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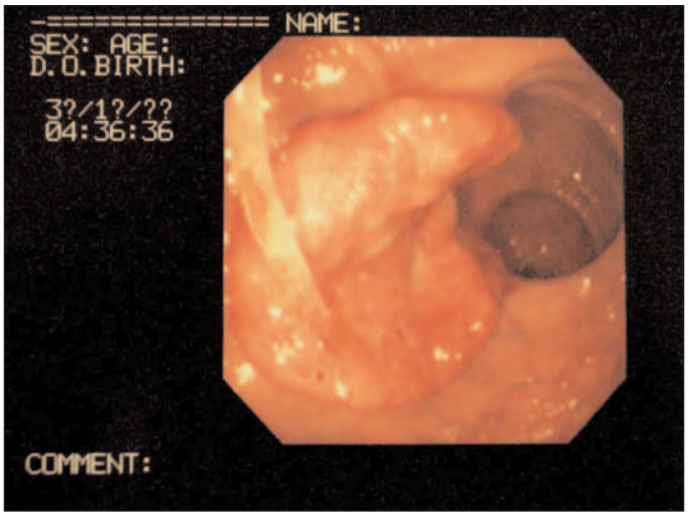

Figure 3a: Rectal adenocarcinoma (T2N0MO).

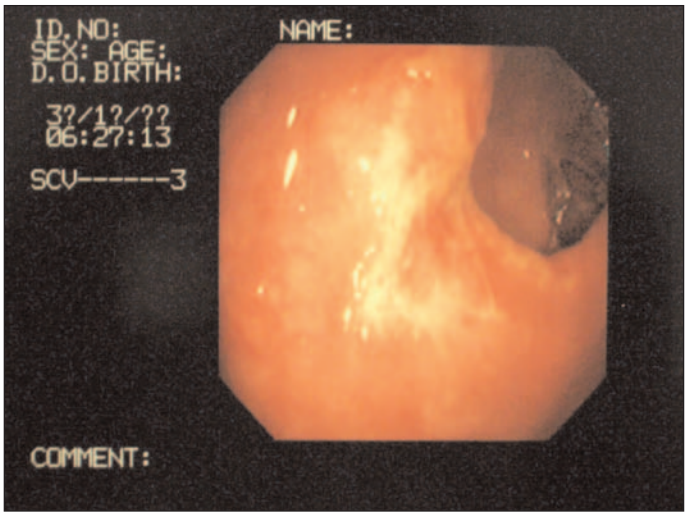

Figure 3b: Appearance after chemo-radiotherapy followed by Papillon boost (There was no residual tumour (ypT0 ypN0) at surgery).

In this issue:

Curative options for local treatment of early rectal cancer

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Background

Local treatment of early rectal cancer is a highly controversial topic. It is not universally accepted as a standard treatment. The main reason why opponents of this treatment are not keen on this approach revolves around the argument that the lymph nodes are not treated by surgical removal, which is vital for pathological staging. The enthusiasts for this treatment approach feel that for early stage tumours, the probability of lymph node spread is low, and removal of the primary tumour alone to preserve sphincter function is adequate as an initial treatment and if necessary, external beam chemo-radiotherapy could be offered to sterilise micro-metastases in the lymph nodes. Should the tumour recur at a later date, can effective salvage treatment be offered without compromising the local control and survival? The opinion differs across the Atlantic and in Europe.

Historically, we have seen this scenario with breast cancer where only the radical surgical treatment was the "gold" standard and all patients with operable breast cancer were offered mastectomy to achieve local cure. Later, local resection followed by radiotherapy became universally accepted standard treatment for early breast cancer, when randomised trials such as the Milan and NSABP (B-06) trials showed that lumpectomy followed by radiotherapy resulted in equal local control and survival compared to mastectomy[1]. So far, there have been very few randomised trials for early rectal cancer and the controversy for local treatment as an alternative option to radical surgery is likely to continue for the foreseeable future.

Assessment for local treatment options

Over the past decade, there has been increasing interest in local treatment options for small tumours in the lower third of the rectum as an alternative to abdomino perineal resection. This treatment option is mainly offered to elderly patients or those with medical co-morbidity (which increases anaesthetic risk) and also in a small percentage of younger patients who cannot accept radical surgery or permanent colostomy. The selection criteria suitable for local treatment are shown in **Table 1**.

The aim is to select patients with tumour confined to the rectal wall, in which there is a low probability of lymph node metastases. The accuracy of pre-treatment staging by radiological methods to differentiate between T1, T2 and T3a tumours is not always reliable and is operator dependent. In our experience, the most reliable method of assessment is to combine radiological assessment together with digital examination and endoscopy carried out by an experienced clinician. The assessment of lymph node metastases, which is usually microscopic, is obviously much more difficult by digital examination and has to rely on radiological assessment such as endo-rectal ultrasound or endorectal MRI. Again, to achieve high accuracy of pick-up rates (>90%), the examination needs to be performed by experienced operators[2]. The main drawback of the radiological assessment is reliance on the shape and size of the lymph nodes, which are not always enlarged or misshapen. Newer MRI imaging techniques using iron oxide contrast may help in some cases. The more difficult cases are the ones with only one or two lymph nodes, which are <2-3mm. The decision to offer local treatment then depends on other factors such as advancing age or other co morbidities, which excludes them from more radical treatment options.

Table 1. The selection criteria suitable for local treatment.

1. Mobile exophytic tumours <6cm from anal verge (Clinical assessment-DRE)
2. Tumour <3cm or occupying less than a third of circumference (Endoscopic assessment)
3. T1/N0/M0 (Radiological assessment-EUS/endorectal MRI)
4. Well to moderately-well differentiated tumours (Histological assessment)
5. No vascular or venous invasion (Histological assessment)

Local treatment options

There are several local treatment options and the choice of treatment depends on the initial staging. The more difficult decision, which is usually the case, is when a malignancy is unexpectedly detected in what was thought to be a benign polyp with no prior investigations.

