Personalized management of elderly patients with rectal cancer

European Journal of Surgical Oncology 44 (2018) 1685–1702

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Review

Personalized management of elderly patients with rectal cancer: Expert recommendations of the European Society of Surgical Oncology, European Society of Coloproctology, International Society of Geriatric Oncology, and American College of Surgeons Commission on Cancer

Isacco Montroni [a, *], Giampaolo Ugolini [b, c], Nicole M. Saur [d], Antonino Spinelli [e], Siri Rostoft [f], Monica Millan [g], Albert Wolthuis [h], Ian R. Daniels [i], Roel Hompes [j], Marta Penna [k], Alois Fürst [l], Demetris Papamichael [m], Avni M. Desai [n], Stefano Cascinu [o], Jean-Pierre Gèrard [p], Arthur Sun Myint [q], Valery E.P.P. Lemmens [r, ac], Mariana Berho [s], Mark Lawler [t], Nicola De Liguori Carino [u], Fabio Potenti [v], Oriana Nanni [w], Mattia Altini [x], Geerard Beets [y], Harm Rutten [z], David Winchester [aa], Steven D. Wexner [v], Riccardo A. Audisio [ab]

[a] Colorectal Surgery, Department of Surgery, Ospedale per gli Infermi, Viale Stradone 9, 48018 Faenza, Italy
[b] Colorectal Surgery, Department of Surgery, Ospedale per gli Infermi Faenza, Viale Stradone 9, 48018 Faenza, Italy
[c] University of Bologna, Bologna, Italy
[d] Department of Surgery, Division of Colon and Rectal Surgery, University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA, USA
[e] Colon and Rectal Surgery, Humanitas Research Hospital, Humanitas University, Rozzano-Milano, Italy
[f] Department of Geriatric Medicine, Oslo University Hospital, University of Oslo, Oslo, Norway
[g] Coloproctology Unit, Department of General and Digestive Surgery, Joan XXIII University Hospital, Tarragona, Spain
[h] Department of Abdominal Surgery, University Hospitals Leuven, Leuven, Belgium
[i] Exeter Surgical Health Services Research Unit, Royal Devon & Exeter Hospital, Exeter, UK
[j] Department of Surgery, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands
[k] Department of Colorectal Surgery, Churchill Hospital, Oxford University Hospitals, Oxford, UK
[l] Klinik für Allgemein, Viszeral, Thoraxchirurgie, Adipositasmedizin, Caritas-Krankenhaus St. Josef, Regensburg, Germany
[m] Department of Medical Oncology, BOC Oncology Centre, Nicosia 2006, Cyprus
[n] Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA
[o] Department of Medical and Surgical Sciences for Children and Adults, Division of Oncology, University-Hospital of Modena and Reggio Emilia, Modena, Italy
[p] Centre Antoine Lacassagne, Department of Radiation Oncology, Nice Sophia-Antipolis University, France
[q] Clatterbridge Cancer Centre, Liverpool, UK
[r] Department of Public Health, Erasmus MC Medical Center Rotterdam, The Netherlands
[s] Cleveland Clinic Florida, Department of Pathology, Weston FL, USA
[t] Centre for Cancer Research and Cell Biology, Queen's University Belfast UK, European Cancer Concord, Leeds, UK and European Cancer Patient Coalition, UK
[u] HPB Unit, Manchester Royal Infirmary, Central Manchester University Hospitals Manchester, UK
[v] Cleveland Clinic Florida, Department of Colorectal Surgery, Weston FL, USA
[w] Unit of Biostatistics and Clinical Trials, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy
[x] Healthcare Administration, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy
[y] The Netherlands Cancer Institute, Amsterdam, The Netherlands and GROW School for Oncology and Developmental Biology, University of Maastricht, The Netherlands
[z] Department of Surgery, Catharina Hospital, Eindhoven, The Netherlands and GROW School of Oncology and Developmental Biology, University of Maastricht, The Netherlands
[aa] National Cancer Programs, National Accreditation Program for Rectal Cancer (NAPRC) American College of Surgeons Chicago, IL, USA
[ab] Department of Surgery, Institute of Clinical Sciences, Sahlgrenska University Hospital, Göteborg, Sweden
[ac] Department of Research, Comprehensive Cancer Organisation the Netherlands, Utrecht, The Netherlands

* Corresponding author. Colorectal Surgery, Department of Surgery, Ospedale per gli Infermi, Viale Stradone 9- 48018, Faenza, Italy.
E-mail addresses: isacmontroni@yahoo.com, isacco.montroni@auslromagna.it (I. Montroni).

https://doi.org/10.1016/j.ejso.2018.08.003

ARTICLE INFO

Article history:
Accepted 3 August 2018
Available online 15 August 2018

Keywords:
Rectal cancer
Elderly patients
Multidisciplinary
Frailty
Functional recovery
Recommendations

ABSTRACT

With an expanding elderly population and median rectal cancer detection age of 70 years, the prevalence of rectal cancer in elderly patients is increasing. Management is based on evidence from younger patients, resulting in substandard treatments and poor outcomes. Modern management of rectal cancer in the elderly demands patient-centered treatment, assessing frailty rather than chronological age. The heterogeneity of this group, combined with the limited available data, impedes drafting evidence-based guidelines. Therefore, a multidisciplinary task force convened experts from the European Society of Surgical Oncology, European Society of Coloproctology, International Society of Geriatric Oncology and the American College Surgeons Commission on Cancer, with the goal of identifying the best practice to promote personalized rectal cancer care in older patients.

A crucial element for personalized care was recognized as the routine screening for frailty and geriatrician involvement and personalized care for frail patients. Careful patient selection and improved surgical and perioperative techniques are responsible for a substantial improvement in rectal cancer outcomes. Therefore, properly selected patients should be considered for surgical resection. Local excision can be utilized when balancing oncologic outcomes, frailty and life expectancy. Watch and wait protocols, in expert hands, are valuable for selected patients and adjuncts can be added to improve complete response rates. Functional recovery and patient-reported outcomes are as important as oncologic-specific outcomes in this age group. The above recommendations and others were made based on the best-available evidence to guide the personalized treatment of elderly patients with rectal cancer.

