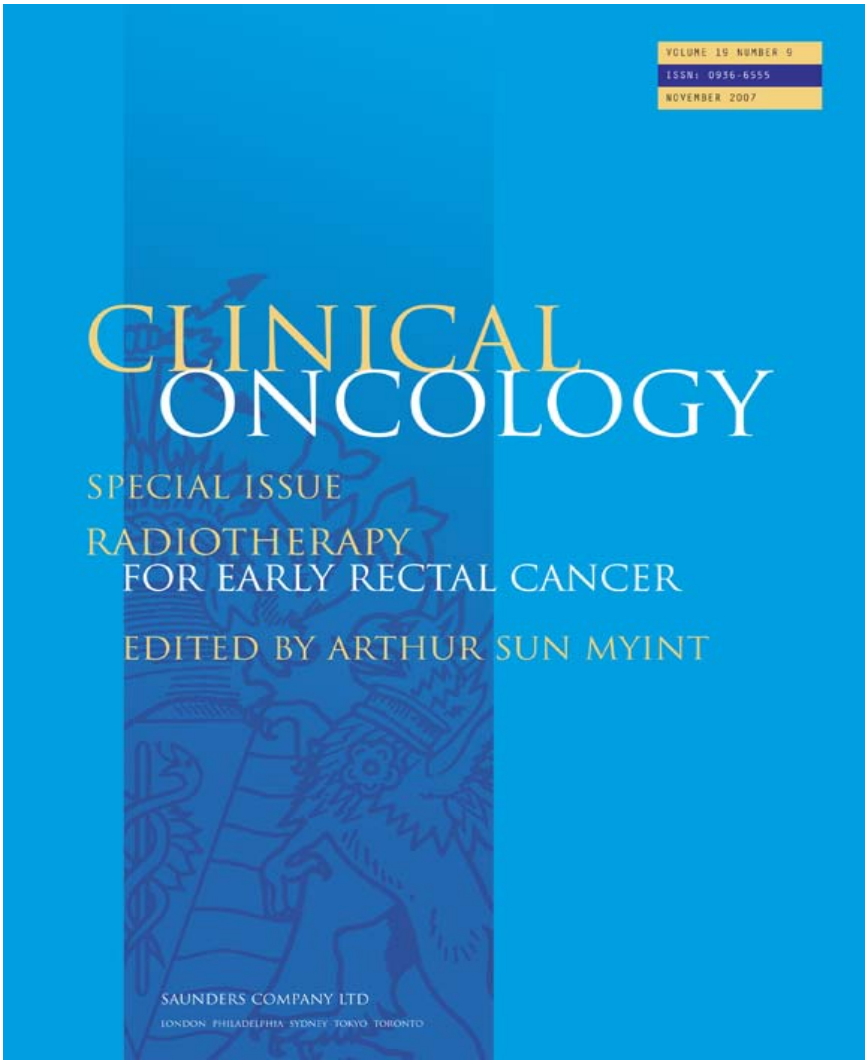

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Overview

Whither Papillon? — Future Directions for Contact Radiotherapy in Rectal Cancer

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ABSTRACT:
Although contact radiotherapy was developed 70 years ago, and is highly effective with cure rates of over 90% for early rectal cancer, there are few centres that offer this treatment today. One reason is the lack of replacement of ageing contact X-ray machines, many of which are now over 30 years old. To address this problem, the International Contact Radiotherapy Evaluation (ICONE) group was formed at a meeting in Liverpool in 2005 with the aim of developing a new contact X-ray unit and to establish clinical protocols that would enable the new machine to safely engage in the treatment of rectal cancer. As a result of these efforts, a European company is starting production of the new Papillon RT-50 machine, which will be available shortly. In addition, the ICONE group is planning an observational study on contact X-ray and transanal endoscopic microsurgery (CONTEM) for curative treatment of rectal cancer. This protocol will ensure standardised diagnostic procedures, patient selection and treatment in centres across the world and the data will be collected prospectively for analysis and audit. It is hoped that the CONTEM trial will provide the scientific evidence that is needed to obtain a broader acceptance of local contact radiotherapy as a treatment option for selected cases with early stage rectal cancer. Lindegaard, J. *et al*. (2007). *Clinical Oncology* 19, 738–741