1. Endoscopic sub-mucosal resection (EMR)
2. Surgical transanal resection (TAR or TEM)
3. Radical radiotherapy (Papillon technique)

1. Endoscopic mucosal resection (EMR)

This method is usually reserved for benign pedunculated polyps with a stalk. The polyp is assessed endoscopically and the base is infiltrated by either saline or gel to raise it away from the muscle and the polyp is then resected using diathermy or a hot loop. The specimen is pinned on a corkboard and sent for histological examination. Some clinicians feel that extended EMR can be used for rectal neoplastic lesions as it can achieve superior results to those of transanal resection (TAR) and transanal endoscopic microscopy (TEM) with regard to complications and recurrence rates[3].

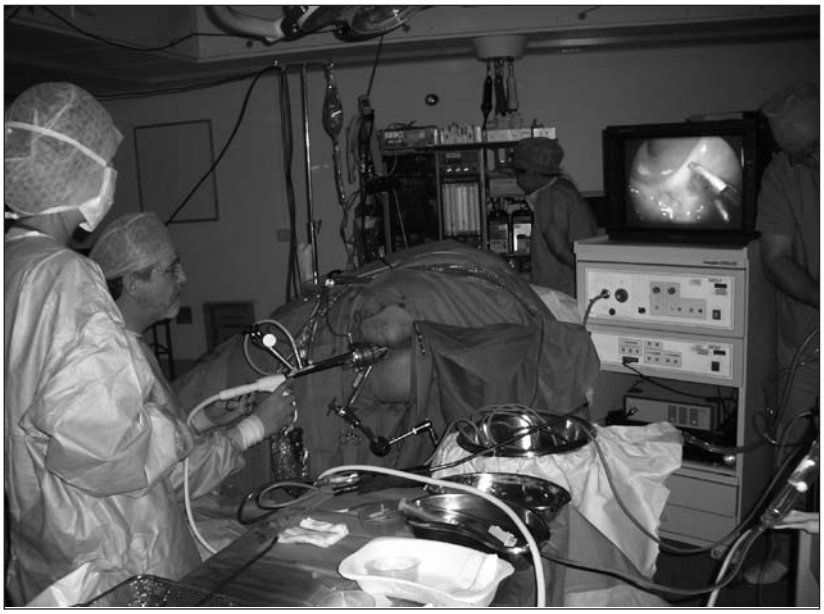

Figure 1: TEM procedure for transanal excision of rectal cancer.

2. Local surgical resection

There are several surgical techniques available for this approach:

1. Transanal resection (Parks)
2. Transsacral excision (Kraske)
3. Transsphincteric excision (York-Mason)
4. Transanal endoscopic microsurgery (Buess)

1. Transanal resection (Parks)
After a full bowel preparation, the patient is positioned for surgery. Lithotomy position is used for posterior rectal lesions and prone jackknife position for anterior lesions. The Park's or Ferguson's type retractor is used in obtaining the exposure and sutures are placed 1cm above, below and to each side of the lesion to provide counter traction during the dissection. Full thickness dissection is carried out from distal to proximal until the lesion is completely excised. Excision can be difficult and piecemeal removal is not uncommon. The orientation of the specimen should be maintained as it is pinned out onto a paraffin board and sent to the pathologist. Despite great care to achieve haemostasis, bleeding complications are common and this method cannot be used for lesions high in the rectum. Local recurrence is not uncommon and even in benign tumours, occurs in about 10-20%.

2. Transsacral excision (Kraske)
The transsacral excision was first described in 1885. It enables surgeons to reach a lesion not amenable by the transanal approach. The patient was placed in the prone position and through the opening in the posterior wall a full-thickness excision of the anterior wall lesion was performed. It is seldom used nowadays because of problems associated with delay in wound healing and rectal fistulas.

3. Transsphincteric excision (York-Mason)
Originally described by Bevan in 1917, York-Mason popularised the trans-sphincteric excision in the 1970s. Similar to transsacral approach, this procedure allowed surgeons to resect lesions up to the mid-rectum. This method also has fallen out of favour because of wound healing problems and fistula formation.

4. Transanal Endoscopic Microsurgery (TEM)
Buess first described transanal resection using Transanal Endoscopic Microsurgery (TEM) in 1984[4]. It was introduced as an alternative technique for local resection of large (>3cm) rectal or recto-sigmoid polyps which are usually benign. It has also been used for malignant lesions in a small number of patients. A 40mm operating rectoscope with 6 times magnification power is used for the TEM procedure. It allows the tumour to be resected further up to 20cm from the anal verge, which is much more than can be achieved with transanal resection. TEM combines an endoscopic view of the rectum under gas insufflations via a stereoscopic telescope with conventional surgical preparation. Gas insufflation prevents prolapse of normal mucosa, which can obscure the operative field. TEM method enables the operator to remove the tumour using full thickness excision under direct magnified vision with sufficient margins of the surrounding normal healthy tissue (**Figure 1**). The advantage of TEM is that it allows less invasive surgery with much more precise removal of the tumour. When TEM is compared to radical surgery, there is

reduced morbidity (3.4% and 18% respectively) and reduced mortality (<1% and 3.8% respectively)[4, 5].

3. Radical radiotherapy (Papillon technique)

In 1946, Lamargue and Gros from Montpellier were the first to use the Phillips RT 50Kv machine to treat rectal adenocarcinoma. They reported a 42% 5-year survival for 26 patients with early rectal cancer among 116 patients treated with radiotherapy for rectal cancer.

Professor Papillon from Lyon then popularised the technique, which bears his name and has treated over 300 patients between 1950 and 1990. He reported a 75% 5-year overall survival with only 9% local failures[6]. In 1976, Sischy from Rochester introduced this technique in the USA and confirmed Papillon results in more than 200 patients treated under his care in the Highland Hospital[7]. Up to now more than 1,000 patients have been treated throughout the world and a general overview of the results suggested long-term local control rates of around 80% to 90% with a 5-year overall survival in the region of 50% to 70%[8]. The criteria for the patient selection and stages were not always clear and in the historic series the investigations carried out were not always optimal by modern standards. However, many elderly patients were spared radical surgery for their rectal tumours. The local control and disease-free survival were similar to that of the surgical series at the time of their treatment. Unfortunately, there were no randomised trials to confirm the efficacy of this technique, as the numbers of patients treated in each institution were very small and obviously not sufficient for a large randomised trial.