Introduction

Rectal cancer requires complex treatment and a multidisciplinary team (MDT) approach involving professionals from all relevant specialties. Elderly patients with cancer have been shown to receive inappropriate care, being either under-treated due to their chronological age, or over-treated for their degree of frailty [1]. In addition, because elderly patients are typically excluded from clinical trials, treatment guidelines may not be accurate in this age group. De Angelis et al., on behalf of EUROCARE-5, showed a global increase in survival for rectal cancer from 2005 to 2007 compared to 1999–2001 (57·6% vs 52·1%), however this survival improvement was not present in elderly patients [2]. The National Cancer Intelligence Network demonstrated that elderly patients with solid tumors in the UK receive less surgery than their younger counterparts. This is particularly relevant for colorectal cancer (CRC) patients, where the cancer resection rate falls from 68% in the group of 64–74 years of age to 40% in patients 80 years and older. Unfortunately, this was associated with a decreased use of multimodal treatments and radical resection whereas the local excision rate was found to be higher than for younger patients, resulting in poorer outcomes [3]. The recently published Critical Research Gaps in CRC Initiative has also highlighted the need for increased understanding of Health-Related Quality of Life (HR-QoL) issues for patients with colon and rectal cancer, so as to ensure the best possible outcomes for those living with and beyond their disease. It also emphasized the importance of improved two-way communication between healthcare professionals and patients, and for the patient to be actively involved in decision making in relation to his/her own care [4].

Epidemiology

Rectal cancer is diagnosed at a median age of 70 years. The risk of developing rectal cancer, however, increases until late in life, the risk being highest among individuals of about 85 years old [5,6]. This means that in an ageing population, the average age at which a patient is diagnosed with rectal cancer will continue to increase in the near future, unless counterbalanced by (population) screening for rectal cancer. This will affect the complexity of decision making due to associated comorbid illnesses: half of patients with rectal cancer aged 70–84 years also suffer from cardiovascular disease, while 20% have already experienced a previous diagnosis and treatment of cancer [6].

The Netherlands Cancer Registry is a robust and all-inclusive registry that captures treatment data and outcomes from 1989 to 2017. Because of the large number of patients and the comprehensiveness of clinical information, this database has been utilized to evaluate trends in treatment of elderly rectal cancer patients for this task force. Older patients are less likely to undergo surgical treatment [3]; this is partly due to high comorbidity rates, but also the presence of alternative treatment options [7,8]. Neoadjuvant chemoradiation (nCRT) is also delivered at a lower rate, even to patients who are fit for surgery: the proportion decreasing from 40% in all patients with locally advanced, but not metastatic disease (M0) to 8% in the age group 80–84 years (2013–2014) [6]. In that period in the Netherlands, short course radiotherapy (5×5 Gy) was considered a viable alternative for older patients, while less than 30% of younger patients were treated preoperatively with 5×5 Gy, compared to 40% of patients 80–84 years old [6]. In the metastatic setting, also large age-related differences in daily practice could also be observed: while 75% of patients younger than 70 years old received systemic treatment, of which more than half was treated also by targeted agents; this dropped to 45% of patients treated systemically among patients aged 75–79 years, of which less than one quarter received targeted agents in combination [6].

Postoperative outcomes of rectal cancer surgery have improved impressively, including for the elderly. Between 2005 and 2015, postoperative mortality in the Netherlands has decreased from 7% to less than 3% among patients aged $\geq$70 years. Ninety-day mortality declined from 10% to 3% in the same period. Despite clear advances in the peri-operative setting (more adequate patient selection, better preoperative work-up, increased quality of the surgical intervention), long-term disease-free survival of elderly patients still lags behind compared to younger patients [6]. In terms of 5-year absolute survival, the difference is as large as 30% between M0 patients who underwent surgery. Older patients who received neoadjuvant treatment exhibited a better survival than their counterparts who only underwent resection, although selection bias plays a role due to the observational nature of these data. An even stronger selection bias is present when comparing outcomes

Abbreviations

ACS CoC	American College of Surgeons Commission on Cancer
ADL	Activities of Daily Living
APR	Abdominoperineal Resection
ASA	American Society of Anesthesiologists
BoR	Bill of Rights
cCR	Complete Clinical Response
CIMP	CpG island methylator phenotype
CPET	Cardiopulmonary Exercise Testing
CRC	Colorectal Cancer
CRLM	Colorectal Cancer Liver Metastasis
CRT	Chemoradiation
CXB	Contract x-ray brachytherapy
DLI	Diverting Loop Ileostomy
DFS	Disease-Free Survival
EBRT	External-Beam Radiation Therapy
ER	Enhanced Recovery
ERAS	Enhanced Recovery After Surgery
ESCP	European Society of Coloproctology
ESMO	European Society for Medical Oncology
ESSO	European Society of Surgical Oncology
EURECCA	EUropean REgistry of Cancer CAre
FI	Fecal Incontinence
FR	Functional Recovery
HR-QoL	Health-Related Quality of Life
ICHOM	International Consortium for Health Outcomes Measurement
IPSS	International Prostate Symptom Score
IWWD	International Watch and Wait Database
LARS	Low Anterior Resection Syndrome
LC	Long course (radiation)
LE	Local Excision
MDT	Multidisciplinary Team
NACRE	Neoadjuvant Treatment for Advanced Rectal Carcinoma (trial)
NCCN	National Comprehensive Cancer Network
nCRT	Neoadjuvant chemoradiation
NICE	National Institute for Health and Care Excellence
OPERA	Organ Preservation of Early Rectal Adenocarcinoma (trial)
OS	Overall Survival
PROMs	Patient Reported Outcome Measures
PFS	Progression-Free Survival
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
SEER	Surveillance, Epidemiology and End Results
SIOG	International Society of Geriatric Oncology
TAE	Transanal Excision
TAMIS	Transanal Minimally Invasive Surgery
taTME	Transanal Total Mesorectal Excision
TEM	Transanal Endoscopic Microsurgery
TEO	Transanal Endoscopic Operation
TME	Total Mesorectal Excision
TUG	Timed Up and Go
W&W	Watch and Wait
5-FU	5-fluorouracil

of older patients undergoing surgery and those receiving radiotherapy only, since the most frail patients tend not to receive surgery, therefore having a poorer survival. Recent data suggest that also for older patients, long-term survival has started to improve: an improvement in relative 5-year survival could be noted from 55% in 2000–2004 to 64% in 2010–2014. This was a relatively larger improvement in survival when compared to younger patients (60–69 years old: from 62% to 70%) [6] (Fig. 1).