Key words: Contact X-ray, CONTEM, early rectal cancer, papillon, preoperative chemoradiotherapy, transanal endoscopic microsurgery

Historical Overview

Before the Second World War there was a shortage of radium in Germany and superficial X-ray was used for intracavitary treatment in cervical carcinoma. This inspired Chaoul from Berlin to extend its usage to treat inoperable rectal carcinomas and he showed that high doses of low-energy X-ray could be safely delivered directly to a rectal tumour [1]. In 1946, Lamargue and Gros from Montpellier showed that local control and even long-term survival (42% at 5 years) could be achieved in rectal adenocarcinoma treated using contact X-ray delivered by a 50 kV Phillips unit [2]. On the basis of these initial reports, Papillon from Lyon popularised the technique for clinical use, with which his name remains associated today. Between 1950 and 1990, Papillon treated more than 300 patients and reported 75% 5-year overall survival with only 9% local failures [3]. In 1976, Sischy from Rochester introduced this technique in the USA and validated the results of Papillon [4]. Over the last 50 years, more than 1200 patients have been treated throughout the world and a general overview of the results suggests a long-term local control rate of 80–90% with 5-year overall survival in the region of 50–70% [5]. However, the selection criteria were not always clear and the diagnostic investigations carried out were often suboptimal by modern standards, despite which many elderly patients with rectal cancer were spared radical surgery and the results matched the contemporary surgical outcome for both local control and disease-free survival.

Although contact radiotherapy has been used as a treatment option for early rectal cancer for decades, this approach has only been practised in a few centres in France, the UK and the USA. There are several reasons for this. First, surgery remains the mainstay in the management of rectal carcinoma and most patients with early low rectal cancer who are operable have radical surgery, usually abdominoperineal excision of the rectum with permanent stoma. Second, even when local surgical excision was offered to patients with very small early tumours, a 'watch policy' was usually adopted after surgery [6]. Third, most of the radiotherapists who were referred these patients had no experience with contact radiation.

Improving Surgical Outcome

Published results using local surgical resection alone for early rectal cancer have been characterised by high rates of

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local recurrence, between 21 and 45% for pT1 and pT2, respectively [6,7]. This could be due to suboptimal surgical technique with piecemeal removal in most cases; the pathologist was unable to report on the surgical clearance. In addition, the importance of prognostic factors such as lymphatic and vascular invasion predicting a much higher risk of local recurrence and lymph node metastases were not fully realised. As a result, no adjuvant treatment was given to these patients. When postoperative radiotherapy was offered to patients with involved resection margins, there were delays in starting radiotherapy, sometimes beyond 12 weeks, and no additional boost with contact radiotherapy was used [8]. Even if the histology suggested a more advanced tumour, such as T2 or T3, further radical surgery was usually not offered as the patients were often not fit for major surgery. Instead, these patients received palliative external beam radiotherapy.

Since then surgical techniques have improved and highly trained colorectal surgeons now use ultra low anterior resections or transanal endoscopic microsurgery (TEM) [9]. In addition, gastroenterologists offer endoscopic mucosal resection for patients with early rectal cancer [10]. This technique offers a magnified operative view to ensure a better surgical clearance around the tumour [11]. In a randomised trial, Winde *et al*. [12] showed that there was no difference in local control or survival (5-year survival 96%) when patients who had radical surgical resection were compared with those who had TEM. The hospital stay, operative morbidity and mortality were much lower in the TEM group. However, the recently published results of the TEM Users Group from the UK showed a higher local recurrence rate in both pT1 (23%) and pT2 (34%) tumours when treated by surgery (TEM) alone [13]. Therefore, not all tumours staged as T1 are suitable for treatment by surgery alone, regardless of the surgical technique used. For these high-risk T1 and T2 tumours, increasing the dose of radiation to the tumour bed using contact radiotherapy may have improved local control, as shown by the very high rate of local control approaching 95—97% observed by three independent groups who have all used a contact boost in addition to external beam radiation [14—16].

