The Perfect Total Mesorectal Excision Obviates the Need for Anything Else in the Management of Most Rectal Cancers

Richard John Heald, CBE, MChir, FRCS¹ Ines Santiago, MD¹ Oriol Pares, MD¹ Carlos Carvalho, MD¹
Nuno Figueiredo, MD, PhD¹

¹ Digestive Unit, Champalimaud Cancer Center, Champalimaud Centre for the Unknown, Lisbon, Portugal

Clin Colon Rectal Surg 2017;30:324–332.

Address for correspondence Richard John Heald, CBE, MChir, FRCS, Digestive Unit, Champalimaud Cancer Center, Champalimaud Centre for the Unknown, Avenida Brasília, 1400 - 038 Lisbon, Portugal (e-mail: bill.heald@me.com).

Abstract

Keywords

- rectal cancer
- total mesorectal excision
- precision surgery
- total mesorectal irradiation

This article discusses the local control of primary rectal cancer and its locoregional spread in the light of modern advances. In recent years, the use of neoadjuvant chemoradiation has spread widely. However, its true benefit is not always balanced with its morbidities. Often total mesorectal excision (TME) is the best option. We will discuss the indications for immediate surgery for chemoradiation in advance and the importance of a delay in the management plan. To understand this selection, it is mandatory to know the true extent of tissue at risk for tumor dissemination and spread. Considering that TME may be enough for many patients and that most local recurrences are failures of surgical technique we introduce a new concept of total mesorectal irradiation. This exploits the new reality that precise, focused neoadjuvant therapy can offer a better response with fewer complications. Together these important changes in cancer board (multidisciplinary team) planning can also offer selected patients complete control of their cancer with no need for surgery.

Arguably the three most significant developments in the last 50 years in rectal cancer management have been:

1. The extraordinary and unexpected reduction of local recurrence by the total mesorectal excision (TME) surgical technique.^{1–4} This was even true, to some extent, when imperfectly performed during the “learning curve.” In the early years of demonstrating the surgery the senior author (R.J.H.) observed that “just trying to do the surgery in the correct plane seems to improve the outcomes.”
2. The identification of the mesorectal fascia (MRF) on magnetic resonance imaging (MRI) as the key preoperative potential “margin,” and its histopathological correlation with the surgical specimen. From this developed much that is good in modern management: rational multidisciplinary team (MDT) planning before surgery, selective criteria for neoadjuvant therapy, and definable objectives for the operation—open, laparoscopic, or robotic. Only when the MRF has been breached by direct extension of primary cancer or by extramural vascular

invasion, or when the metastatic spread is apparent, does “anything more than a perfect TME” appear indicated. Indeed in some units (such as Basingstoke—the home of TME), MRF invasion is taken as the only indication for neoadjuvant therapy. Many other units also irradiate “bad” intramesorectal disease: Extramural vascular invasion (EMVI), T3c (> 5 mm extrarectal spread), N2 disease (> 3 positive nodes) (Royal Marsden practice).

3. The observation by Habr-Gama et al that chemoradiotherapy (CRT) can permanently eliminate some cancers so that surgery becomes unnecessary.^{5–8} Ancillary to this observation is the crucial recognition that time is required for the CRT to take its full effect, so that the arbitrary performance of the surgery 6 weeks after the end of CRT as standard practice was missing a fundamental reality, that the pathology on the specimen provided simply a “snapshot” of a downstaging and downsizing process that was almost always incomplete. Neither how long this process takes, how is it affected by choice of short

or long course radiotherapy (RT), or whether the selection of chemo agents influences the outcome—none are fully understood. Furthermore, the best efforts of the molecular biologists and geneticists have failed to provide any predictive factors to help us identify which cancers will respond, let alone which may disappear altogether. At present, the better understanding of the meaning of time in the response process seems the major factor that many doctors have failed fully to comprehend: time to complete the CRT course, the time interval before imaging, the time before surgery, or time before cure—all are defining variables with no established standards. Any staging report on a case which has undergone neoadjuvant therapy, MRI, or pathology examination, is incomplete without the time that elapsed after the therapy (e.g., yMR T0 N0 at 10 weeks, or ypT1 N1 at 6 weeks—if these examples represented significant downstaging one might become and the second might have become a complete response [CR]).

Despite these uncertainties, and despite the lack of evidence for overall survival benefit, neoadjuvant and adjuvant therapies are widely administered across the United States and Europe to most rectal cancer patients whether their cancers appear contained within the mesorectal envelope or not. This article generates the interesting hypothesis that treatment outside the TME volume is unnecessary in most cases except where it is demonstrably threatened by extension of primary cancer or where there are metastases. Our theme is to give primacy to the mesorectal envelope as the primary field of spread of rectal cancer and to examine how this dominates our thinking in its management. As surgery becomes more exact and intensity-modulated RT more available, precise definition of the areas at risk for cancer residues becomes a major priority. Sparing them from surgical interference or unnecessary radiation has the potential to reduce a great deal of unnecessary comorbidity.