Methodology

We present a set of expert recommendations for the management of elderly (age >70 years [9]) patients with rectal cancer as developed by a dedicated expert task force, which evaluated the existing literature both before and after the meeting and critically appraised patient evaluation and treatment options. Recommendations were discussed and agreed upon by an interdisciplinary task force comprised of 29 members representing the following organizations: European Society of Surgical Oncology (ESSO), European Society of Coloproctology (ESCP), International Society of Geriatric Oncology (SIOG), and the American College Surgeons Commission on Cancer (ACS CoC). All participants obtained a mandate to represent their respective societies. The task force convened on December 2, 2017 and consisted of specialized surgeons, medical and radiation oncologists, geriatricians, pathologists, epidemiologists, hospital administrators, and a patient care representative from the member organizations. The paucity of robust data on rectal cancer management in the elderly and the heterogeneity of the patient population prevent the following recommendations from being based on Level 1 evidence. The recommendations are, instead, based on agreement by an expert task force, who reviewed all available evidence, and also on expert opinion. Therefore, no formal levels of evidence are assigned. A summary of the recommendations is presented in Table 1.

Frailty assessment and multidisciplinary evaluation

Frailty is defined as 'a state of decreased physiologic reserve caused by the accumulation of aging processes across multiple organ systems, which affects the patient's resistance to stressors' [10]. Aging increases patient heterogeneity. Therefore, no one tool can accurately identify the multiple differences between patients [11]. Accordingly, geriatric assessment is required to evaluate for frailty [12]. It has been said that a comprehensive geriatric assessment may be too time-consuming to be routinely used in a busy practice. However, there are tools that can be easily integrated into clinical practice that can screen for frailty and identify those patients in need of more in-depth frailty evaluation as well as modifications in their treatment algorithm [13].

Focus should be on identifying the main predictors of frailty and post-operative complications such as functional status (including baseline mobility, number of falls), nutritional status and comorbidities. These are also targets for intervention in prehabilitation, which will be discussed further in a later section (Patient Optimization: Prehabilitation). The importance and ease of a simple frailty-screening question was demonstrated by Jones et al. They asked patients the simple question, '*Have you fallen in the past* 6 months?' before elective surgery and found that 33% of the cohort had fallen. This subgroup had more frequent post-operative complications (59% vs 25%; $p = \cdot 004$), more frequent need for discharge to an institutional care facility (52% vs 6%; $p < \cdot 001$), and a higher 30-day readmission rate. These findings were independent of age [14].

An algorithm for office-based frailty screening was discussed by the task force and is provided in Fig. 2. The screening tests can be

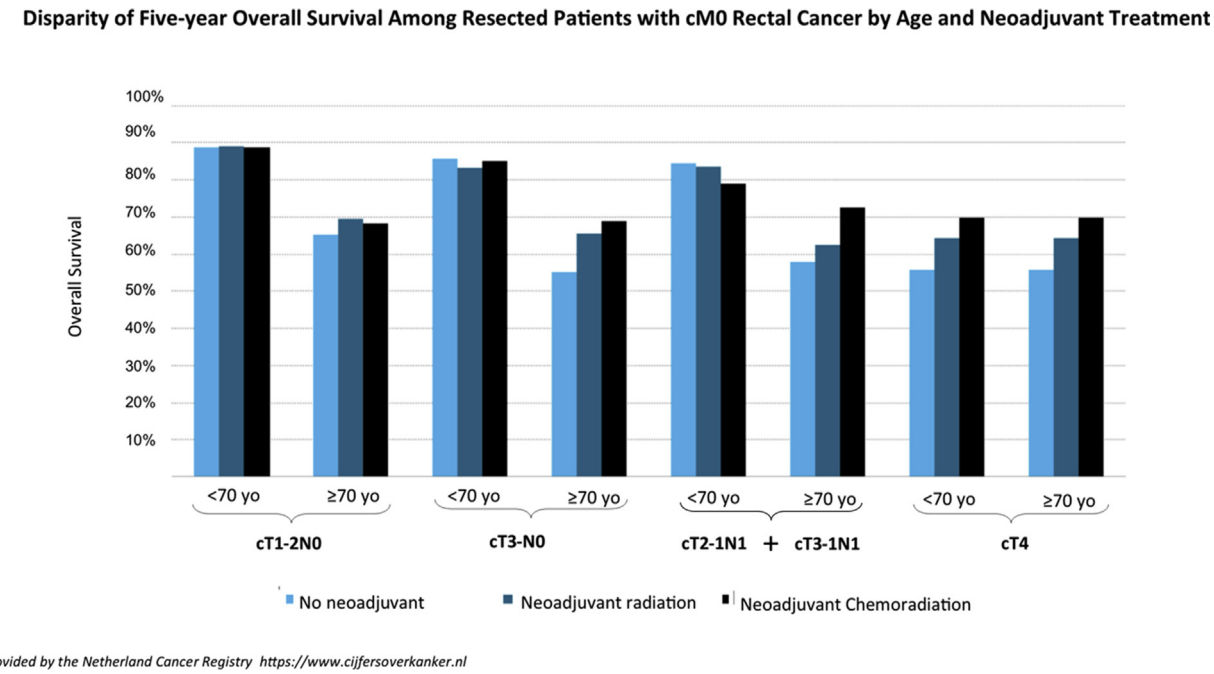

Fig. 1. Disparity of Five-Year Overall Survival Among Resected Patients with cM0 Rectal Cancer by Age and Neoadjuvant Treatment. The graph demonstrates the overall survival in patients who underwent surgery for cM0 rectal cancer depending on their perioperative treatment strategies. Except in the cT4 cohort, patients older than 70 years had a lower overall survival than patients younger than 70 years. Elderly patients are receiving less neoadjuvant treatments but, specifically for N1 lesions, if they do receive preoperative chemoradiation, their 5-year overall survival is similar to their younger counterparts. In general, patients who underwent neoadjuvant chemoradiation had a higher 5-year overall survival than similar patients who did not. Older patients who received neoadjuvant treatment exhibited a better survival than their counterparts who only underwent resection.

performed by a nurse or a physician. The components besides history of falls are G8 score, Mini-Cog score, and Timed up and Go (TUG). The G8 score is determined through a series of 8 questions evaluating age, perception of health, nutritional metrics, mobility, and medication usage and was able to delineate which elderly cancer patients had an abnormal comprehensive geriatric assessment in a cohort study [15]. The Mini-Cog score evaluates for cognitive dysfunction and can be used to predict increased post-operative complications, length of stay, and mortality [16]. TUG, where a patient is timed walking 3 m from a seated position, has been shown to be an independent risk factor for major post-operative complications [17].

