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Improvement of the Curative Management of Rectal Cancers by Better Use of Radiotherapy

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INTRODUCTION

THIS TITLE was preferred to "Future improvements of radiotherapy" since the purpose is to convince the reader that it is not necessary to wait for new developments to improve results. Immediate improvements can result from the transfer of the best known strategies and techniques of radiotherapy to standard practice; quality management evaluation; and wider participation in large clinical trials addressing pending questions.

TRANSFER THE STATE OF ART TO STANDARD PRACTICE

Curative management with radiotherapy alone

Despite consistent evidence in the literature, the expertise and availability of intrarectal radiotherapy techniques for selected T1, T2 low rectal adenocarcinomas remain a rarity. However, approximately 90% of patients with small superficial tumours of the low rectum can be cured with a functional sphincter by 50 kV contact X-ray therapy, sometimes combined with interstitial ^{192}Iridium brachytherapy [1–3]. Transrectal ultrasound imaging considerably reduces the uncertainty of clinical staging and provides a safe selection of patients. These techniques of radiotherapy are highly cost effective and the few pelvic failures are often amenable to salvage surgery.

Selected T2, T3, adenocarcinomas of the low rectum may also be cured by radiotherapy alone, with adequate management by external radiotherapy with a target volume confined to the posterior pelvis, followed by a local boost with intracavitary radiotherapy techniques when a good regression is observed 4–6 weeks after the end of external irradiation. When residual infiltration is not amenable to boost techniques, the strategy is considered preoperative. Using this approach, approximately two-thirds of these patients can be cured with a functional sphincter [1]. This approach, first demonstrated with patients inoperable for medical reasons, can now be safely applied to patients that otherwise would be candidates for abdominal-perineal amputation.

Preoperative radiotherapy: a new gold standard for T3, T4

Preoperative radiotherapy should now be the recommended strategy in T3, T4, rectal adenocarcinomas. This statement is consistent with the results of several large randomised clinical trials, totalling approximately 5500 patients entered in 15 trials comparing preoperative radiotherapy versus surgery alone [4, 5]. Although local relapse rates vary from trial to trial, preoperative radiotherapy steadily reduces the risk of local recurrence by 50% compared with surgery alone. In the last Stockholm 2 trial [6], a significant reduction of the local relapse rate was obtained (26% surgery alone versus 11% preoperative radiotherapy, $P<0.001$). In addition, a significant reduction in deaths from cancer and metastases was observed in the preoperative group resulting for the first time in an improved survival.

The review of these randomised trials also demonstrates the impact of the choice of radiotherapy parameters: the target volume should only encompass the posterior pelvis thus limiting the dose to critical organs such as the bladder and small bowel. Some controversy still exists between classical dose–time parameters (40–45 Gy in 20–25 fractions in 4–5 weeks versus short duration regimes with larger doses per fraction such as 25 Gy in five fractions and 1 week, as in the two Stockholm trials). Of interest, short regimes could not demonstrate an increased use of conservative procedures, while more classical regimes often facilitate surgical procedures and increase the frequency of sphincter preservation in mid and low rectal cancers. Conversely, postoperative radiotherapy failed to demonstrate a significant advantage in local control, and is associated with a poorer acute and late tolerance than preoperative radiotherapy.

Quality assurance

Quality management of radiotherapy is well demonstrated by the correlation between individual anatomical factors and risk of complications. Letschert and colleagues [7] demonstrated a 30% risk of acute and late symptoms when the irradiated small bowel volume was less than 80 cc but a 60% risk was shown when a volume larger than 300 cc was irradiated in a series of postoperative radiotherapy [8]. This finding also favours preoperative radiotherapy since the exclusion of the small bowel from the target volume is more effective than with postoperative irradiation.

A National Consensus Conference held in Paris, France in December 1994 concluded that preoperative radiotherapy should now become the standard initial approach for T3, T4 adenocarcinomas of the rectum [9, 10]. Unfortunately, according to the French Tumour Registries [11], only 33% of such patients actually receive preoperative radiotherapy. This emphasises the need to generalise the practice of a multidisciplinary decision process to define treatment strategy in every institution and not only in a few specialised centres.