Why Is the Mesorectum Special?

This article urges to carefully consider what is different about the mesorectum (MR) as a vehicle for spread or containment of cancer. ▶**Fig. 1** shows a posterior coronal oblique cut through the MR, far back, from a series of slices taken parallel to the long axis of the anal canal. This particular cut passes posterior to primary cancer just in front of the sacrum demonstrating one obviously malignant lymph node. Normal ischiorectal fat below the levators and coccyx is included for comparison (▶**Fig. 1**).

The right-hand picture (white arrow from the L) shows healthy mesorectal tissue—a richly lymphovascular visceral mesentery with a high probability of containing viable cancer in the presence of such primary cancer—including, in this case, a large involved lymph node. The primary cancer is seen in front of it on the sagittal slice.

It is immediately apparent that mesorectal fat is strikingly different from the ischiorectal fat behind, which is lobulated but largely homogeneous and featureless. The MR above the levator is unlobulated but alive with streaking features, some of which undoubtedly correspond to arteries and veins, and others possibly represent dilated lymphatics with slow flow due to tumor clogging. Thus mesorectal fat, although unremarkable to the eyes or hands of an operating surgeon, is very different when its content is examined on MRI in a way that supports our hypothesis, that is, that the mesorectum is indeed the “primary field of the lymphovascular spread of rectal cancer.” In the presence of a rectal adenocarcinoma, it may contain cancer in blood vessels, lymphatic vessels, nodes, or in other situations such as perineural permeation or even randomly in the fat. It, therefore, appears highly dangerous tissue for a cancer surgeon to leave inside a patient and is very different indeed from “ordinary” fat. Indeed it is the nourishing and enveloping tissue of everything “rectal.”

Fig. 1 Two very different types of fat.

The Fundamentals: Embryology and Ontogenetics

Classic oncological surgery principles were based on the assumption of local centrifugal tumor spread irrespective of tissue boundaries and dictated wide but imprecise tumor clearance in the pre-TME era. The insufficiency of imaging techniques and the principles behind them became inadequate when dramatic improvement in patient outcome followed the implementation of TME after curative surgery for rectal cancer. This dramatic outcome shift, as well as, the higher incidence of local and overall recurrence rates with incomplete TME, may be easily explained by the ontogenetic compartment theory of local tumor spread,⁹ whose principles are deeply seeded in embryologic development. According to this theory, primordia are established during early embryology (specifically organogenesis period) as a result of the interaction between mesoderm-derived mesenchyma and ecto/meso/endoderm-derived epithelia. They are the first tissue complexes with morphogenetic determination and their position with respect to the embryo's polarity will determine their morphogenetic outcome. Even though different primordia are packed together during differentiation, cell mixing is suppressed at their boundaries by dynamic molecular signal gradients. In the adult body and from an ontogenetic anatomy perspective each developmental/ontogenetic compartment is a differentiated tissue entity derived from a single primordium. Ontogenetic anatomy is quite different from classic functional anatomy in the sense that a functional anatomic unit, such as an organ may derive from multiple primordia and therefore be included in multiple ontogenetic compartments. Conversely, multiple functional anatomic units may originate in a single ontogenetic compartment. According to the ontogenetic theory of local tumor spread, tumors initially remain contained within ontogenetic compartments. Compartment borders are tumor suppressive during early stages of local tumor spread. For transgression, phenotypic changes in tumor cells must occur, which then induce local permeation through inflammation or other phenomena. They are thought to occur relatively late in cancer progression. Resection along tumor-bearing ontogenetic compartment borders, frequently different from functional unit borders, such as organs, is believed to lead to better local tumor control and disease-free survival in early tumor stages. Ontogenetic compartment borders may be difficult to delimit in the adult body due to fusion, but one area of the body in which they are well demarcated is the pelvis. The MR is a subcompartment of the primitive hindgut (which in the adult encompasses the rectum and left colon and corresponding meso). It contains the rectum, is surrounded by mesorectal fat but rich in neurovascular structures, lymphatics, and lymph nodes.