If a patient has any predictors for frailty (G8 score <15, Mini-Cog score <4, TUG >20 s, or a fall in the past 6 months), a formal geriatric assessment is indicated [18]. If the patient is identified as frail on this in-depth assessment by a geriatrician, adapted care based on frailty is indicated and the entire therapeutic plan should be adjusted. In addition, if a patient is deemed to be frail by any abnormality on the office-based 4-item screening tool, a geriatrician should be involved in the decision making. It should also be stated that these complex patients should preferably be treated at a high-volume center for rectal cancer treatment. Presenting a patient's frailty assessment at the MDT should be considered with the same importance as presenting the pathology or the pre-operative staging. Because elderly patients' perspectives could be different from what clinicians are accustomed to in the younger population, the clinician presenting the patient at MDT should ensure that the patient's goals of care are presented to guide discussion and, ultimately, treatment recommendations.

Patient-centered care

In an attempt to make cancer care equitable for all patients regardless of age, gender, socio-economic or educational status, the European Cancer Patient's Bill of Rights (BoR) was developed by the European Cancer Concord. The goals were to identify inequalities in cancer care and to serve as an empowerment tool for patients. The BoR articulated patient's rights through 3 Articles: the right to receive accurate information and be proactively involved in his/her care, the right to equal and timely access to care supplemented by research and innovation, and the right to receive care in a system that emphasizes outcomes, patient rehabilitation, quality of life (QoL) and affordable health care [19,20]. The BoR also stresses patient-centered outcomes. Especially in elderly patients, it is essential to differentiate the goals of care. It is equally important to capture and report Patient-Reported Outcome Measures (PROMs) as oncologic outcomes. Studies reporting HR-QoL are often of poor quality with inadequate methodology [4]. Prospective studies are needed to provide enhanced data to improve prediction of post-operative complications. The aim is to provide patient-centered, tailored care to deliver improved outcomes, including functional results, while ensuring optimal HR-QoL.

Patient optimization

Risk predictors

Cardiopulmonary exercise testing (CPET) has been shown to be a useful preoperative risk-stratification tool that can predict post-operative outcomes in colonic, hepatic, and major abdominal surgery [21–23]. The Six-Minute Walk Test is another measure of physical capacity that can be measured pre-operatively and correlates with postoperative outcomes in colorectal, abdominal, and thoracic surgery [24–26]. It is a useful screening tool that requires no specialist equipment or training and can be employed to define patients requiring more in-depth assessment.

Table 1
Summary of expert recommendations for the management of elderly patients with rectal cancer.

General Recommendations	-All management decisions for an elderly patient with rectal cancer should consider: Physiological Age Life Expectancy Risks versus benefits of treatment vs nontreatment Treatment tolerance Patient goals/wishes Possible treatment barriers
Multidisciplinary Team	-Frailty and not chronological age should be used in risk stratification. -Mandatory Frailty screening: G8, mini-Cog, Timed Up and Go, history of falls. -If frail, geriatrician should be routinely involved in Multidisciplinary Team. -If patient is fit, should treat with algorithms developed for younger patients.
Patient optimization	- Multidimensional prehabilitation should be utilized pre-treatment and especially considered in the window for neoadjuvant chemoradiation (nCRT). -Required elements include: exercise, nutrition, treatment of anxiety/depression.
Surgical Treatment	**Rectal resection with Total Mesorectal Excision (TME):** -Open/Laparoscopic/Robotic/transanal TME (ta TME) techniques for TME surgery are not contraindicated based on chronological age alone and should be considered in elderly patients. **Laparoscopy**: -Laparoscopy is safe and effective in the elderly population and should be utilized as the preferred option by experienced surgeons. -Robotic approaches can be considered based on surgeon preference, but have not been shown to be superior to laparoscopy and are associated with higher costs. **taTME**: - taTME is advised when utilized by expert surgeons as it has shown to be associated with decreased conversion rates. It should be noted that long-term data are lacking. **Local Excision (LE)**: -Clinicians should balance oncologic outcomes with goals of care/frailty. -LE is not recommended after radiation therapy secondary to increased morbidity. **Surgical Emergencies:** -Efforts should be made to preempt surgical emergencies (bleeding, obstruction, perforation) and treat them early when they occur.
Treatment of Locally Advanced Disease	**Neoadjuvant chemoradiotherapy:** - Can be considered to increase local control, but should be noted that increased toxicity can prevent potentially curative surgery. -Capecitabine is contraindicated in renal failure. -Contact X-ray brachytherapy can be used as an adjunct for small residual tumors (<3 cm) following external beam radiation therapy (EBRT) or as monotherapy for early rectal cancer (cT1) less than 3 cm, in order to increase rate of complete clinical response, but is only available at selected centers. -EBRT ± contact radiation can be considered for patients not suitable for surgery in order to improve local control. **Watch and Wait:** -Should be considered in elderly patients with complete clinical response, but need experienced MD expertise by surgeon/radiologist/medical oncologist and radiation oncologist to be performed safely. -No single reliable predictive factor of complete response is available, but can evaluate size and rate of tumor shrinkage as useful prognosticators. -Required to take into account patient's goals/wishes. **Adjuvant chemotherapy:** - The benfit of adjuvant chemotherapy after nCRT and surgery is uncertain.
Treatment of Synchronous Liver Metastases	**Liver Metastasis**: -Liver surgery should only be performed with curative intent. -Neoadjuvant chemotherapy and radiation therapy (if indicated) is suggested, if primary asymptomatic. -Synchronous resections should be avoided.
Outcomes	**Enhanced recovery pathways:** -Should be applied to elderly patients based on reduced length of stay and overall complications. -Most important elements to include are early discontinuation of intravenous fluids, early oral intake, timely removal of the urinary catheter (when possible given pelvic dissection), early mobilization, very limited administration of opioids and adoption of minimally invasive surgery. -Involvement of both patients and caregivers is crucial to increase compliance. **Functional Recovery:** -Should be recorded as pivotal post-treatment endpoint, especially in the elderly. -Consideration should be given to the morbidity of 'permanent' diverting loop ileostomy and prediction used to preferentially perform colostomies in patients who are not likely to undergo reversal. **Patient-Reported Outcome Measures (PROMs)**: -PROMs should no longer been considered secondary outcomes and instead be recorded by the clinical team post-treatment. -Prospective observational studies are needed to define outcomes. **Health Care Cost**: -Recommend shift towards value-based care as target for finance allocation. -Focus should be on early diagnosis and frailty assessment as tools to help contain costs.

