Total mesorectal excision is now the gold standard adjunctive surgical therapy for rectal carcinoma.

J. J. Mahany, Jr. *Oak Leaves in Fall Color*, 2002. Photograph. Letchworth State Park, New York.

The Role of Total Mesorectal Excision in the Management of Rectal Cancer

Paul F. Ridgway, MD, MMedSc, AFRCSI, and Ara W. Darzi, MD, FRCS, FRCSI, FACS

Background: *Total mesorectal excision (TME) was described 20 years ago and is now being established as the therapeutic gold standard for middle and lower third rectal cancers in a number of countries worldwide.*

Methods: *The authors reviewed published data regarding TME since its first description in 1982. Emphasis was placed on basic principles, achievable recurrence rates, evidence for use of adjunctive strategies, and the potential of TME.*

Results: *Local recurrence rates following TME approximate 6.6% from published series, accounting for more than 5,000 patients. The available evidence for TME is largely composed of retrospective series, although benefits of TME compare favorably to established conventional controls. Recent studies have clarified the benefit of adjunctive radiotherapy with TME. There is considerable scope for development of TME within the minimal access setting, providing first principles are observed.*

Conclusions: *Despite initial controversy, TME is now a feasible, reproducible, adjunctive surgical therapy in the management of rectal cancer.*

Introduction

Adjuvant therapy for rectal carcinoma has been the subject of much debate over the past two decades. The controversy has centered on defining the cohort of patients who would benefit from chemoradiotherapy regimens and whether this should precede definitive surgical intervention. Surgical intervention itself has been somewhat undervalued in these trials, evidenced by poor control of the procedural technique in many adjuvant trials.[1] This imbalance is beginning to be redressed in trials specifically designed to evaluate new methods of surgical therapy.[2]

Surgical therapy for rectal cancer has evolved since Ernest Miles first described the abdominoperineal resection in 1908.[3] By the 1920s, he had reduced the recurrence rate from almost 100% to approximately 30%,[4] thus ensuring his technique as the gold standard

From the Department of Surgical Oncology and Technology, Division of Surgery, Anaesthetics and Intensive Care, Imperial College Faculty of Medicine, St. Mary's Hospital, London, United Kingdom.

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Address reprint requests to Prof. Sir Ara Darzi, Department of Surgical Oncology and Technology, 10th Floor QEQM Wing, St. Mary's Hospital, London W2 1NY, United Kingdom. E-mail: a.darzi@ic.ac.uk

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at that time and also advocating extensive aggressive cancer therapy. In retrospect, it is perplexing that such extreme surgery was standard, given its considerable local failure rate and its potential to engender urinary, sexual, and gastrointestinal dysfunction. Several modifications were proposed to promote locoregional control and survival, with little success.[5,6] Better suture material, as well as devices enabling low anastomoses, heralded a shift toward sphincter-saving approaches with respect to cancer of the rectum. Anterior resection replaced abdominoperineal resection as the mainstay of therapy, although adequate consideration of circumferential margins and lymph node harvests were often neglected in early reports in the 1950s. Not surprisingly, there was concern that sphincter-saving surgery might increase local recurrence. It was in this setting that total mesorectal excision (TME) was first described in 1982 by Heald and colleagues[7] (Fig 1).

Review Methods

We reviewed published data regarding TME since its first description in 1982. Special focus was placed on its relevance with respect to local recurrence rates and current adjuvant therapy in rectal carcinoma. MEDLINE databases were searched for articles and data published between January 1982 and May 2002 with relevant evidence regarding TME in rectal carcinoma. To exclude learning curve bias, we selected only those series with more than 50 cases to establish a composite locoregional recurrence rate. Seminal publications prior to 1982 were included where appropriate. Also, we reviewed only articles in which the full text was in English. Emphasis was placed on the principles of TME, locoregional recurrence rates, evidence for usage, and future potential of TME.