Radiological Imaging of Primordial Compartments: The MRI Revolution

The MR is beautifully delimited radially by the MRF on modern T2-weighted images except above the level of the peritoneal reflexion, where it is delimited anteriorly and bilaterally by

peritoneum. Its caudal limit occurs where the MRF tapers distally to merge with the surface of the internal sphincter. The considerable confusion arises as a result of a variable tendency for the presacral fascia to anchor itself to the visceral MRF creating a layer called the presacral fascia around S2–S3. The surgeon dissecting from above tends to cut this because the potential space beyond it, which is outside both the layers is attractive for dissection. This space is however not without dangers as it exposes bare sacrum and coccyx where damage to veins becomes a significant risk and bleeding a potential threat. Lower down the mesorectal (visceral) fascia covering the MR tapers on to the internal sphincter muscle as it inserts into the puborectal sling. Cranially and posteriorly, the mesorectal compartment ends at the origin of the superior rectal artery and termination of the superior rectal vein into the inferior mesenteric vein. The preaortic plexus of sympathetic nerves is immediately behind these origins, splitting around them, and its careful preservation by a careful surgeon protects the patient's orgasm and continence. The compartment is pierced laterally by the middle rectal vessels and autonomic nerves passing toward the rectum through the MR—a crucial area of adherence to the parietes whose tethering effect gave it the old surgical name of “lateral ligament.” There is no ligament (→ Figs. 2–6).

Thus, embryologically and ontogenetically the outline of the MR is determined as a discrete fascial covered envelope, being developed from the visceral primordial “hindgut” or anlagen with its midline arterial supply, the inferior mesenteric artery, developed with its source from the midline front of the aorta, whereas urogenital organs are supplied by paired vessels more from its side or paired terminal branches.⁹ Similar layers can be identified around the whole gastrointestinal (GI) tract and the gynecological organs. Thus the “TME concept”

Fig. 2 Coronal oblique high-resolution T2-weighted image of a male patient. Middle rectal vessels/nerves are piercing the lateral mesorectal fascia. In most patients surgeons find a few nerves entering the mesorectum at this point and usually only a few small vessels which need only a small touch with the diathermy. Large middle rectal vessels like these are a rarity.

Fig. 3 Coronal oblique high-resolution T2-weighted image of a male patient. Middle rectal vessels piercing through the mesorectal fascia. In about one person in 5 to 10 a substantial vessel, even a pedicle, may be found at this point of adherence of the Mesorectum to the inferior hypogastric plexus.

has been applied to planning for upper GI and gynecological malignancies as well.^{10–12} Each visceral anlagen is separated from the surrounding parietes by two layers of fascia—one covering the visceral envelopes, for example, MRF—and one lining the parietes, for example, Gerota's, presacral, Waldeyer's, and pelvic sidewall fasciae. For the surgeon, the ultimate consequence in the cancer patient is the existence of identifiable avascular areolar planes—where traction countertraction and precise monopolar electrosurgical dissection can produce “cancer-safe” planes around an oncologically optimal surgical specimen. This so-called “holy plane”—that is, the innermost dissectable plane—around the MR liberates the visceral core and makes possible the precise, painstaking

Fig. 4 Sagittal high-resolution T2-weighted image of a male patient. Posterior limit of the mesorectal fascia and Waldeyer's septum behind it.

Fig. 5 Axial oblique high-resolution T2-weighted image of a male patient. Origin/drainage of the superior rectal artery/vein into the inferior mesenteric artery/vein.

surgery which can give us a near-perfect TME (→ **Figs. 2 and 3**). This is perhaps the most logical radical surgery in the whole of cancer surgery, as it is one of the distinct ontogenetic anlagen (or at least the distal half of the hindgut and its integral mesentery).

How Often Is the Cancer at Presentation Completely within the MRF?

Definition and incidence of MRF involvement—the key pre-operative question—is the MRF totally “safe or unsafe” on presentation?

Our article title uses the word “most”—which implies that cancer encompassed by the MRF is substantially more common than cancer which has “escaped” these confines locally—thus making treatment of tissues outside it necessary. Brown and

Fig. 6 Axial oblique high-resolution T2-weighted image of a male patient. Vessel and (more laterally) nerve containing presacral compartment.

coworkers have defined “unsafe” as cancer lacking a clearance of 1 mm between it and the MRF. She has shown convincingly that skillfully crafted small field fine slice T2-weighted images taken at right angles to cancer-bearing segment produce a reliable “cut off point” for clearance at 1 mm.¹³ She believes that requiring 2 mm or more leads to “overtreatment.” In the MERCURY study, (Magnetic Resonance Imaging and Rectal Cancer European Equivalence Study) 354/408 (87%) patients had “brown-safe” margins.¹⁴ Based on this evidence we can safely say that a typical Southern English population yields at least 85% of patients where all MRI-detectable cancer is contained within the mesorectal envelope with “brown-safe” margins.