Prehabilitation

Despite modern and sophisticated efforts and pathways to decrease postoperative morbidity and mortality, up to 40% of elderly patients who have undergone elective colorectal surgery had not returned to their baseline walking capacity at 3 months postoperatively [27]. The 187 articles published and cited on PubMed concerning pre-operative prehabilitation in the past 5 years have failed to fully clarify how to measure the effectiveness of prehabilitation, the most appropriate prehabilitation plan, and the optimal timing (length and interval) of prehabilitation. A recent clinical trial aimed to address these and other questions as to how a 6-week pre-operative exercise regimen effects pain, fatigue, insomnia, and perception of health status in elderly patients with rectal cancer. The study indicated improvement of perception of pain, physical health, and fatigue in the exercise group, but this did

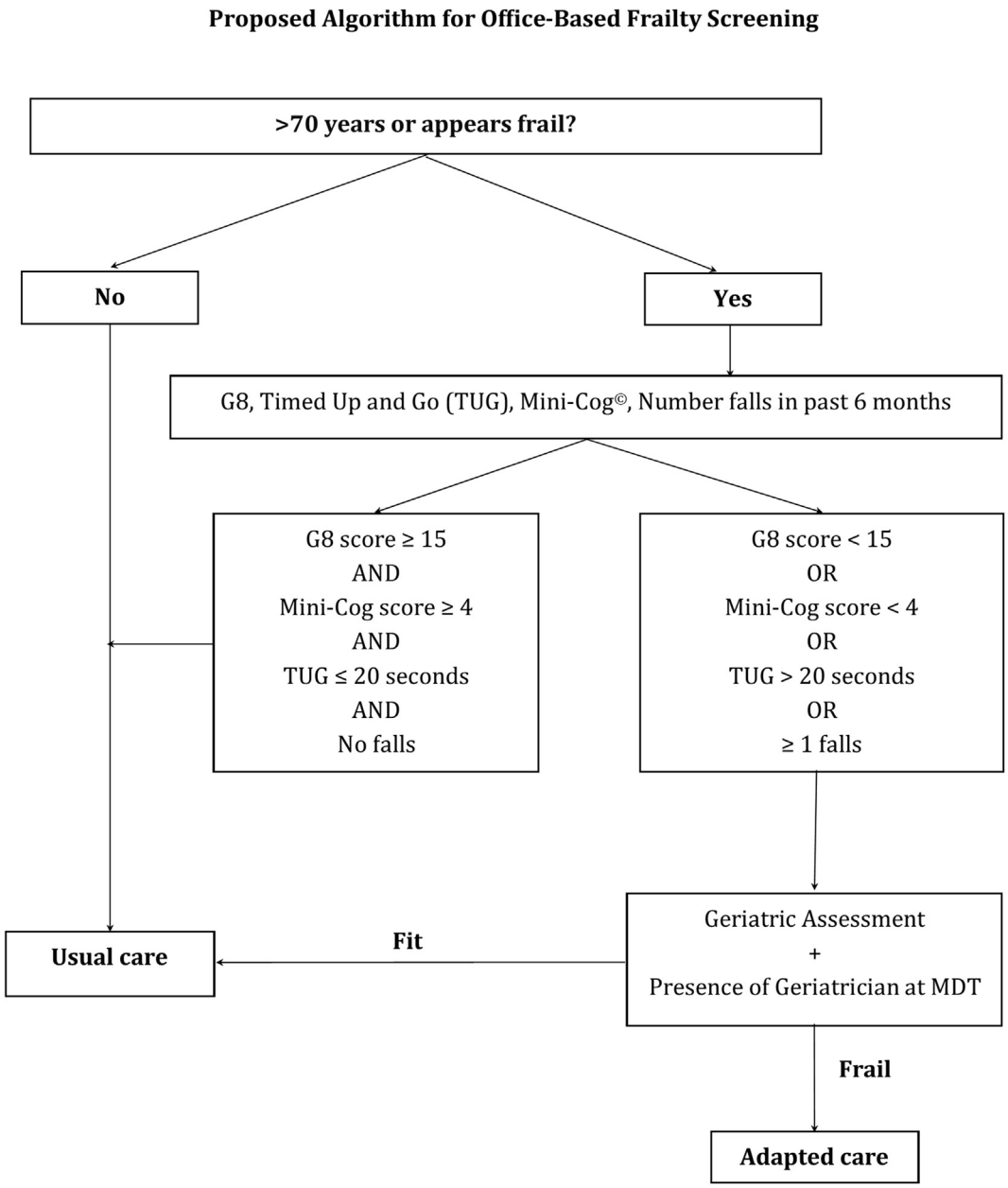

Fig. 2. Proposed Algorithm for Office-Based Frailty Screening. The algorithm suggests screening for frailty in the office setting and with referral for comprehensive geriatric assessment for any abnormality in the initial screening tests. If frail, a geriatrician should be routinely involved in Multidisciplinary Team. If the patient is fit, they should be treated with algorithms developed for younger patients.

not reach statistical significance [28]. This pilot study reiterates the need for a larger study to better evaluate these endpoints. A prospective study is currently recruiting in the UK (the PREPARE-ABC study), but it will be a number of years before data are available [29].

Medical prehabilitation includes the management and optimization of preoperative conditions, such as diabetes and cardiovascular function and the promotion of smoking cessation. Additional goals are to improve muscle strength and nutritional and emotional and psychological status. It has been shown that functional capacity can be improved by prehabilitation, whether it is via a strenuous preoperative activity schedule (bike and muscle strengthening exercises) or by a 30-min walking and breathing exercise regimen 3 times a week [30]. One of the aims of prehabilitation is to allow vulnerable patients to improve their conditions, thus becoming better candidates for more radical treatments [31]. West el al. evaluated prehabilitation specifically in rectal cancer patients undergoing nCRT, a population where surgery is already delayed based on the treatment plan; this time delay can be allotted for prehabilitation. While nCRT reduced physical fitness, especially in the elderly group, patients who underwent the exercise programme demonstrated improved oxygen uptake and lactate threshold (markers of fitness) between 0 and 6 weeks. In patients who did not exercise, their levels remained unchanged [32].

In conjunction with the described exercise regimens, nutritional optimization via whey protein supplementation can improve functional exercise capacity [33]. This is especially pertinent as many senior adults are found to be malnourished before cancer surgery, which increases the risk of postoperative complications [34]. A recent position paper by the ESSO Task Force in

collaboration with the Enhanced Recovery After Surgery (ERAS) Society highlighted the need for structured collaboration between surgeons and clinical nutrition specialists in order to identify patients in need of nutritional interventions [35].