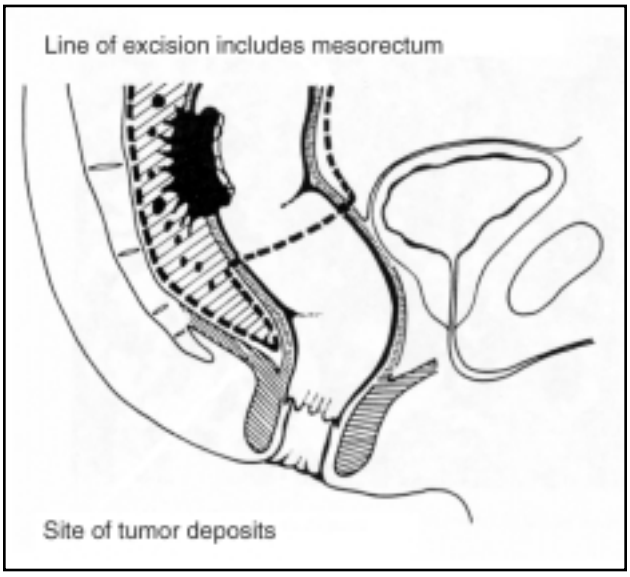

Fig 1. — Total mesorectal excision as depicted in Heald's original publication. This image refers to a patient with a distal mesorectal deposit. From Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery: the clue to pelvic recurrence? *Br J Surg.* 1982;69:613-616. Reprinted with permission of Blackwell Science Ltd.

History

The TME concept is based on the locoregional recurrence preference of rectal carcinoma. It follows intuitively that adequate en bloc clearance of the rectal mesentry, including its blood supply and lymphatic drainage, would minimize possible disease relapse. Early experience by Heald et al[7] documented a 0% 2-year local recurrence rate, without the benefit of adjuvant radiotherapy, in their initial series of 100 cases. Further independent analysis of this prospectively collected series demonstrated an actuarial 4% recurrence rate in patients who had curative resection at 5 years.[8] Hence, precisely controlled surgical technique can offer superior results even in patients who have received combination adjuvant therapy with inadequate surgery.

Despite the reproduction of comparable recurrence rates using TME,[9] its use remains controversial.[10,11] It is not surprising, therefore, that since the initial published method, several other names have been proposed for essentially the same technique: circumferential[12] and sharp[13] mesorectal excision, endofascial[14] and extrafascial[15] excision of the rectum, and total anatomical dissection.[16] The Tripartite Consensus Conference held in Washington, DC, in 1999 clarified semantics by defining the complete excision of visceral mesorectal tissue to the level of the levators as TME.[17,18]

Currently, TME is the gold standard for treatment of middle and lower third rectal cancers in many European countries (United Kingdom, Germany, France, Sweden, The Netherlands, Norway, and Denmark) and will probably be adopted as such in others (Ireland, Italy, and Austria). Also, advocates in the United States are currently supporting the use of TME as the gold standard for treatment of these cancers.[12]

Principles of TME

Although TME has been modified over time, the basic principle of excising tumor and the mesorectum en bloc remains its foundation. This principle is based on the original observations of Moynihan[19] in 1908 regarding potential pathways for lymphatic spread and also on the hypothesis of Heald[20] that the mesorectum represents embryological advantages conferring pro-

tection against tumor dissemination until the terminal stages. Lymphoscintigraphy further demonstrated this in an anatomical study of the lymphatics that drain the rectum.[21]

Heald[20] also identified operative factors that are likely to affect outcomes. These predominately center on a fastidious approach to the technique, involving specimen-oriented surgery and allowing for additional time as needed (Table 1). In today's surgical practice, some may balk at the 3 to 5 hours initially advocated to complete a TME, but the low recurrence rates, confirmed by independent surgeons, are hard to dismiss. Training in the correct techniques of this procedure is paramount. A prospective study in Norway investigated the impact of adopting TME into surgical practice and identified several issues relating to the learning curve.[24] The authors found that with sufficient instruction in TME procedures, comparable oncologic and technical efficacy could be reached in a relatively short time. However, the clinically significant anastomotic leak rate (16%) was more than twice that seen in the non-TME group. It is important to consider that augmented leak rates may indeed be independent of TME, and this difference may be accounted for by the lower level of anastomosis in the TME group as well as the author's assertion that these predominately occurred early in the learning curve. The Swedish experience[25] in 2000 demonstrated the feasibility and benefits of a live operating training program and a structured workshop in training multiple surgeons. Although this was a nonrandomized study, the TME group compared favorably to the published Stockholm I and II radiotherapy trials that served as controls.[26-29] In particular, crude 2-year local recurrence rates were 6% compared with 15% and 14% in the Stockholm I and II trials, respectively ($P<.001$). However, this does not approximate the initial series by Heald (albeit only one third the size of the Swedish TME project), and rates of 9% were seen if no adjuvant radiotherapy was used in the TME group.