The recent MERCURY-2 study has concentrated on cancers below 6 cm and reports MRF and the intersphincteric plane data separately. They found MRF involvement in 15/279 (5.4%) and intersphincteric plane involvement in a further 10/279 (3.9%) making the overall MRF involvement 9%.^{15,16} Nagtegaal and Quirke have reviewed the earlier literature extensively and concluded that single-center reports vary widely from 1 to 28%.¹⁷ This is not surprising since tertiary referral centers tend to receive more advanced cancers. Imaging quality varies, and initial and post-CRT data are not always clearly separated in the reporting. This highlights the problems which centers face receiving a flow of challenging cases from other units.

It would thus appear that in an average Western practice approximately 90% of all rectal cancers and their MRI-detectable satellites or extensions do appear to be contained within the mesorectal envelope. Most of these data, however, were initiated before screening was fully implemented, which may explain why more recent studies, such as ACO-SOG Z6051 trial from Australia, report final pathological margin involvement of 4.9% and ACOSOC from the United States of 10%. Overall positive circumferential resection margins (CRM) rate of 10% (7.7% open and 12.1% lap) could be observed, with distal margin involvement of 2.7%.^{18,19} In developed countries less than 10% MRF unsafe cases may be hoped for by surgeons in the future as a result of sequential improvements at various stages of management. Thus, we shall be aiming to achieve single figure percentages for new referrals and less than 5% for final histopathology reports of involved margins. For the title of this article “most” equals somewhere around 9 out of 10 cases, to which must be added those with metastases which we consider to be outside our terms of reference in this article—local control is our theme.

How Often Is the Perfect TME Achieved in Everyday Surgical Practice?

In further pursuit of our hypothesis, the next question that must be answered is how often the TME operation, as delivered in practice, can really be considered “perfect” anatomically. The technical surgery, especially deep in the pelvis, whether performed open, by laparoscope or robot, abdominally or transanally, is challenging and difficult. As Sir Edmund Hillary, the conqueror of Mt. Everest, once opined “If it is more difficult some people will do it less well than

others.” It has been clear for years that many large trials mandating TME were falling far short of the “perfect” TME of our hypothesis: the Dutch TME trial, for example, reported 23% margin involvement on the excised specimens where the trial rules specified “mobile cancers” and therefore had excluded many of the “worst,” that is, fixed tumors. Most “mobile” cancers should be removable by a careful “TME surgeon” with clear margins. It is therefore inherently probable that most of the involved margins in the Dutch TME trial were not cancers penetrating the MRF but surgical errors generating imperfect mesorectal envelopes.^{20,21}

More recently Laurberg and coworkers from MRI examination of post TME patients report mesorectal residues in one-third of all TME patients from Aarhus, Denmark.²² These figures also suggest that the truly perfect TME is much more rarely achieved than routine histopathological “audit inspection” data would imply. This is probably because only a clear shiny fascial covering over the most distal lobular expansions of the mesorectum from the very depths of the pelvis can really prove from examination of the specimen that it is truly complete—most kindly pathologists will settle for less—many surgeons probably “get away with” leaving behind residues because they have cut cleanly through mesorectal tissue and left no obvious defect for the pathologist to identify (→Figs. 7 and 8).

The location of most local recurrences bears out the belief that residues of the MR are the commonest source of local recurrence (LR). Syk, Blomqvist, and coworkers from Stockholm reported that 50/90 LRs referred to the Karolinska for MRI evaluation had apparent origin from radiologically

Fig. 7 Distal view of a truly complete total mesorectal excision.

Fig. 8 Near-perfect total mesorectal excision specimens.

detectable remnants of MR.²³ In another study from the same institution 37 patients with LR following curative resection for rectal cancer were identified from a population of 880 patients operated on by surgeons trained in the TME procedure. Two radiologists independently examined 33 available computed tomography (CT) and MRI images to evaluate the recurrences. Only two recurrent tumors appeared to originate from lateral pelvic lymph nodes.²⁴ These observations leave us in little doubt that LRs are seldom due to a failure of the surgeon to perform prophylactic lateral lymph node dissections. Indeed the senior author of this article has never performed such an operation—only ever dissecting outside the pelvic sidewall fascia and the autonomic nerve plexuses when the direct extension of primary cancer dictated it, or, extremely rarely, when a node is so obvious at surgery that it seems to invite removal. His published LR rates throughout a long rectal cancer career have always been below 5% for “curative” and 8% for all resections, including “inoperable” cases.²⁵ In a broadly similar way patients enrolled in the MERCURY study standard TME surgery alone was performed with no lateral node dissections. MERCURY reviewed but did not follow the very different Japanese practice based on a major study of pelvic sidewall lymph nodes dissected from 930 of 1,977 patients in 12 Japanese centers.²⁶ Only 14% yielded positive histology which was more common in low tumors (14.9 vs. 8.2%) and locally advanced tumors (16.6% T3+ vs. 7.1%). MERCURY patients with MRI suspicious pelvic sidewall nodes had worse survival which did appear to be improved with the use of preoperative therapy. These nodes were however associated with primary tumors which also had other adverse features—and the lateral nodes were NOT an independent prognostic indicator. Current practice in Europe following MERCURY is largely to irradiate the whole pelvis for cancers with nodes outside the MRF identified on MRI as positive. One Japanese study examined 51 patients with low rectal cancer who received 50 Gy neoadjuvant RT randomized to TME and nodal dissection, or TME alone. No difference was observed in recurrence rates, but the node dissection group experienced significantly worse postoperative sexual and urinary function.²⁷ The view from MERCURY is that pelvic sidewall nodes identified as metastatic are markers of “bad disease” with a worse prognosis—justifying irradiation but not surgical intervention.²⁸ Further evidence against the idea of prophylactic attention to glands outside the mesorectum comes from work done to establish the common sites of LR to assist planning for RT. These show most recurrences low down in the pelvis distal to and medial to the lateral internal iliac compartments.²⁹

