a high risk of local or distant recurrence compared with standard preoperative chemoradiotherapy and adjuvant chemotherapy.

Despite the amelioration brought by clinical trials, national audit registries in surgical oncology have led to improvements with a greater impact than any of the adjuvant therapies currently under study. Moreover, they offer the possibility to perform research on patients that are usually excluded from clinical trials such as elderly. EURECCA will advance future treatment improvements and spread these to every cancer patient in Europe. It provides opportunities to treat all patients evidence-based while it offers a unique insight in social-economical matters, such as the consequences of commercialisation, treatment availability, and screening initiatives. Approximately 110 million people will be represented by EURECCA, much more than can possibly be covered by systematic reviews that currently represent the highest level of evidence. In contrast, usually less than a percent of all (rectal) cancer patients participate in clinical trials. However, evidence and recommendations produced by EURECCA or other similar population-based projects will be scored much lower on the level of evidence scale. Possibly, the way levels of evidence are assigned should be reconsidered in the future.

Concluding, clinical trials will always play a major role in improving rectal cancer treatment. To further improve outcomes and diminish variation, EURECCA will establish the basis for a strong, multidisciplinary, international audit structure that can be used as a template for similar projects worldwide. Although it is not uncommon for American surgical journals to slightly exaggerate the title of articles,[33] we are convinced that the EURECCA format can truly conquer the world.

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