Table 1. — Operative Factors Associated With Compromised Outcome

Factor	Action
Disruption of "tumor-mesorectal package"	Scrupulous, unhurried, sharp dissection techniques
Contamination of field by viable tumor	Seal transacted bowel Hypotonic or antiseptic washout
Dissection along embryological plane	Meticulous knowledge of anatomy Meticulous hemostasis Adequately informed assistant
Increased anastomotic leak rate	Low threshold for defunctioning stoma, particularly in men[22]
Urinary and sexual dysfunction	Identification and preservation of relevant autonomic nerves[23]

Fig 2. — Specimen-orientated surgery of abdominoperineal resection with TME (posterior view).

The principle holds that specimen-oriented surgery (Fig 2) must be accompanied by specimen-oriented histopathology, which is essential for appropriate staging and audit. It also emphasizes careful evaluation of circumferential margins since macroscopic evaluation by the operating surgeon is not reliable.[30] Heald recommends a Quirke-based detailed histopathological approach as an audit method for surgeons.[31,32] This not only provides objective data that may be extrapolated to define competence, but also may provide an immediate stimulus to surgeons regarding their technique. Although perhaps controversial, the advent of TME has highlighted the previously disregarded inter-surgeon and inter-institution variability noted in locoregional recurrence following curative rectal cancer surgery,[33] even when institutional selection bias is taken into account. Such inherent variability would not be tolerated in the realm of medical and radiological oncology.

TME With or Without Radiotherapy

The initial report by Heald[7] expounded the virtue of TME as an adjunctive therapy in its own right but shied away from suggesting TME as a replacement for chemoradiotherapies of the time. Adjunctive combination therapies came to the fore with the positive findings of Krook and colleagues,[34] published in 1991. A National Institutes of Health consensus statement followed shortly afterward, which cemented the acute change in postoperative management of rectal tumors. Now patients were routinely receiving chemoradiotherapy, and trials regarding preoperative timing of adjuvant radiotherapy were coming to fruition. Preoperative radiotherapy provides a number of potential benefits: the disease may be "down-staged" (particularly with long-course radiotherapy), small extramural deposits may be cleared, techniques to exclude the small intestine from the field of therapy are more effective, the field should be relatively better oxygenated, and there is no new anastomosis. Various large nonrandomized trials demonstrated decreased local recurrence and obstructive complication rates; however, no

survival benefit was conferred. The Stockholm II short-course experience was the first large randomized, controlled trial to suggest improved 5-year survival rates.[29,35] This effect was probably due to the four-field method and high dosages, which ensured efficacy but engendered increased perisurgical morbidity.

Intuitively, the oncologic locoregional benefits of adjunctive radiotherapy would marry well with augmented clearance by TME. The combination of techniques would be expected to convey low local failure rates. The well-designed Dutch randomized, controlled trial[36] addressed this issue. In particular, the design can be complimented for standardization of surgical technique, an issue rarely addressed previously in trials investigating adjunctive therapy efficacy. Although only 2-year results are available, local recurrence rates are low in both groups (8.2% for TME only, 2.4% for TME and preoperative short-course radiotherapy). The investigation confirmed the locoregional oncologic benefit, but a survival benefit was not demonstrated (approximately 82% for both groups at 2 years). However, follow-up is still at an early stage. Taking into account the multicenter design of this trial, even with the standardization, the 8.2% recurrence rate appears reasonable. It is noteworthy that this series did not reach the 2-year survival rates achieved by some of the individual reports (Table 2), but individual patient selection bias confounds any absolute conclusions on this point.

Neither the Dutch trial nor the Stockholm trial was specifically designed to evaluate groups that may have increased benefit from preoperative radiotherapy. In particular, the Dutch experience offered generic evidence regarding decreasing local recurrence rates, but the follow-up is too short to extrapolate survival advantages. Thus indications for radiotherapy, as well as adjuvant chemotherapy, must be reasonably taken from conventional experience until survival benefit can be demonstrated. Enker[44] proposed that preoperative adjuvant therapy be considered for patients with locally advanced disease, postoperative therapy for patients with N2 disease, and chemotherapy for those at risk for distant failure. These recommendations still appear sensible today, although individual case analysis in multidisciplinary settings obviously denotes the best way to define tailored treatment pathways.