Total Mesorectal Irradiation—Potential of TME Primacy in Refining RT and Reducing Unnecessary Damage to Organs at Risk

This restatement of TME as the first and often an only field of the spread of rectal cancer comes at a perfect time for a redefinition of RT fields—already overdue, as they are widely considered too large. In the now passing era of

three-dimensional (3D) conformal RT unnecessarily broad areas are being irradiated, largely independent of stage, nodal involvement, and tumor height. Furthermore, CT has been the basis of imaging for RT planning for 15 years but pelvic MR; now the accepted gold standard is still not included in most protocols.

There are three volumes of interest in RT planning which now take center stage: the innermost is the gross tumor volume (GTV) defined as the primary tumor plus detectable spread and involved lymph nodes. Around the GTV is the clinical target volume (CTV) which encompasses other tissues “believed to be at risk” for the microscopic spread. This currently takes no account of what has been learned from other disciplines and has been argued in this article. Outside both GTV and CTV is the planning target volume (PTV) which allows for uncertainties of daily set up, the variability of interfraction tumor position and intrafraction organ motion. PTV currently comprises an expansion of 1 to 1.5 cm around the CTV which substantially increases the irradiated volume, often doubling it or even more.

In the new world of modulated beams, volumetric modulated arc therapy, quality image-guided RT, and real-time tracking a paradigm shift is occurring in the accuracy of what radiation oncologists can deliver. A further modern potential is for dose escalation by targeting MRI-defined areas of high risk by a simultaneous integrated boost (SIB).

Our title's hypothesis implies that the tissues outside the MR seldom contain cancer except when the MRF is penetrated. “MRF unsafe” has already become the principal indication for neoadjuvant RT in the practice of many MDTs. We have recently published the suggestion for a debate that “total mesorectal irradiation (TMI) is the next logical step.”³⁰ The proposal is that the volume encompassed by the MRF becomes the CTV and that the GTV becomes the target for the SIB. Thus all MRI-detectable cancer receives the highest dose. The MR, which we have argued is almost always the only volume at risk for microscopic spread, becomes the target for the standard dose. The PTV becomes a geometric homogeneous expansion of the CTV by only 0.5 cm, a significant reduction from the standard 1.5 cm, which can be justified by the increased accuracy of delivery. Standard radiation volumes can thus be restricted to the same midline oncological envelope that is the objective of painstaking surgical excision by modern TME. The completeness of the radiation is almost certainly greater than the surgical completeness of the TMEs which are such a difficult surgical challenge.

Anal sparing is a further crucial advance. Surgical pathology data establishes that, in contrast to upper GI cancers, the intramural downward spread of more than a few mm is rare in rectal cancer and usually associated with a bad prognosis irrespective of treatment.³¹ We believe therefore that exclusion of the entire anal canal or even just its inferior part from the CTV is a reasonable strategy to prevent the functional impairment added by RT when low anastomoses are performed and to promote proper healing after certain abdomino-perineal excision (APE). We also believe that not every APE should be irradiated and that routine irradiation of all low cancers is not obligatory.

When MR shows the presence of radiological risk factors for LR such as tissues outside the mesorectum containing a tumor or EMVI or when the MRF has been breached, an “extended TMI” should be planned. This is implicit in the planning of the GTV which extends the heavily irradiated volume as directed by the imaging—thus expanding all three volumes. The practice of treating all patients by a standard plan is no longer acceptable once the new machines are available. It is of paramount importance to improve delivery by personalizing treatment volumes based on state-of-the-art imaging and extensive planning. The concept of a surgical TME can now be shadowed by an exactly imaged and irradiated RT volume which we have called a “TMI.” This carries the probability of more effective low-morbidity radiation with a real possibility of more CRs. Difficult to quantify is the impact of RT on the ability of cells spilled at surgery to implant into the exposed tissues of the pelvis or the anastomosis if the intraluminal washout is omitted. There can be no doubt however that such implantation does contribute to LR and that prior RT will make such an event less likely.