Prehabilitation improves functional recovery and can have an influence on patient independence and active life expectancy [36]. In addition, fewer postoperative complications were recorded in patients who improved their walking ability during prehabilitation, while patients whose functional capacity declined during the pre-treatment time had poorer outcomes [37]. Based on these early results, one might consider that the response to the prehabilitation regimen would be an additional screening tool for elderly patients planning to undergo surgery for cancer. In addition, engaging patients in a prehabilitation program can contribute to active engagement in their care and recovery.

Treatment options

Elective surgery for the primary malignancy

Radical surgery for rectal cancer in elderly patients has been questioned in the past given the high rate of complications and the lack of ability of many senior adults to overcome them, such that Total Mesorectal Excision (TME) had, in the past, not been advised after 75 years of age [38].

Over the last decade, the prejudice about life expectancy has progressively decreased; in the USA, a 75-year old male in good health has an 18-year life expectancy, and an additional 10 years at the age of 82 (6 years and 2 years, respectively in cases of multiple, major comorbidities) [39]. Secondly, there is a better understanding of frailty and how several measures may be implemented in the preoperative period to improve patients' fitness. Thirdly, there has been a substantial improvement in both open and minimally invasive TME techniques leading to fewer complications and more efficient recovery (Fig. 3). Overall, since frailty and not age has been well established as a primary surgical risk factor, radical oncologic (TME) surgery currently is advised for all patients who can undergo an extensive procedure, independent of their chronological age. A general treatment algorithm for elderly patients with rectal cancer is presented in Fig. 4.

Minimally invasive surgery and TME

Several datasets are now available from randomized and high-quality non-randomized trials showing that laparoscopic rectal cancer surgery is safe, has comparable oncological results to open surgery, and improves functional recovery based on fewer overall complications, less blood loss, shorter hospital stay and shorter bowel-function recovery times [40].

Well-known randomized trials have shown oncological non-inferiority of laparoscopic versus open TME (COLOR II [41], CLASSICC [42], COST [43], and COREAN [44] trials). Despite the limitations of these studies, they all showed the safety of a minimally invasive approach together with the already established functional benefits. None of these studies excluded elderly patients based on their age. However, they contained variable numbers of elderly patients and elderly patients were underrepresented compared to younger patients. In recent years, significant evidence has been added by Cochrane reviews [45], meta-analyses and systematic reviews [46].

Recent results from two RCTs raised some concerns about oncological adequacy of minimally invasive surgery compared with open surgery based on the inability to achieve a noninferior pathological composite outcome [47,48]. These studies have been openly criticized because of the extremely wide confidence interval and a low study design quality [49]. While the clinical validity of a pathological composite outcome measure itself is questionable, the long-term oncological results of the ACOSOG Z6051 study, showed equivalent disease-free survival (DFS) and local recurrence rate in the two groups [50].

In 2016, Li Y et al. [51] published a meta-analysis of 11 comparative studies including 1066 laparoscopic and 1034 open colorectal resections; in their pooled analysis they proved how laparoscopy is safe and carries a lower risk of infectious complications (both pulmonary and at the surgical site), shorter length of stay and a reduced incidence of postoperative ileus while maintaining the same cardiovascular risk as compared to open surgery.

Unfortunately, while recognizing the essential role of laparoscopic rectal cancer surgery, a huge variability in the adoption of minimally invasive strategies is recorded globally. Population data show that laparoscopic TME is performed in 10%–50% of all rectal cancer cases based on national adoption rates. A high conversion rate (up to 30%), also recorded in recent trials, is a critical issue of this technique and may impact diffusion of laparoscopy, specifically in the deep pelvis. With the establishment of centers of excellence for rectal cancer treatment, an opportunity may arise to increase patient access to well-trained, specialized surgeons and possibly increased access to minimally invasive techniques leading to a decrease in conversion rate [52–55].

Robotic surgery was also initially introduced with the goal of reducing the high conversion rate reported for laparoscopic pelvic surgery. To date, no current, good-quality data are available supporting robotic TME surgery over standard laparoscopy, particularly in elderly patients. Recent publication of the only randomized international study available on this topic, the ROLARR trial, failed to demonstrate a lower conversion rate in the robotic group while confirming equivalent oncological and functional results at a significantly, currently non-clinically justifiable, higher cost, especially in this sub-group of patients [56]. Another randomized controlled trial confirmed the equivalent TME-quality and oncologic metrics when comparing robotic to laparoscopic surgery [57].

Transanal TME (taTME) is a new technique that is rapidly spreading across Europe and the United States. Several series have been published describing the potential benefit of approaching the mesorectum from the bottom-up [58–60]. Specific publications on the role of taTME in the elderly are not currently available but data provided from the International taTME registry [61] managed by the Pelican Cancer Foundation [62] have been analyzed. The database currently includes more than 2700 cases recorded from 253 centers in 41 different countries with 1655 patients (60.3%) aged >70 years. Data from the registry are not submitted to any randomization, so an obvious selection bias is present (excluding patients not considered fit for this approach). Nevertheless, this database allows understanding of the actual benefits and potential harms of this new technique. The second potential bias is that taTME is mainly a 'restorative' type of procedure so most of patients recorded are suitable for a LAR with colo-anal anastomosis.

At a mean follow-up of $14 \pm 12 \cdot 2$ months (median of 11 months (1–68)), there were a significantly higher number of comorbidities and increased American Society of Anesthesiologists (ASA) Score in the elderly group as compared to younger patients. Interestingly, extremely high rates of sphincter-preserving procedures were achieved with this technique (94%), which is also true in elderly patients in the cohort (92%), and very low conversion rates (5% for young and elderly) were recorded. The overall 30-day mortality and morbidity were respectively 1% and 38%. No higher rates of surgical complications (bleeding, leak, abdominal-pelvic infection, wound complications, re-operation, re-admission) were recorded in