Evidence Supporting the Use of TME

It is surprising that despite the widespread acceptance of TME as a gold standard method of surgical therapy of rectal cancer, no randomized, controlled trial has

Table 2. — Local Recurrence Rates Following TME From Selected Series With More Than 50 Patients*

Authors	No. of Patients	Study Design	Local Recurrence Rate (%)	Study Dates	Follow-Up
Heald[7] 1982	113	Retrospective	0	1978-82	2 yrs
McAnena[37] 1990	57†	Retrospective	3.5	1979-87	4.8 yrs (mean)
MacFarlane[8] 1993	135*	Retrospective	5	1978-91	7.7 yrs (median)
Enker[38] 1995	246	Retrospective	7.3	1980-92	5 yrs
Zaheer[39] 1998	514‡	Retrospective	5.7§	1982-89	5 yrs
Heald[40] 1998	519	Retrospective	6 8	1978-97 1978-97	5 yrs 10 yrs
Havenga[9] 1999	1,411†	Retrospective	7.6§	1978-94	5 yrs
Bolognese[41] 2000	71	Retrospective	12.6	1980-92	73.5 mos (median)
Martling[25] 2000	381	Prospective with historical controls	6	1994-97	24 mos
Bissett[15] 2000	124	Retrospective with controls	10	1980-96	5 yrs
Kapiteijn[36] 2001	1,748†	Randomized, controlled trial	8.2 and 2.4¶	1996-99	2 yrs
Tocchi[42] 2001	53	Retrospective	9	1990-95	68.9 mos (mean)
Wibe[43] 2002	686	Retrospective	7	1993-97	14-60 mos
Total	6,058		6.6	1978-99	2-10 yrs

* Patients were high risk (as defined in Krook et al[34]).
† Patients underwent "curative" surgery.
‡ Includes some partial mesorectal excision data.
§ Composite of individual data.
¶ With or without preoperative short-course radiotherapy.

Heald et al[7] and Zaheer et al[39] are the only studies without confounding adjuvant radiotherapy.

been performed to cement the benefit of TME over conventional, less radical approaches. Methodology and reporting in studies have been shown to be less than adequate in many studies involving local recurrence following resection for rectal carcinoma.[1] Reliance on retrospective series exposes the data for the usual criticisms of patient and disease selection. Also, much of the literature is composed of retrospective series (Table 2) compared with published conventional local recurrence rates ranging from 5% to more than 40%. McCall and colleagues[45] sought to clarify the variability by reviewing over 10,000 published cases from 51 large series where no adjuvant therapy was used. They found an overall 18.5% mean rate of local recurrence, although 10% of these cases included mesorectal excision; therefore, this may underestimate actual rates if TME was not employed. The rate of 18.5% reflects a composite figure for all stages, which is as high as 28.6% in Dukes C lesions, which are lesions that TME may offer a cure.

Hence, the proponents of TME suggest that randomized, controlled trials may be unnecessary or even unethical, given the consistently lower rates seen where TME is used. It is unlikely that such a trial will now be performed, given the relative reproducibility of the current data despite the criticisms regarding its lack of robust nature. Although this represents a basic flaw in the introduction of TME as a gold standard in many countries, the disadvantages of the technique have been documented over the past two decades and do not signify events that would necessitate interval abandonment of the procedure while further evaluation was performed, as seen in laparoscopic techniques for malignancy. We suggest that the lessons learned from the port-site metastasis story of structured training and validation of good technique be closely examined when a unit decides to adopt TME. In modern surgical practice, there is no room for the individual surgeon's operative preference replacing the pursuit of oncologic excellence.

Drawbacks Associated With TME

Whereas adherence to oncologic principles must remain paramount in surgical decision making, selection of TME is not without potential costs. These include increased risk of anastomotic dehiscence, higher rates of gastrointestinal, sexual, and urinary dysfunction, and longer operative time.

Anastomotic Dehiscence

TME mandates radical clearance of vascular and lymphatic structures at the proposed anastomotic site, which would normally support adequate healing. This, combined with suggestions that TME is associated with a lower incidence of abdominoperineal resection and thus lower anastomoses, may account for the higher anastomotic leak rates seen following TME-associated surgery. Anatomically, however, post-TME vascular inflow into the rectum is thought not to be impaired below approximately 4 cm from the anal verge, thus compounding the debate. Leak rates following TME range to more than 20%, although there is some evidence that a proportion of these can be learning curve related[24] and reduced by appropriate instruction down to levels appreciated with conventional therapies.[25] Law and colleagues[46] prospectively investigated the phenomenon in 196 patients, specifically identifying male sex and absence of a diversion stoma as independent risk factors for clinically significant leakage. They suggested that all men should have routine synchronous diversion procedures, although the differences seen may be accounted for by technically easier anastomoses performed in the wider female pelvis. Therefore, it is sensible to adopt a policy of diversion for both men and women in cases where the anastomosis is lower than 6 cm, below which most major leaks occur.[46] This is particularly relevant if the surgeon is early in the TME learning curve. The South East Asian trial, NMRC-ICR01, may provide further information regarding dehiscence rates when its randomized comparison of TME with colorectal or coloanal pouch anastomosis is completed.