Good MRI Staging and a Perfect TME are Important for Adjuvant Chemotherapy Decisions

Independently from the classic TNM stage, EMVI, positive margins, and an incomplete TME are major adverse prognostic determinants not only for LR but also for metastatic disease and overall survival.^{32–34} With careful MRI staging, good quality TME, and selective preoperative RT the incidence of LR in rectal cancer has dropped to less than 5% in most centers. However, many patients still die with metastatic dissemination, suggesting the need of further adjuvant “systemic” treatment.³⁵ In colon cancer, adjuvant chemotherapy may reduce the risk of metastasis and death by 30% in “high-risk” tumors.³⁶ Unfortunately, in rectal cancer patients that have received preoperative chemoradiation, clinical trials have shown no advantage of adjuvant chemotherapy.^{37,38} This may depend on various reasons, including resistance to the adjuvant drugs induced by previous chemoradiation, bad surgery, or simply because patients may only receive adjuvant chemotherapy too late.^{39,40}

When the MRI does not show extramesorectal disease, a threatened MRF or intersphincteric space, nor EMVI, there is no significant benefit of preoperative RT. Therefore, with the current functional price to be paid, most patients may go straight to surgery. If the surgical pathology confirms negative margins with a complete mesorectum but reveals a mucinous, a pN (pathologic classification of regional lymph nodes)-positive or a pEMVI (pathologic classification of extramural venous invasion)-positive tumor, postoperative adjuvant chemotherapy may, like in colon cancer, help to prolong survival.^{32,41,42} When, by comparison, the distance of the tumor to the fascia is not considered and every patient with a clinical T3 regional node positive rectal cancer is submitted to preoperative chemoradiation many will endure unnecessary radiation, and the possible benefit of further

adjuvant chemotherapy may also be compromised. Thus, another advantage of good MRI mesorectal staging and “perfect TME” is a better selection of patients who avoid RT and may retain better conditions, or better timing, to receive adjuvant chemotherapy and potentially reduce the risk of metastatic spread.

Summary and Horizons

As we look toward the horizon in the second decade of the 21st century, we see a remarkable profusion of new technologies. More people are being cured but the intemperate polytherapy of 20 years is leaving far too many of them damaged and functionally impaired. In particular, the toxic combination of conventional 3D conformal RT and low colorectal or coloanal anastomosis often delivers poor anal function. Robots in surgery, image guidance, and intensity modulation in RT: together these can deliver more precise surgery for the earlier cancers and precise radiation of relevant tissues in the more advanced. Expensive new technologies thus have the potential to produce near-perfect outcomes without the common toxicities of today. The title hypothesis of this article—that the tissues containing cancer—overt or occult—are mostly within the MRF—suggests that either TME or TMI embracing specifically the MR, and where necessary the expansion of the GTV are the only therapies required locally for the primary. The “wild card in the pack” is the discovery that radiation combined with chemotherapy is capable of cure with virtually no comorbidity—possibly in around one-half of optimally irradiated cases, including some of the most advanced—by eliminating the surgery altogether. Many people within the professional “fold” would choose preoperative CRT for their rectal cancer principally specifically for the hope of a CR. The world has been slow to harness this extraordinary leap forward for the benefit of patients—in most units across the world a report of pathological complete response (pCR) does not lead to the “soul-searching” among the doctors that it should....” Could we have saved our patient that surgery altogether?” There are clues that point toward the greater use of short-course RT and perhaps in the future even single-dose RT. Accurately modulated shorter courses of RT are almost certainly superior to the 6-week schedules of 3D conformal RT that are currently so widely used. The key to all the new understandings of RT is the recognition of the importance of timing that a tumor regression grade 2 on an MRI or a pCR on a pathology report is but a “snapshot” of irradiated cancer at a particular moment in its course of regression.