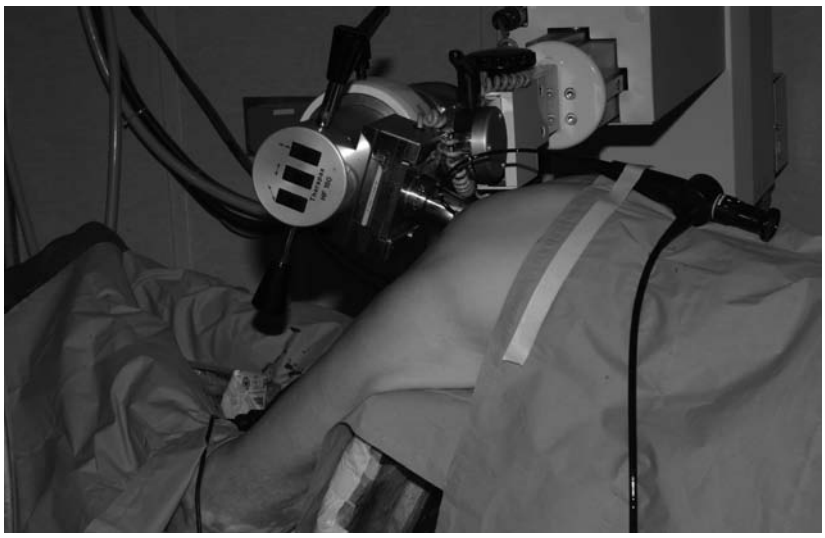

Figure 2: Contact radiotherapy: Clatterbridge technique.

Treatment technique

Contact radiotherapy can be delivered as a day patient provided the patient has enemas at home to clear the bowel, which is essential for successful treatment. The patient is treated in a knee-chest position and a rectoscope is inserted through the anal sphincter using local anaesthesia (lidocaine 2% gel). After clinical and endoscopic assessment, the first dose of 30-40Gy is delivered using either a 50Kv Phillips machine (Lyon) or at Clatterbridge, a Therapax 50Kv machine is used with 0.5mm Al. filter (**Figure 2**). This delivers a 100% D max on the surface of the tumour with the dose falling to 45% at 5mm and 30% at 10mm. A second fraction is delivered in 1-2 weeks time giving further 30Gy. The third fraction is delivered in another 2 weeks time (3-4 weeks from start). The assessment before the third session is very important. If the tumour is visible or palpable, further treatment with contact radiotherapy alone is not sufficient as this suggests a much more deeply infiltrating tumour (despite radiological staging of tumour as T1 or T2). External beam radiotherapy alone giving 39Gy in 13 fractions over two and a half weeks or chemoradiotherapy with 45Gy in 25 fractions over 5 weeks with 5FU infusion 750-1,000mg/m^2 in week 1 and 5 is offered, usually after the third fraction of 20Gy (80Gy contact total). If the tumour response is favourable (i.e. no palpable tumour after 2 sessions) then a further 2 fractions are offered 2 weeks apart. A total dose of 90-120Gy is given in 4-5 fractions over 6-8 weeks. It is important to note that no general anaesthesia is necessary for contact radiation and no mortality has been reported due to this procedure.

The role of contact radiotherapy in improving the outcomes for rectal cancer

Radiation therapy has been shown to reduce local recurrences and currently there is increasing use of radiation either pre-operatively or less often post-operatively to improve surgical outcomes. However, so far there is no definite evidence that radiation improves survival after surgery[9]. There are two strategies to make the radiation more effective. One approach is to combine chemotherapy with radiation and the other is to increase the dose of radiation.

Chemo-radiotherapy

In an attempt to improve the surgical outcomes further, radiation has been used concurrently with chemotherapy. Chemotherapy used was 5 Fluorouracil (5FU) for the last 40 years, however, in the last decade there was an explosion of newer chemo-therapeutic agents. Infusional 5FU remains the mainstay for most of the chemotherapeutic regimes and either Irinotecan or Oxaliplatin can be added weekly or daily in the first and fifth week. More recently, Capecitabine an oral agent that is more convenient to use, replaces the 5FU infusion in different combinations with Irinotecan and Oxaliplatin. The ongoing trials include anti-EGF and VEGF with other drug combinations. The main drawback of chemo-radiation is the sensitisation of normal tissues with its resultant acute and long-term complications, which may be detrimental to patients' quality of life. Surgeons are concerned about surgical complications such as delay in wound healing, increased anastamotic leakage and this has lead to the avoidance of pre-operative chemo-radiation. At the moment, although this may be possible in early stage disease it is unavoidable in the majority of patients who usually present with more

advanced tumours where chemo-radiotherapy is essential for downstaging to render them operable. There is an urgent need to find alternative treatment strategies to improve surgical outcomes.

Increasing the radiation dose

It has been established from historic studies that a minimum of 40GY or equivalent is required to have any impact on local control in rectal cancer. The standard dose fraction used in most randomised chemo-radiotherapy studies is 45Gy in 25 fractions over 5 weeks. Recently, in some clinical trials, a reduced field boost to primary tumour bearing area has been used to give an additional 5.4Gy in 3 fractions over 3 days, however, most trials would not give beyond this. There was a randomised trial from the Bernie Cumming's group in the Princess Margaret Hospital assessing the dose response in rectal tumour[10]. Three dose levels were chosen 40Gy, 46Gy and 50Gy. There was significant improvement in local recurrence-free survival of 77%, 89.8% and 91.3% (*P*= 0.036). However, the complication rates went up from 12.5% to 39.4%, which was highly statistically significant (*P*=<0.009). This is clearly unacceptable. An alternative treatment option to increase the dose of radiation around the tumour without increasing the dose to the normal surrounding tissues, in order to reduce complications, is to use contact superficial X-ray (50Kv) therapy as a boost aimed and delivered at the primary tumour.