Gastrointestinal Dysfunction

The ability to defer defecation is an important consideration for rectal cancer patients who retain their sphincters following therapy. Again, the level of anastomosis appears to be a significant indicator of continence outcome following TME,[46] where cases with lower anastomoses fare poorer. Factors that may suggest unsuitability for sphincter preservation in these ultra-low anterior resections with TME have been difficult to identify.[37] Similar confounding factors such as patient motivation permeate conventional literature with equal relevance. Overall, however, patients should be reassured by continence rates of over 80% where operative nerve-sparing principles are fastidiously followed.

Urinary and Sexual Dysfunction

Because radical clearance is proposed in TME, there was considerable concern in the early years regarding postoperative urinary and sexual function. In fact, there is little evidence to suggest that TME compromises genitourinary function once nerve-sparing techniques are employed.[23,44] Enker[44] reported results from a questionnaire demonstrating that sexual function

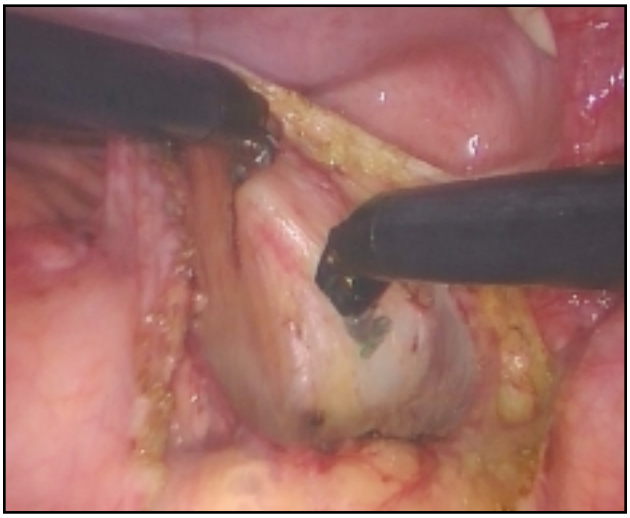

Fig 3. — Robot-assisted TME dissection.

could be maintained in more than 80% regardless of sex. However, age and abdominoperineal resection were factors suggesting patients were less likely to retain function. A small series by Pocard and colleagues[47] provided physiological data regarding urinary function following TME. Their 20-patient cohort, which included coloanal and ileoanal anastomoses, revealed no postoperative difference in urodynamic profiles or function postoperatively once nerve-sparing techniques were used.

The Future of TME

Partial mesorectal excision has been proposed as a possible evolution of the TME technique.[39] Although this may have some relevance to techniques involving local excision of early rectal tumors as well as those appearing high in the rectum, in general, such a policy contravenes basic TME principles regarding distal mesorectal spread[48] (Fig 1) and may engender higher recurrence rates. The Mayo experience[39] acknowledges this, suggesting that the mesorectal excision should be tailored to the tumor. However, reliably defining this subgroup that may benefit from a smaller anastomotic leak rate is beyond current imaging techniques and may find few supporters among TME proponents.

The application of TME in minimal access approaches has been delayed while the surgical community awaits results of the trials regarding oncologic safety of laparoscopic techniques for malignancy. However, early reports suggest that port-site metastases may not be a significant clinical problem once surgical technique has been properly validated. If these trial results are favorable, laparoscopic-assisted TME will be at the forefront of modification of minimal access therapies for lower and middle rectal carcinomas. Technical reports, including nerve-sparing methods, have already been published.[49,50] At our institution, we found that robotic-assisted approaches (Fig 3) facilitate TME via minimal access. Robot-assisted techniques provide improved 3-dimensional visualization of pelvic anatomy as well as unprecedented degrees of freedom, thus allowing the meticulous dissection required for successful outcome.

Conclusions

Despite initial controversy, TME has been established as a feasible, reproducible adjunctive surgical therapy. It is a timely reminder to surgeons in the development of maximal adjunctive chemoradiotherapy strategies that superlative oncologic surgical technique should not be underrated.

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