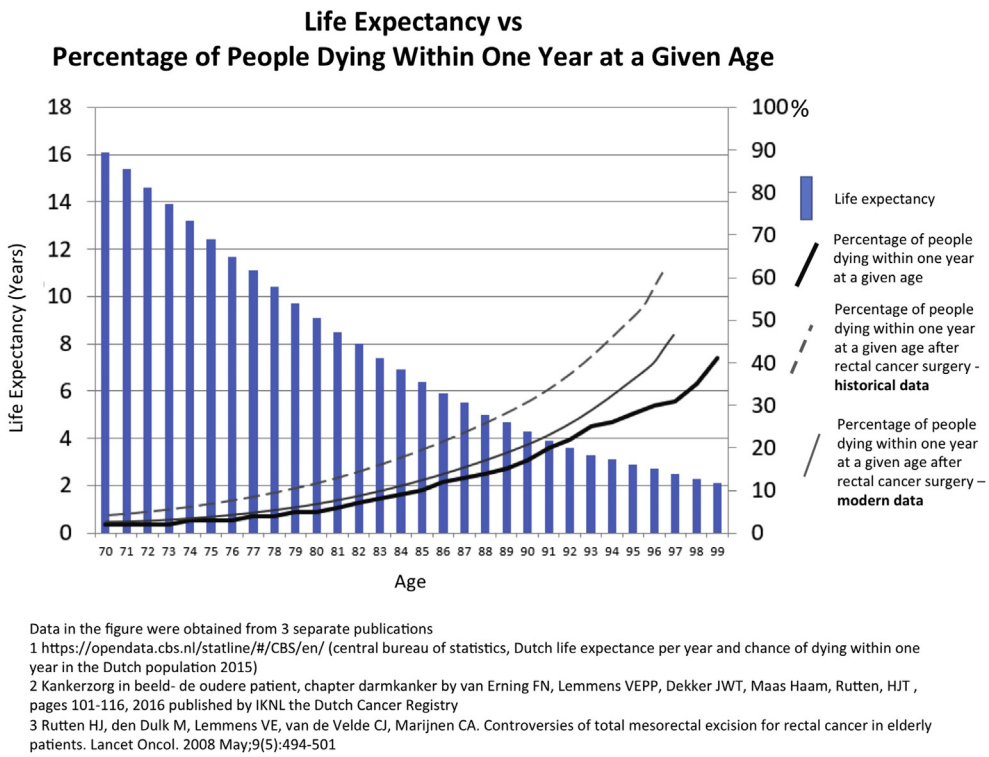

Fig. 3. The Impact of Rectal Cancer Surgery on Life Expectancy in Elderly Patients. The graph demonstrates life expectancy in the elderly, which is generally higher, at a given age, than previously believed. Using historical data, total mesorectal excision was associated with an increased mortality and was, therefore, not advised. Modern surgical data suggest that elderly patients undergoing surgery today have a similar life expectancy to their peers without rectal cancer. Therefore, in properly selected patients, rectal cancer surgery is advised.

elderly compared to younger rectal cancer patients in the registry. Instead, elderly patients tend to have more overall complications secondary to higher rate of pneumonia and cardiac events, which is consistent with what has been reported for other surgical techniques. While no increased 30-day mortality is demonstrated in elderly patients, a higher 1-year mortality rate is recorded compared to younger patients, which could be multifactorial taking into consideration a reduced life expectancy.

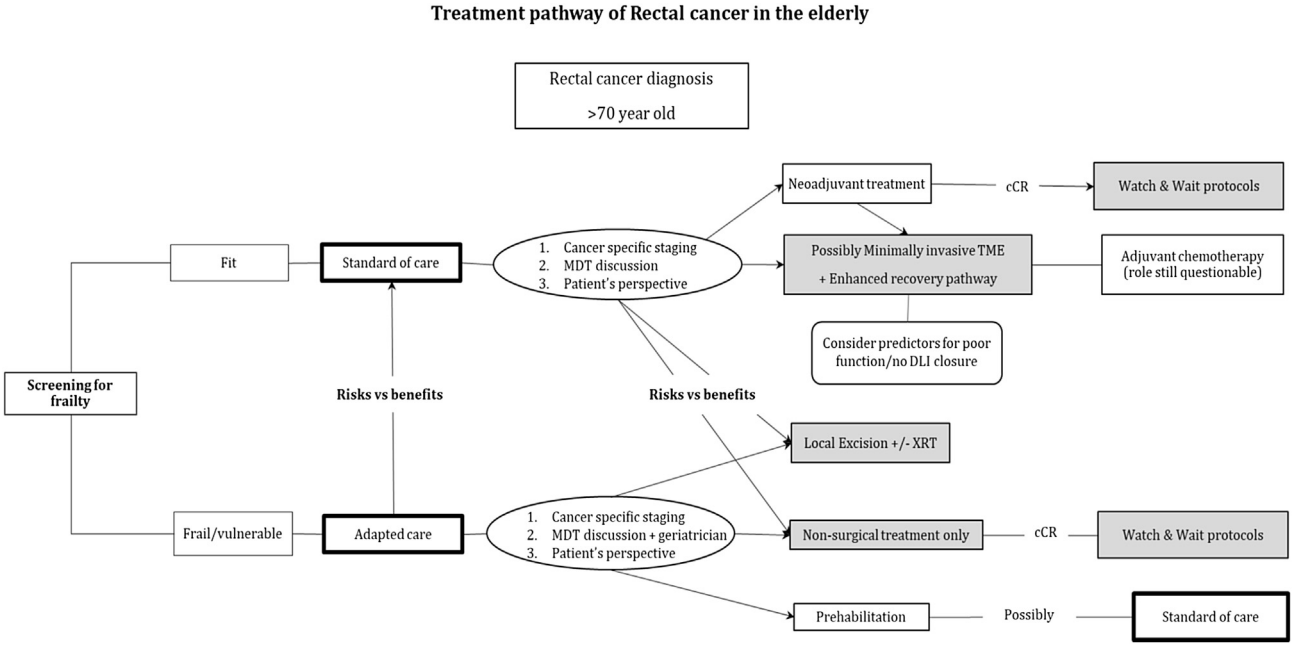

Fig. 4. Proposed Treatment Pathway for Elderly Patients with Rectal Cancer. The treatment pathway is proposed for elderly patients with rectal cancer to guide treatment. It should be noted that treatment should be personalized for the individual patient with input from the patient and the treating multidisciplinary team.

Overall, this technique, in expert hands, appears to be safe and feasible in the elderly, which is reflected in the fact that the majority of patients recorded in a voluntary international registry are above 70 years of age. An excess of 90% rate of restorative procedures and a very low conversion rate, which extends the known benefits of MIS to more patients, could be the biggest functional advantages of this technique in the elderly. Longitudinal functional outcomes (i.e. diverting-ileostomy closure rates and sexual and urinary functional outcomes) are too immature to be analyzed due to short follow up.

Consensus recommendations are, in brief, that age is not a contraindication to MIS while data seem to point to laparoscopy as the preferred option to perform TME surgery. This is particularly relevant for elderly patients where quicker return to active life, achieved with a less invasive, equally oncologically appropriate, procedure is the most desirable outcome. Surgeons should be aware not only of data from the international literature, but also of their own personal/institutional outcomes, in order to provide their patients with the most effective strategy/technique available by the individual surgeons' hands that is sustainable by their national system.