Contact 50Kv X-ray therapy boost

Professor Papillon from Lyon popularised contact radiation as a radical treatment for small rectal tumours in elderly patients who were medically compromised. Professor Jean Pierre Gerard, who has worked with Professor Papillon for many years, later took over and started using combined modality treatment with external beam and contact radiotherapy. The patients were treated by contact radiation initially, delivering 60-80Gy then followed by a course of external beam radiation giving a further 39Gy in 13 fraction over two and a half weeks, using a small planned volume to include the primary tumour and adjacent peri-rectal lymph nodes. He has now treated over 100 patients and has confirmed the efficacy of contact radiation. Local control was achieved in 88% with 83% of the patients surviving 5 years[8].

Although radical radiotherapy is usually offered to patients who are either elderly or medically unfit, it could also be offered to a small number of selected patients who are relatively young and fit but refuse surgery, as they are not prepared to accept permanent colostomy. The surgical techniques have changed over the years and most colorectal trained surgeons can now offer low or ultra low anterior resections except in about 20-30% of patients with operable rectal cancer[11]. The concept of sphincter preservation has now become an important issue in the management of rectal cancer. With this in mind, Professor Gerard conducted a randomised trial (Lyon R96-02) comparing external beam radiation alone (39Gy/13#/17 days) against the same EBRT with contact boost giving further 60-80Gy to evaluate whether increased sphincter preservation could be offered to those whose tumours were downstaged by escalating the dose of pre-operative radiation by boost with contact radiotherapy[12]. Between 1996 and 2001, 88 patients with T2/T3 rectal tumour <6cm from anal verge and less than two-thirds circumference were enrolled into the study. Significant improvements were seen in favour of the contact x-ray boost for complete response (24% vs. 2%) and for complete or near complete sterilisation of the operative specimen (57% vs. 34%). More important was a significant increase in sphincter preservation observed in the boost group (76% vs. 44%; *P*=0.004). However, unlike external beam boost, there was no significant increase in the early acute and late reactions. The main criticism for this approach is the lack of availability of a contact radiotherapy machine that could be used by others. This problem has now been addressed and a new mobile contact 50Kv machine will be available shortly. A consensus meeting was held at Clatterbridge last March to discuss future International collaborative trials in early rectal cancer using this approach and the next meeting has been planned for April 2006.

Follow up

Patients who are offered local conservative treatment should be followed up closely. The patients should be seen every 6-8 weeks initially for the first two years for DRE and sigmoidoscopy with biopsy, if necessary. CT scan should be carried out at 12 and 24 months and if there is any suspicion of recurrence, MRI should be carried out. This close follow-up policy was observed carefully at Liverpool compared to other investigators where follow-up was usually typically12-16 weeks. This may be one of the reasons why we were able to offer successful salvage surgery before the recurrent tumour became fixed and inoperable[13]. Although most of the recurrences developed within the first two years, our experience has shown that late recurrence could occur up to 5 years after the treatment. Therefore, it is important to follow these patients up carefully beyond 5 years so that recurrences can be detected early enough to enable curative salvage surgery.

Discussion

The number of patients with early rectal tumours at presentation are relatively small (<5%) and as the treatment decision on local treatment is difficult, the individual cases should be discussed among the specialist multi-disciplinary team.

In future, expanding use of endoscopic procedures is likely to pick up increasing numbers of small malignant polyps. Patients with pedunculated polyp will have endoscopic resection (EMR) initially. If the resection margins are clear in T1NOMO lesion (SM1or SM2); no further treatment is necessary[3]. The treatment of SM-3 or T2 lesion is more controversial and in such patients who are fit and willing to accept colostomy if necessary, should be offered radical surgery. If the patient is elderly and is not medically fit then they can be offered external beam radiotherapy followed by contact radiotherapy boost.

Across the Atlantic, a high rate of local recurrences up to 22% were observed in the Mayo Clinic study and the Cancer and Leukemia Group B CALGB Intergroup Phase 11 studies[14]. There were several factors responsible for this. Firstly, the staging investigations were not complete in all cases before surgery. Secondly, sub-optimal surgical techniques such as transanal resection (TAR) were used in most cases. Thirdly, although postoperative radiotherapy was offered to patients with involved resection margins there were delays in starting radiotherapy, sometimes beyond 12 weeks. Finally, contact boost or brachytherapy implant to increase the dose of radiation to the scar was not routinely used (personal communication). The opponents of local treatment often use this almost historic data to criticise high local failure rates following local treatments.

More recently, the technical advances in surgery have led to the increasing use of TEM for local resection. In a randomised trial, Winde *et al.* has shown that there was no difference in local control or survival (5-year survival 96%) between patients who had radical surgical resection compared to the TEM group. The hospital stay, operative morbidity and mortality were much lower in the TEM group[15]. In the UK, since 1996, the majority of local resection for early cancer has been carried out using TEM technique and data on this procedure have been collected centrally at Oxford, through a TEM user group, which meets every year to update the database and share their experiences.

In 1992, one of the authors (SM) introduced the Papillon technique into the UK and established contact treatment at Clatterbridge which is the only centre offering the Papillon treatment in the UK at present. Independently, the other author (MJH) introduced the TEM technique into the UK[16] and there are approximately 30 centres using TEM for early rectal cancers. Since 1993, the two authors set up a joint anorectal specialty clinic combining the two treatment modalities. The management plan in Liverpool includes, either TEM or contact radical radiotherapy for smaller <3cm T1NOMO tumours in elderly patients or those who are not medically fit for major radical surgery. For larger >3cm tumours, T1T2/ NOMO, pre-operative chemo-radiotherapy or radiotherapy has been used to down-stage and down-size the tumours followed 6-8 weeks later by further assessment. If there is no residual tumour detected by rectal examination, sigmoidoscopy and radiological examination, then the management options are either to 'watch and wait' or offer immediate radical surgery. If there is small residual tumour, then TEM is offered to remove the residual tumour for histological examination. If the resection margins are involved after TEM, then radical surgery is offered, provided that the patient agrees. If the patient is not medically fit for operation or refuses major surgery, then a Papillon boost giving further 60-80Gy is offered[13]. HDR brachytherapy (10Gy) can be given initially for bulky residual disease after EBRT[17]. Since 1993, we have treated 155 patients with a multi-modality approach and there were 15 recurrences (9.6 %). Twelve of these patients were salvaged (80%). There were 5 patients (3.2%) with distant relapse and one nodal relapse in a patient who had contact radiation alone without initial external beam.