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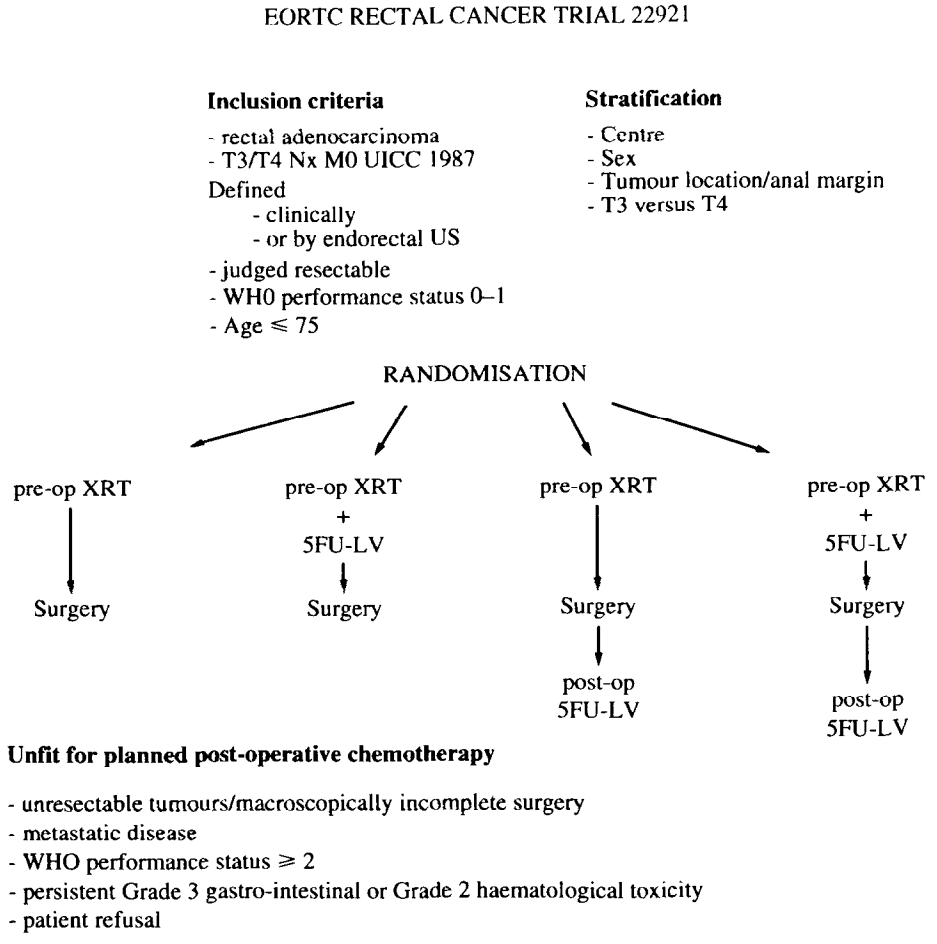

Figure 1. EORTC rectal cancer trial 22921. XRT, radiotherapy; pre-op, preoperative; post-op, postoperative.

Concomitant preoperative radio-chemotherapy: the logical next step

Induction chemotherapy has shown a high frequency of non-responders (30–50%). It is also likely to select resistant clonogens and to accelerate tumour repopulation. Conversely, the combined approach should provide additive and supra-additive effects and reduce the overall treatment time compared to induction of adjuvant chemotherapy. Review of the literature of preoperative radio-chemotherapy of rectal cancers [4, 5] consists of 10 trials totalling 437 patients. Four of these trials studied the radiotherapy–5-fluorouracil (5-FU)–leucovorin combination and determined the maximum tolerable dose of 5-FU (350 mg/m^2) with low-dose leucovorin (20 mg/m^2). Two cycles were delivered during radiotherapy of 45 Gy in 25 fractions and 5 weeks with a 95% compliance, a 75% response and a 90% resectability rate in T3, T4.

These phase II trials led to the design of the EORTC trial 22921 ([12], Figure 1), comparing preoperative radiotherapy with or without concomitant 5-FU–leucovorin to no postoperative treatment versus postoperative 5-FU–leucovorin for 4 months. This trial should provide the answer to two major questions: does preoperative radio-chemotherapy work better than preoperative radiotherapy? Is it necessary to deliver postoperative chemotherapy? A total of 1000 patients will answer the two questions.

CONCLUSION

This short review of current possibilities of radiotherapy and radio-chemotherapy shows that the transfer of present knowledge to standard practice is likely to improve the outcome of the majority of rectal cancers by reducing considerably (by a factor of 50%) the risk of local relapse in moderately advanced and advanced rectal cancers, thus providing the patient with a significant improvement of quality of life. The observation of this strategy in a population and not only in research trials should result in a measurable improvement of survival.

The risk of local failures will continue to fall thanks to the combined efforts of surgeons, radiotherapists and medical oncologists. Hence, the rate of sphincter preservation may soon become the central question of future trials comparing treatment strategies for low rectal cancers.

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