Background for the Contact X-ray and Transanal Endoscopic Microsurgery Protocol

With the introduction of the new contact X-ray machine there is now a requirement for a clinical protocol. An observational study on contact X-ray and TEM (CONTEM) in the curative treatment of rectal cancer has been planned by the International Contact Radiotherapy Evaluation (ICONE) group. The design of the CONTEM protocol is based on the multimodality approach, which has been developed over the years by the experienced contact X-ray users in France, the UK and the USA. The idea is to optimise the combined use of local surgery, local contact X-ray, external beam radiotherapy and concomitant chemotherapy by adopting a response-adapted strategy according to known prognostic factors (Fig. 1).

For patients with well or moderately differentiated T1N0 tumours, local control can be obtained with contact X-ray as the sole treatment in 85—90% of patients with limited morbidity and a good sphincter function [5]. Similar results can be obtained with TEM [17—20]. Survival rates are also comparable between contact X-ray and TEM, with 5-year survival approaching 90%, depending on patient selection [21]. For small T1 tumours (<2 cm) TEM may therefore be the only necessary treatment. However, adverse pathological features may necessitate postoperative radiation [22]. According to the pathological risk factors predicting the increased risk of local or nodal recurrence, contact X-ray can be used to treat subclinical disease at the tumour bed and external beam radiotherapy to electively treat the regional nodes [20,23].

For more advanced disease (T2—3,N0—1), contact X-ray combined with external beam radiotherapy at doses in the range of 45—50 Gy can produce a complete clinical response in about 70 and 50% of patients with T2 and T3 disease, respectively [3,16,23—25]. In well-staged patients, 5-year overall survival of around 85% in T2 and over 50% in T3 have been reported [5,26]. It may therefore be concluded that for carefully selected early T2N0, contact X-ray combined with external beam radiotherapy and subsequent TEM is a viable alternative to total mesorectal excision (TME). For T3 disease, the results are clearly inferior to TME surgery and curative radiotherapy should only be offered to frail elderly patients not expected to be able to sustain major surgery or to patients who absolutely refuse TME. Interstitial brachytherapy as a final boost may be an option when contact X-ray and external beam radiotherapy and concurrent chemotherapy fail to achieve complete clinical remission in such patients, providing rates of local control and 5-year survival higher than 60% [16].

In recent years, concurrent chemoradiotherapy has gained acceptance as the standard preoperative treatment in rectal cancer because the addition of chemotherapy significantly reduces the risk for local recurrence [27—30]. The optimal chemotherapy schedule for combining with concurrent radiotherapy has so far not been established in phase III studies [30]. However, recent phase I—II studies suggest that currently the most effective and tolerable chemotherapy regimen is XELOX-RT, comprising capecitabine and oxaliplatin [30—34]. In addition, the combination of capecitabine and oxaliplatin has shown the largest response and resection rates in patients with solid liver metastases and is also the first-line regimen of choice for disseminated disease [34].

Discussion

Although contact radiotherapy has been used in the treatment of rectal cancer for over 70 years, there are no large randomised trials against standard surgery to establish it as an alternative treatment option. Unlike breast cancer, the number of patients treated in each centre is not sufficient to set up a large randomised trial. The ICONE group have therefore agreed to collaborate in setting up