So far, there is some agreement on management of T1 tumours; however, treatment of T2 rectal cancer is much more controversial. Lezoche and his colleagues from Rome reported long-term results of 106 patients with T2 rectal cancer treated by pre-operative chemo-radiotherapy followed by TEM and observed only one recurrence (2.8%) at median follow up of 38 months (range 24-96)[18]. This group has now conducted a small randomised trial using pre-operative chemo-radiotherapy followed by TEM versus radical surgery. There were 20 patients in each group. Although the numbers of patients in each cohort is small (n=20) at median follow up of 4 years, this trial has shown equivalent local control and survival (personal communication). In Poland, Bujko and his colleagues have started another randomised trial with similar design and have accrued over 17 patients so far. The TEM users group in the UK is considering starting a similar trial.

The optimal management of patients who achieved complete remission following pre-operative chemo-radiotherapy is an interesting one. In our series, there were 7 patients who achieved this and after careful discussion with the patients, we adopted a watch and wait policy on 5 and 2 were offered anterior resection. In both patients, there was no residual tumour on histology. See **Figures 3a** and **3b** (front cover). None of the 7 patients had a recurrence at median follow up of 36 months (range 12-108 months). Thirty nine patients had incomplete clinical response and had TEM to remove the residual tumour. In 9 patients (23%) there was no histological evidence of a residual tumour (yPTO, yPNO, MO). None of these patients had a recurrence at the median follow up of 36 months.

There are several reports of a similar experience from Sao Paulo, where 71 patients (26.8%) who achieved complete clinical response were observed following chemo-radiotherapy (Observation group) and they were compared to 22 patients (8.3%) who showed incomplete clinical response initially and had surgery, but achieved complete pathological response (yPT0,yPNO,M0) on histology (Resection group). There was no difference between the patients' demographics and tumour characteristics between the two groups. Median follow-up was 57.3 months in the Observation group and 48 months in the Resection group. There were 3 systemic recurrences in each group and 2 endorectal recurrences in the Observational group. Two patients in the Resection group died of disease. Five-year overall and disease-free survival rates were 88% and 83% respectively in the Resection Group, and 100% and 92% in the Observation Group. The investigators concluded that stage 0 rectal cancer disease is associated with excellent long-term results irrespective of treatment strategy. Surgical resection may not lead to improved outcome in this situation and may be associated with high rates of temporary or definitive stoma construction and unnecessary morbidity and mortality. However, it is important to note that only 71 patients (26.8%) out of a total of 265 patients achieved complete clinical response following pre-operative chemo-radiotherapy and the others (who had incomplete response), needed standard surgical treatments.[19]

Other investigators have confirmed that pathological complete remission (pCR) can be achieved in about 20% of cases following pre-operative chemo-radiotherapy using 5FU and radiotherapy and that those who achieved path. CR have better long-term disease-free and overall

survivals[20]. This topic will be discussed at the 3rd Pelican annual workshop seminar on management of complex low rectal cancers in November 2005.

Pre-operative chemo-radiotherapy using newer agents such as Oxaliplatin or Irinotecan with 5FU or Capecitabine can achieve higher pCR in the region of 30-40% and it would be interesting to see whether this could lead to higher sphincter-sparing operations. One can postulate that if contact radiotherapy can be offered as a boost (as in Professor Gerard's Lyon R96-02 trial), then there may be a greater chance of sphincter preservation being achieved at the time of surgery. Contact radiation boost can either be given by 50 KV X-rays or HDR contact using micro Selectron. We hope that the NCRI rectal group may consider the possibility of increased sphincter preservation by contact radiation boost in their next rectal trial.

Conclusion

Local treatment of early rectal cancer is a controversial and a complex issue that needs to be addressed and discussed. The clinician in charge has the responsibility of explaining all the treatment options that are available to the patient without personal bias. The advantages and disadvantages of each treatment option available should be clearly explained so that patients and their relatives can consider these options carefully and decide on which treatment option they wish to pursue. All the discussions need to be carefully documented as the patients may be prepared to accept the higher risk of local recurrence with radiation in order to avoid a stoma. Complex and difficult cases should be referred to specialist centres with experience and expertise so that all available treatment options can be considered.

The local treatment issue will become a major problem when colorectal screening is introduced, as increasing numbers of patients will be diagnosed with early rectal cancer. One can predict that not all the patients diagnosed with early very low rectal tumour will be suitable for low anterior resections nor that they would agree for permanent or even temporary colostomy. We need to have a robust treatment plan of management so that appropriate treatment can be offered to patients without compromising their chance of cure while at the same time respecting patients' wishes and their choice of treatment option.

As the ageing population is likely to expand in the next decade, the demand for local treatment will increase. It is important to balance the benefits of radical surgery, in terms of lower local recurrences, against the increased mortality and morbidity from such procedures, versus slightly higher local recurrences and much lower mortality and morbidity from conservative local treatments such as TEM and contact radiotherapy. At present, unlike breast cancer, randomised trial level 'A' evidence for local treatment as a standard for rectal cancer is not yet forthcoming. Therefore, we may just have to accept the level 'B' evidence from non-randomised trials as it is difficult to organise a randomised trial due to a relatively small (5%) number of patients treated for early rectal cancer at each institute. We would need a multi-centre international effort to set up a large randomised trial which is a major undertaking and may not be possible for the foreseeable future. Until such time, the controversy for local treatment is likely to continue.

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ABSTRACTS

Colon

Capecitabine as adjuvant treatment for stage III colon cancer

Twelves C, Wong A, Nowacki MP, Abt M *et al* 2005
New England Journal of Medicine **352:** 2696–2704
(University of Leeds and Bradford NHS Hospitals' Trust, Leeds, UK and other sites worldwide)

- **Capecitabine was shown to be an effective alternative to fluorouracil plus leucovorin in the adjuvant treatment of colon cancer**
- **There was a lower incidence and delayed onset of grade 3 or 4 toxic effects with capecitabine as compared with fluorouracil plus leucovorin**

The benefits of fluorouracil-based adjuvant chemotherapy in terms of reducing the risk of relapse and prolonging survival in patients with resected colon cancer are well established. Survival advantages have been demonstrated with bolus intravenous fluorouracil plus leucovorin administered according to either the Mayo Clinic or Roswell Park regimen. However, it is recognised that many patient with cancer would prefer oral chemotherapy, provided efficacy is not compromised. This phase 3 trial has compared the oral fluoropyrimidine capecitabine (Xeloda ™) and the Mayo Clinic fluorouracil plus leucovorin regimen as an adjuvant treatment in resected stage III colon cancer.