Each of the preceding sections has been written by a specialist who has developed a particular interest in rectal cancer in his field—a trend which is crucial if the management of this eminently curable cancer is to progress to the high point in the battle against a malignant disease that we believe it can. The very title of this book looks to the future and challenges each of us to improve each step of diagnostic detail and planning and to balance the ever-changing options in the choice of treatment skillfully. The initial hypothesis of the article title focuses our attention on the mesorectal envelope which will in the future, with screening and earlier diagnosis, contain a large

majority of rectal cancers when they are first seen. Looking toward the horizon of improvements in operative surgery on the one hand and radiochemotherapy on the other we can imagine that much more nearly perfect mesorectal specimens will be achieved and LR rates are reduced to 1 to 2%. Threatening to engulf the future MDTs in doubt and controversy is the possibility that chemotherapy will press for ever earlier exhibition—perhaps even from the moment of a positive biopsy. After the initial planning phase, could the future possibly be a choice between immediate TME and chemo + TMI + surveillance—followed by TME only in those who fail to achieve a permanent CR? Whatever transpires the colorectal MDT of the next decade will witness much excitement and perhaps the abandonment of many of our most cherished “mores”—particularly the replacement of the intemperate rush to “get the cancer out” by careful fastidious planning.

References

- Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978–1997. *Arch Surg* 1998;133(08):894–899
- Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery—the clue to pelvic recurrence? *Br J Surg* 1982;69(10):613–616
- Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986;1(8496):1479–1482
- MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. *Lancet* 1993;341(8843):457–460
- Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. *Ann Surg* 2004;240(04):711–717, discussion 717–718
- Habr-Gama A, Perez RO, Proscurshim I, et al. Patterns of failure and survival for nonoperative treatment of stage c0 distal rectal cancer following neoadjuvant chemoradiation therapy. *J Gastrointest Surg* 2006;10(10):1319–1328, discussion 1328–1329
- Habr-Gama A, Sabbaga J, Gama-Rodrigues J, et al. Watch and wait approach following extended neoadjuvant chemoradiation for distal rectal cancer: are we getting closer to anal cancer management? *Dis Colon Rectum* 2013;56(10):1109–1117
- Habr-Gama A, Gama-Rodrigues J, São Julião GP, et al. Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. *Int J Radiat Oncol Biol Phys* 2014;88(04):822–828
- Heald RJ, Moran BJ. Embryology and anatomy of the rectum. *Semin Surg Oncol* 1998;15(02):66–71
- Santiago IA, Gomes AP, Heald RJ. An ontogenetic approach to gynecologic malignancies. *Insights Imaging* 2016;7(03):329–339
- Höckel M. Cancer permeates locally within ontogenetic compartments: clinical evidence and implications for cancer surgery. *Future Oncol* 2012;8(01):29–36
- Shinohara H, Haruta S, Ohkura Y, Udagawa H, Sakai Y. Tracing dissectable layers of mesenteries overcomes embryologic restrictions when performing infrapyloric lymphadenectomy in laparoscopic gastric cancer surgery. *J Am Coll Surg* 2015;220(06):e81–e87
- Taylor FG, Quirke P, Heald RJ, et al; MERCURY study group. One millimetre is the safe cut-off for magnetic resonance imaging prediction of surgical margin status in rectal cancer. *Br J Surg* 2011;98(06):872–879
- MERCURY Study Group. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. *BMJ* 2006;333(7572):779
- Daniels IR, Fisher SE, Brown G, Heald RJ, Moran BJ. Complexities and controversies in the management of low rectal cancer: proceedings of the 3rd Pelican Surgical Symposium 2005. *Colorectal Dis* 2006;8(Suppl 3):3–4
- Battersby NJ, How P, Moran B, et al; MERCURY II Study Group. Prospective validation of a low rectal cancer magnetic resonance imaging staging system and development of a local recurrence risk stratification model: The MERCURY II study. *Ann Surg* 2016;263(04):751–760
- Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? *J Clin Oncol* 2008;26(02):303–312
- Stevenson AR, Solomon MJ, Lumley JW, et al; ALaCaRT Investigators. Effect of laparoscopic-assisted resection vs open resection on pathological outcomes in rectal cancer: The ALaCaRT randomized clinical trial. *JAMA* 2015;314(13):1356–1363
- Fleshman J, Brandt M, Sargent DJ, et al. Effect of laparoscopic-assisted resection vs open resection of stage II or III rectal cancer on pathologic outcomes: The ACOSOG Z6051 randomized clinical trial. *JAMA* 2015;314(13):1346–1355
- Kapiteijn E, Putter H, van de Velde CJ; Cooperative investigators of the Dutch ColoRectal Cancer Group. Impact of the introduction and training of total mesorectal excision on recurrence and survival in rectal cancer in The Netherlands. *Br J Surg* 2002;89(09):1142–1149
- Kapiteijn E, Marijnen CA, Nagtegaal ID, et al; Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001;345(09):638–646
- Bondeven P, Hagemann-Madsen RH, Laurberg S, Pedersen BG. Extent and completeness of mesorectal excision evaluated by postoperative magnetic resonance imaging. *Br J Surg* 2013;100(10):1357–1367
- Syk E, Torkzad MR, Blomqvist L, Nilsson PJ, Glimelius B. Local recurrence in rectal cancer: anatomic localization and effect on radiation target. *Int J Radiat Oncol Biol Phys* 2008;72(03):658–664
- Syk E, Torkzad MR, Blomqvist L, Ljungqvist O, Glimelius B. Radiological findings do not support lateral residual tumour as a major cause of local recurrence of rectal cancer. *Br J Surg* 2006;93(01):113–119
- Moore E, Heald RJ, Cecil TD, Sharpe GD, Sexton R, Moran BJ. Almost all five year disease free survivors are cured following rectal cancer surgery, but longer term follow-up detects some late local and systemic recurrences. *Colorectal Dis* 2005;7(04):403–405
- Yano H, Moran BJ. The incidence of lateral pelvic side-wall nodal involvement in low rectal cancer may be similar in Japan and the West. *Br J Surg* 2008;95(01):33–49
- Nagawa H, Muto T, Sunouchi K, et al. Randomized, controlled trial of lateral node dissection vs. nerve-preserving resection in patients with rectal cancer after preoperative radiotherapy. *Dis Colon Rectum* 2001;44(09):1274–1280
- Shihab OC, Taylor F, Bees N, et al; MERCURY Study Group. Relevance of magnetic resonance imaging-detected pelvic side-wall lymph node involvement in rectal cancer. *Br J Surg* 2011;98(12):1798–1804
- Nijkamp J, Kusters M, Beets-Tan RG, et al. Three-dimensional analysis of recurrence patterns in rectal cancer: the cranial border in hypofractionated preoperative radiotherapy can be lowered. *Int J Radiat Oncol Biol Phys* 2011;80(01):103–110
- Pares O, Greco C, Santiago IA, Heald RJ. Total mesorectal irradiation (TMI). The “next step” in multidisciplinary management of rectal adenocarcinoma. A position paper from the Champalimaud Centre for the Unknown. *Dis Colon Rectum* 2016
- Karanjia ND, Schache DJ, North WR, Heald RJ. ‘Close shave’ in anterior resection. *Br J Surg* 1990;77(05):510–512