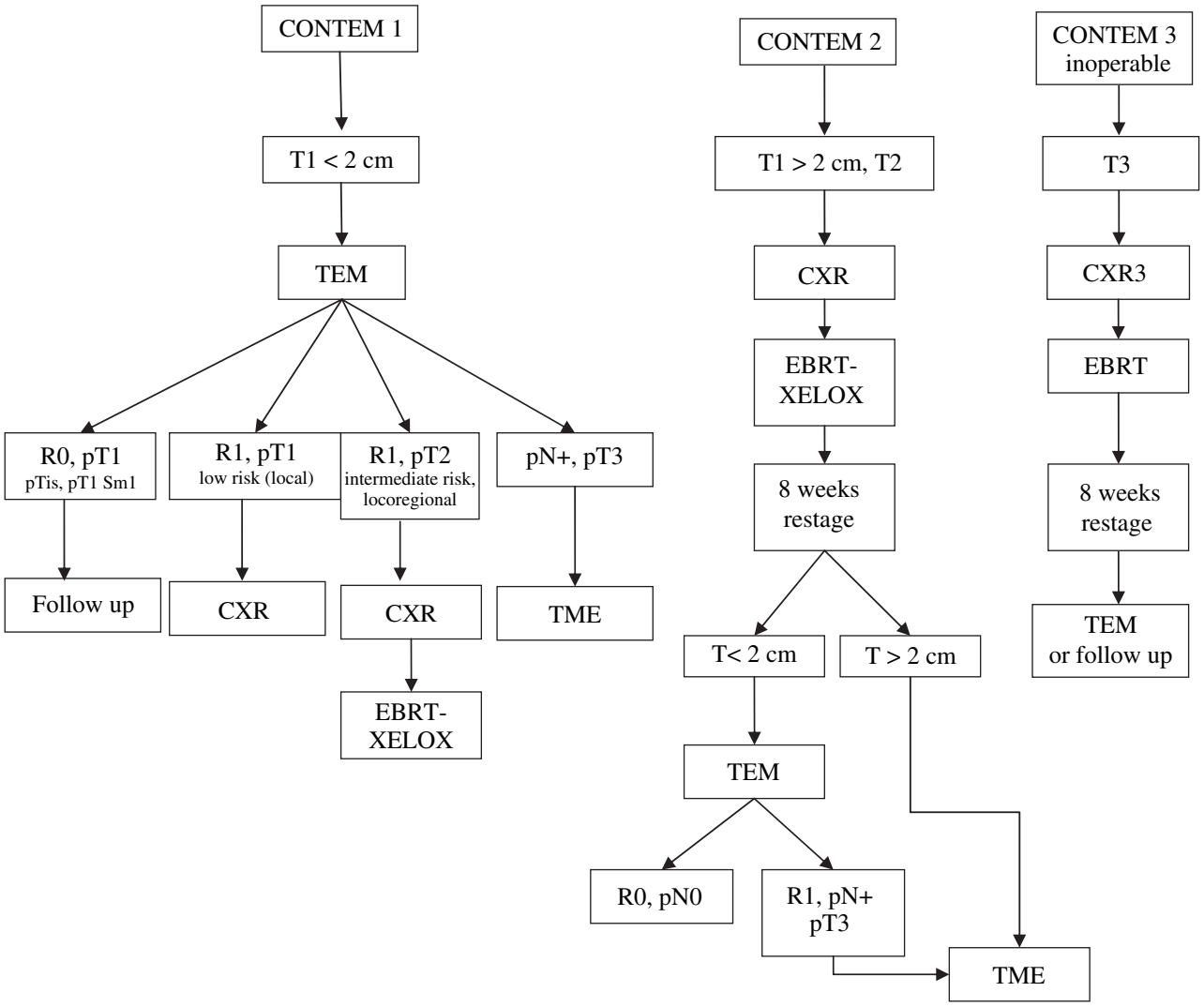

Fig. 1 — Overview of CONTEM trials.

a high-quality observational study (see Fig. 1) with a strict protocol from which useful prospective data could be collected and the information used to establish internationally agreed guidelines for the treatment of patients with early rectal cancer.

Conclusion

The availability of equipment for contact radiotherapy will enable collaborative efforts through ICONE to define the future role of contact radiotherapy in the management of early rectal cancer.

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