A total of 1987 patients with resected stage III colon cancer were randomly assigned to receive either oral capecitabine (1004 patients) or bolus fluorouracil plus leucovorin (Mayo Clinic regimen; 983 patients) for a period of 24 weeks. Randomisation occurred within 8 weeks of surgery. The primary aim of the study was to show at least equivalence in disease-free survival between capecitabine and bolus fluorouracil plus leucovorin. The primary safety end point was the incidence of grade 3 or 4 toxic effects due to fluoropyrimidines. Secondary end points included relapse-free survival, overall survival, and safety. Assessment of the rate of disease-free survival at three years was a prespecified secondary end point.

Disease-free survival in the capecitabine group was at least equivalent to that in the fluorouracil plus leucovorin group (**Figure 1**). The hazard ratio comparing disease-free survival in the capecitabine group with that in the fluorouracil plus leucovorin group was 0.87 (95% CI, 0.75 to 1.00). The upper limit of the CI (1.0) was significantly below both the predefined margins, 1.25 and 1.20, for at least equivalence (P<0.001 for both comparisons). Capecitabine improved relapse-free survival (hazard ratio, 0.86; 95% CI, 0.74 to 0.99; P=0.04) and was associated with significantly fewer adverse events than fluorouracil plus leucovorin. The three-year rates of relapse-free survival were 65.5% in the capecitabine group and 61.9% in the fluorouracil plus leucovorin group (P=0.12). Overall survival in the two groups did not differ significantly (P=0.07). The onset of pedefined key grade 3 or 4 toxic effects was significantly reduced throughout treatment with capecitabine as compared with fluorouracil plus leucovorin (P<0.001).

The results support capecitabine as an alternative to fluorouracil plus leucovorin in the adjuvant treatment of colon cancer. The authors conclude that capecitabine or oxaliplatin-based therapy should be considered for all patients requiring adjuvant therapy for colon cancer.

This peer reviewed publication in *NEJM* reflects the X-ACT data as presented at ASCO 2004. The ASCO 2005 meeting updated the study. At this meeting the results were updated with some extra follow up time. In summary, the update confirms all the previous findings. DFS is equivalent for capecitabine – and almost superior, in statistical terms. RFS is superior for capecitabine and OS is also equivalent. In fact for overall survival the curves are coming closer together with increased follow-up. This is not surprising since the study was designed and powered to show just this endpoint.

A poster presentation was also given on post-study chemotherapy exposure for those unfortunate patients who have relapsed. This showed that chemotherapy types and regimens used are almost identical for both groups. Therefore, it is unlikely that this could be viewed in some way as a confounding variable in the overall survival analyses.

Professor J Cassidy

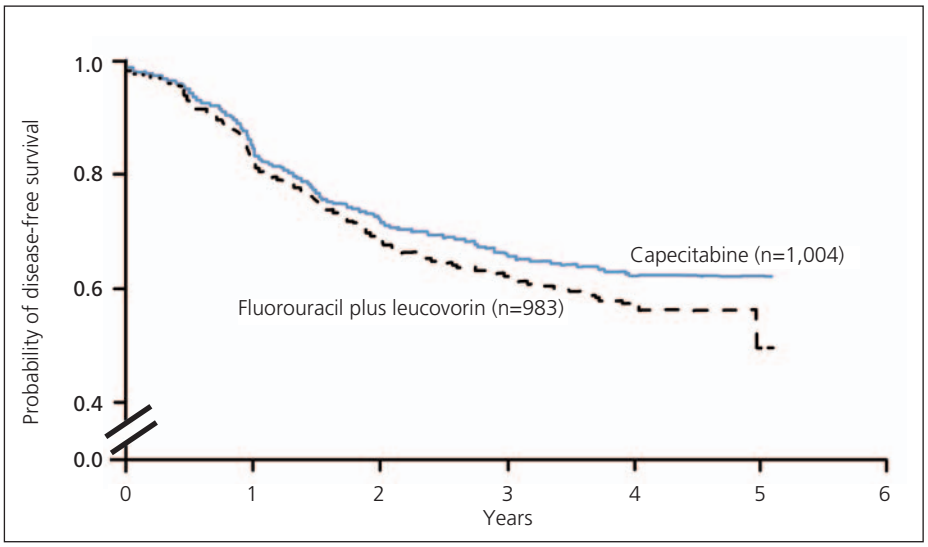

Figure 1. Kaplan-Meier estimates of disease-free survival among patients receiving fluorouracil plus leucovorin or capecitabine (intention to treat population). The upper limit of the confidence interval of the hazard ratio was significantly below both the predefined margins, 1.25 and 1.20, for equivalence (P<0.001 in both cases). The analysis for superiority showed a trend favouring capecitabine (hazard ratio, 0.87 [95% confidence interval, 0.75 to 1.00]; P = 0.05).

Early safety findings from a phase III trial of capecitabine plus oxaliplatin (XELOX) vs. bolus 5-FU/LV as adjuvant therapy for patients with stage III colon cancer

Schmoll HJ, Tabernero J, Nowacki M *et al* 2005
ASCO GI Meeting, Florida

In a large phase III study (X-ACT) in stage III colon cancer, adjuvant capecitabine was at least equivalent to bolus 5-FU/LV for disease-free survival (DFS). In the MOSAIC trial, oxaliplatin + 5-FU/LV (FOLFOX4) resulted in superior DFS compared to 5-FU/LV, and has recently been approved for adjuvant therapy. As in metastatic colorectal cancer, capecitabine should be considered as an alternative to iv 5-FU in combination with oxaliplatin in the adjuvant setting. This study compared the safety and efficacy of XELOX to bolus 5-FU/LV (the standard regimen at the start of the study) as adjuvant therapy for stage III colon cancer.