- 32 Chand M, Swift RJ, Chau I, Heald RJ, Tekkis PP, Brown G. Adjuvant therapy decisions based on magnetic resonance imaging of extramural venous invasion and other prognostic factors in colorectal cancer. *Ann R Coll Surg Engl* 2014;96(07):543–546
- 33 Quirke P, Steele R, Monson J, et al; MRC CR07/NCIC-CTG CO16 Trial Investigators; NCRI Colorectal Cancer Study Group. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. *Lancet* 2009;373(9666):821–828
- 34 Bernstein TE, Endreth BH, Romundstad P, Wibe A; Norwegian Colorectal Cancer Group. Circumferential resection margin as a prognostic factor in rectal cancer. *Br J Surg* 2009;96(11):1348–1357
- 35 Engelen SM, Maas M, Lahaye MJ, et al. Modern multidisciplinary treatment of rectal cancer based on staging with magnetic resonance imaging leads to excellent local control, but distant control remains a challenge. *Eur J Cancer* 2013;49(10):2311–2320
- 36 Gill S, Loprinzi CL, Sargent DJ, et al. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? *J Clin Oncol* 2004;22(10):1797–1806
- 37 Bosset JF, Calais G, Mineur L, et al; EORTC Radiation Oncology Group. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. *Lancet Oncol* 2014;15(02):184–190
- 38 Sainato A, Cernusco Luna Nunzia V, Valentini V, et al. No benefit of adjuvant fluorouracil leucovorin chemotherapy after neoadjuvant chemoradiotherapy in locally advanced cancer of the rectum (LARC): Long term results of a randomized trial (I-CNR-RT). *Radiother Oncol* 2014;113(02):223–229
- 39 Sakai K, Kazama S, Nagai Y, et al. Chemoradiation provides a physiological selective pressure that increases the expansion of aberrant TP53 tumor variants in residual rectal cancerous regions. *Oncotarget* 2014;5(20):9641–9649
- 40 Cheung WY, Neville BA, Earle CC. Etiology of delays in the initiation of adjuvant chemotherapy and their impact on outcomes for Stage II and III rectal cancer. *Dis Colon Rectum* 2009;52(06):1054–1063, discussion 1064
- 41 Sohn B, Lim JS, Kim H, et al. MRI-detected extramural vascular invasion is an independent prognostic factor for synchronous metastasis in patients with rectal cancer. *Eur Radiol* 2015;25(05):1347–1355
- 42 Petersen SH, Harling H, Kirkeby LT, Wille-Jørgensen P, Mocellin S. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. *Cochrane Database Syst Rev* 2012;(03):CD004078