Patients with resected stage III colon cancer received XELOX (capecitabine 1,000mg/m^2 bid d1-14 + oxaliplatin 130mg/m^2 d1, q3w x8) or iv bolus 5-FU/LV (Mayo Clinic, LV 20mg/m^2 + 5-FU 425mg/m^2 d1-5, q4w x6; or Roswell Park [RP], LV 500mg/m^2 +5-FU 500mg/m^2 d1, w-16 in 8w cycles x4).

1,719 of the 1,886 patients randomised between April 2003 and September 2004 were evaluable for safety. Treatment arms were well balanced: median age (years, range), XELOX (59.7, 22–83), 5-FU/LV (60.6, 24–82); gender (% M/F), XELOX (55/45), 5-FU/LV (52/48); nodal status (% N1/N2), XELOX (65/35), 5-FU/LV (64/36). Grade 3/4 adverse events (AEs) were 39.3%/5.9% (XELOX) and 33.2%/8.9% (5-FU/LV).

Table 1 shows the most common treatment-related grade 3/4 AEs. 60-day all cause/treatment-related mortality within 28 days from last dose were 0.9%/0.6% for XELOX and 1.1%/0.6% for 5-FU/LV.

Early safety data from the largest population of patients treated with XELOX indicate that XELOX causes less myelosuppression and stomatitis, but more skin and neurosensory toxicity than 5-FU/LV, and compares favourably with FOLFOX4. XELOX has now been incorporated in the 3-arm AVANT adjuvant trial (FOLFOX4 vs. FOLFOX4 + bevacizumab vs. XELOX + bevacizumab).

Capecitabine combined with oxaliplatin is an effective and well-tolerated therapy for advanced colorectal cancer

The XELOX regimen of capecitabine combined with oxaliplatin has already been demonstrated to be an effective and well tolerated therapy for advanced colorectal cancer. In addition, since capecitabine generates 5FU preferentially at the tumour site it is logical to expect that cytotoxic synergy with oxaliplatin will also preferentially occur at sites of disease. One might expect both improved efficacy and reduced systemic toxicity in such circumstances. The XELOX regimen has been compared with a "standard" intravenous infusional regimen widely known as FOLFOX. Efficacy results of this comparison are not yet available but are expected for around the time of ASCO 2006. In the meantime this toxicity analysis shows precisely what we expect. XELOX is generally better tolerated. Minor differences are apparent – but we need to wait for full analysis of this trial to be able to reach the appropriate risk-benefit conclusions.

Professor J Cassidy

Table 1. Tolerability of the five different regimens

Gr 3/4 AEs (%)	5-FU/LV (n=838)	Mayo (n=591)	RP (n=237)	XELOX (n=881)	FOLFOX* (n=1,108)
Diarrhoea	17.1	13.5	26.2	15.6	11.8
Stomatitis	7.9	11.2	0	0.6	2.7
Nausea	3.9	2.2	8.4	4.1	5.1
Vomiting	2.5	1.7	4.6	5.0	5.8
Neurosensory	0	0	0	8.1	12.4
Hand-foot syndrome	0.2	0.2	0.4	3.6	2.0
Neutropenia	10.9	14.0	3.0	5.3	41.1

Radiotherapy in the conservative treatment of rectal cancer. Evidence-based medicine and opinion

Gerard JP 2005
Radiotherapy and Oncology **74:** 227–233
(Département de radiothérapie. Centre Antoine Lacassagne, Nice, France)

- **Preoperative radiotherapy may improve sphincter preservation**
- **A 5-7 week delay between radiotherapy and surgery is necessary**
- **Radiation dose escalation improves clinical tumour response**

Resectable rectal adenocarcinoma stage T3-4 Nx, M0 tumours represent 80% of all rectal cancers and are treated basically by radical surgery resulting in 20–40% of the cases in permanent colostomy. This review of randomised trials has been carried out to investigate if the effect of radiotherapy measured in terms of tumour response (shrinkage, down-sizing or down–staging etc.) can increase the chance of sphincter saving procedure (SSP). Such a conservative treatment should preserve good sphincter function and quality of life and not increase the risk of local risk or death by cancer.

Between 1990 and 2003 three randomised controls comparing post vs. preoperative radiotherapy (with or without chemotherapy) showed that preoperative treatment was superior in terms of control and toxicity and this can now be considered as a standard treatment. The dose, fractionation, and radiation technique is still a question of debate.

During the last 20 years many randomised trials have compared surgery alone or with preoperative radiation and immediate surgery. None of these trials has shown any difference in SSP. The Lyon R90-01 trial was specifically designed to investigate the time interval between the end of radiotherapy and surgery. This trial indicated that to take advantage of tumour shrinkage in response to the radiotherapy and to increase the chance of a SSP, a delay before surgery was mandatory. An interval of 6 weeks was recommended.

Three trials have compared radiotherapy alone with concurrent chemotherapy in patients with T3-4 resectable rectal adenocarcinomas accessible to digital rectal examination. These trials have failed to show that concurrent chemotherapy with radiotherapy increases sphincter preservation despite one trial showing a significant increase in tumour response in the chemoradiotherapy arm.

It is accepted that radiation dose escalation increases tumour response and control in most cancer. The Lyon R96-02 trial found, in comparison with the previous Lyon R90-01 trial, that dose escalation with contact X-ray (85 Gy in three fractions) was able to significantly increase clinical tumour response and sphincter saving procedure, with 10 out of the 45 patients being also able to preserve their rectum with radiotherapy alone or transanal full thickness tumour excision. In both arms of the trial sphincter function was considered as good or excellent by the majority of patients.

There is good evidence that preoperative external beam radiotherapy (EBRT), even with 5FU based chemotherapy, may improve sphincter preservation in rectal cancer. There is strong evidence that an interval of 5-7 weeks between the end of radiotherapy and surgery is necessary to observe a significant clinical and pathological tumour response. The decision whether or not to carry out SSP will ultimately remain with the surgeon, although he must also consider the patient characteristics such as age, sex, psychological profile. A (nearly) complete clinical tumour response may be the major endpoint to influence the surgeon decision in favour of SSP. At the moment radiation dose escalation followed by a delay of 5-7 weeks offers the best preoperative treatment. It remains to be seen if modern chemotherapy and targeted biotherapy (capecitabine, oxaliplatin, irinotecan, bevacizumab etc.) combined with EBRT will improve tumour response.

Professor Gerard's Regaud Lecture delivered at the ESTRO meeting in Amsterdam last year has important messages regarding the future management of rectal cancer. He reviewed the evidence available from the German, European, Swedish, Dutch, Polish and French trials. These were large randomised phase III trials and he concluded that the long awaited results from some of these trials were quite clear.

Firstly, the German CAO/ARO/AIO 94 trial has confirmed that preoperative treatment was superior in term of improved local control (LR 6% vs.13 %) and reduced toxicity (27% vs. 40%), compared to post operative treatment in locally advanced (T3 or T4 or N1) rectal carcinoma. However, there was no improvement in overall survival.

Secondly, preoperative (short course) radiotherapy with immediate surgery did not increase sphincter preservation as shown in the Swedish and Dutch trials. Sphincter preservation was 44% vs. 41 % and 67% vs. 65% respectively, in these trials.

Thirdly, the Lyon R90-01 trial has shown that preoperative radiotherapy with delayed surgery increases sphincter preservation (44% vs. 76%). This trial was specifically designed to answer the question of interval between the end of radiotherapy and surgery. It was possible that significant increase in tumour response resulting in tumour shrinkage in the long interval (6 weeks) arm has contributed to increase in sphincter preservation. An interval of 6 weeks delay before surgery was recommended. However, he pointed out that other phase III preoperative chemoradiotherapy trials namely; EORTC22921, Polish and French FCD92-03 trials have not shown any increase in sphincter preservation. Longer interval and significant down staging does not even appear to modify the surgeon's attitude in these trials, which may have influenced some of the outcomes.

Finally, radiation dose escalation using contact radiotherapy to increase tumour response was evaluated compared to external beam radiotherapy alone in the Lyon R96-02 trial. This trial has clearly demonstrated that dose escalation with contact radiotherapy increased sphincter preservation from 44% to 76% (P=0.004) without undue increased in toxicity.

In conclusion, he remarked that sphincter preservation in rectal cancer is a complex problem. The surgeon remains the Key person in decision making regarding sphincter preservation. The best way to increase the chance of sphincter preservation is to achieve a complete or near complete clinical tumour response. The best treatment option, in Prof Gerard's opinion to improve tumour response is to increase the radiation dose by contact radiotherapy following external beam radiotherapy. The long awaited results from EORTC and the German trials came to a similar conclusion that preoperative chemoradiotherapy compared to radiotherapy alone or post operative chemoradiotherapy, improved local control. The way forward in improving outcomes for rectal cancer is to use local superficial (50Kv) or HDR contact radiotherapy boost to increase radiation dose around the tumour after a course of preoperative external beam chemoradiotherapy (EBCRT) and surgery to follow 6 weeks later. This will surely increase the chance of clinical complete response leading to sphincter preservation and improve local control. It would be interesting to see whether this approach will also improve the survival which has not yet been shown in any of the published randomised trials.

Dr A Sun Myint

Provider volume and outcomes for oncological procedures

Killeen SD, O'Sullivan MJ, Coffey JC *et al* 2005
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(Department of Surgery, Cork University Hospital and University College Cork, Cork, Ireland)

A relationship between high provider volume (both hospital and surgeon) and better outcome for complex surgical procedures has long been postulated and a range of studies have been carried out which would appear to support this notion. There is currently an international trend towards regionalisation of cancer services, a strategy that would appear to be supported by volume-outcome studies. However, there is substantial variation between studies both in terms of methods and results. The aim of this study was to conduct a systematic review to determine whether high provider volume is associated with improved outcome for oncological procedures.

A review of the English language literature incorporating searches of the Medline, Embase and Cochrane collaboration databases was performed. The inclusion criteria were: patient cohort treated from 1984 onwards, community- or population-based sample, data referring solely to operations for malignant disease, and assessed health outcome as a dependent variable and volume as an independent variable. The studies were scored quantifiably to assess generalisability with respect to any observed volume-outcome relationship and analysed according to organ system. Numbers needed to treat were estimated where possible.

The volume-outcome literature was found to be heterogenous. A total of 68 studies were identified and 41 fulfilled inclusion criteria. There was no consensus definition of low- or high-provider volume. All studies showed either an inverse relationship of variable magnitude between provider volume and mortality, or no volume-outcome effect. The majority of clinical studies, except two that scored low for quality, revealed a statistically significant correlation between volume and outcome; no study demonstrated the opposite relationship.

The findings would appear to support volume-based referral initiatives. Given the low numbers needed to treat to achieve a reduction in mortality, pancreatectomy, oesophagectomy, gastrectomy and oncological rectal resections should be performed by high-volume providers. Since few studies simultaneously assessed the effect of surgeon volume and hospital volume it is difficult to estimate if the surgeon volume or the hospital volume has the stronger influence. This would appear to vary from procedure to procedure with surgeon volume more important in technically demanding operations such as pancreatectomy, oesophagectomy, gastrectomy and rectal cancer procedures.

The results would appear to support the centralisation of oncology services.

■ **High-volume providers have significantly better outcome for complex cancer surgery**

There has been a general trend on both sides of the Atlantic in the last ten years towards the centralisation of cancer surgery, particularly for those procedures traditionally associated with high morbidities or significant peri-operative mortality.

Opponents of these changes believe that the transfer of cancer surgery to regional institutions may threaten the viability of other surgical services at smaller hospitals and at the same time, create case loads at referral centres which exceed capacity. The results of this review are therefore highly informative. More than forty studies involving oesophagectomy, gastric cancer surgery, pancreatic resection, lung and colorectal cancer surgery, support the notion of significantly better outcome for complex cancer surgery by high volume providers. Only two studies were not able to demonstrate this relationship and none described the opposite.

While these studies should be used to allocate cancer surgery resources, the authors do offer appropriate words of caution relating to the paucity of studies involving risk assessment and a lack of standardisation in defining high versus low volume with respect to specific procedures.

Professor Derek Alderson

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