Local excision (rectal sparing techniques and emerging strategies)

Local excision (LE), regardless of the device or technique used to achieve rectal-sparing surgery, has the potential to balance acceptable oncological results and very good functional results by avoiding the morbidity of a radical resection in selected patients. Several techniques and platforms are available depending on surgeons' skills (TAE: transanal excision; TEM: transanal endoscopic microsurgery; TEO: Transanal Endoscopic Operation; TAMIS: transanal minimally invasive surgery). Not utilizing one particular technique, but rather the possibility of achieving an 'en-bloc' R0 resection is the preferred goal.

General recommendations from the current literature suggest that an oncologically appropriate LE can be obtained for malignant T1 cancer if submucosal invasion >1000 μm, lymphovascular invasion, poor differentiation and histology features (mucinous) and budding (grade 2–3) are absent, since each one of those carries a greater than 15% risk of lymphatic metastasis [63,64]. Functional results following a LE are very good (1% urinary dysfunction, < 1% fecal incontinence) and overall morbidity is low (7.4% for TAMIS, 8·4–14·9% for TEM) [63,65], thus many surgeons broadened the indications for LE, including more aggressive tumors (T1 with poor pathology, T2) or performed LE in association with neoadjuvant or adjuvant treatments. While being far from the standard-of-care, these latter strategies seem to be well suited for vulnerable/frail elderly patients with the intent of preserving function and avoiding invasive procedures. The elevated rates of local recurrence/progression of disease recently reported (pooled local recurrence rate 21.9%, DFS 68%) militates against LE being considered as the standard-of-care for fit elderly, or young, patients after nCRT [66,67]. Data showing a significantly higher complication rate around 23%, together with 43% readmission rate, discourages the adoption of LE techniques after radiation therapy [66,68]. Data from meta-analysis of LE followed by adjuvant treatment seems instead to show a different trend: reported weighted average local recurrence rate for pT1/T2 was 14% for LE followed by chemoradiation (CRT) vs. 7% for patients after completion TME [69], showing this could be a viable option for those elderly patients where it is crucial to balance morbidity/mortality, oncological risk, and life expectancy.

LE can be considered in elderly patients with low-risk tumors or in unfit patients with high-risk tumors followed by adjuvant radiotherapy and/or chemotherapy. LE should be avoided when possible after nCRT secondary to a higher complication rate.

Treatment of locally advanced disease

Neoadjuvant chemoradiation

nCRT is the standard treatment for locally-advanced mid-distal rectal adenocarcinoma to increase local control, even when combined with optimal TME surgery [70–74]. The dose of external-beam radiation therapy (EBRT) is typically 45–50 Gy given over 5 weeks. Concurrent chemotherapy is administered as infusional 5-fluorouracil (5-FU) or capecitabine, which have similar efficacy. Addition of oxaliplatin (FOLFOX) or Irinotecan (FOLFIRI) is not standard due to increased toxicity without improvement in tumor response [75–79].

The feasibility of nCRT in elderly patients depends on patient frailty, which should be determined via a strategy similar to that presented in Fig. 2. In elderly patients, renal insufficiency may prevent the use of Capecitabine and care must be taken regarding treatment compliance with the oral drug, especially if the patient lives alone. Induction chemotherapy using FOLFOX (followed by short-course or long-course chemoradiotherapy) may be an option for decreasing distant recurrence (particularly in the setting of a prospective trial), but tolerance in elderly patients must be carefully followed. The RAPIDO trial results will hopefully generate relevant data on this topic [80].

Long-course (LC) nCRT shows no difference from 25/5 (short-course) radiation in terms of tolerance and efficacy. For distal rectal cancer, LC nCRT may be more efficient for local control [81]. However, in elderly patients, the immediate toxicity of nCRT is increasing and may compromise the chance of a TME surgery, which is the main treatment for local control and curative intent [82]. Treatment strategies to decrease toxicity have been explored: 25/5 could be an alternative to decrease toxicity in the elderly population. The phase III trial, Neoadjuvant Treatment for Advanced Rectal Carcinoma (NACRE), is currently enrolling patients age 75 and older and comparing short-course radiation only with standard chemoradiation treatment (50 Gy and capecitabine) [83]. In addition, for upper rectal tumors without nodal involvement, anterior resection without any neoadjuvant treatment is possible, may confer less morbidity with similar rates of local control and should be considered in properly selected elderly patients [84].

The interval between the end of LC nCRT or 25/5 and surgery has no influence on local control or survival [85,86]. Longer intervals increase clinical tumor response and are useful if organ preservation is sought. For inoperable patients, EBRT combined with sensitizing chemotherapy, when tolerated, is the main treatment to achieve local control [87].

To achieve a complete response for rectal adenocarcinoma, RT doses above 65–70 Gy are usually necessary [88]. Standard nCRT can eliminate small T2 tumors, but dose escalation is necessary to achieve a higher chance of complete clinical response (cCR) in such tumors [89]. An alternative to obtain higher rates of cCR is contact X-Ray brachytherapy (CXB), which uses 50 kV X-rays to deliver high doses up to 90–120 Gy [90]. CXB is only available in select centers, but has been shown to increase the rate of cCR. The technique was popularized in the 1960s by Papillon [91] and between 1980 and the present, CXB has been used in several centers around France and other European countries and been utilized in three different clinical situations: adjuvant treatment after LE for T1 N0 lesions in cases where high-risk pathologic features were detected in the specimen [92,93]; T2 and early T3 N0 tumors, mainly in elderly or frail patients, in combination with EBRT to treat both the primary tumor and perirectal subclinical lymph nodes [85,94,95]; and distal locally-advanced tumors to potentially decrease the need for APR [85]. The ongoing Phase III clinical trial, Organ Preservation of Early Rectal Adenocarcinoma (OPERA) is evaluating contact radiation

with nCRT to evaluate the rate of clinical response in early rectal tumors [96].

The UK National Institute of Clinical Care and Excellence (NICE), in the UK, has published its own recommendations on CXB for patients with early rectal cancer not suitable for surgery [97]. However, CXB is only available in select centers. Therefore, an alternative is to offer intraluminal brachytherapy using high dose rate (HDR) brachytherapy. Both HDR and CXB are also useful as palliative treatment for quickly controlling symptomatic bleeding from rectal tumors [98].

Watch and wait

The TME resection specimen after nCRT shows no residual tumor in 15–30% of patients, depending on the original stage of the tumor. This forms the basis of the Watch and Wait approach (W&W), in which a reassessment with MRI and endoscopy aims to identify complete responders. Patients are offered an active surveillance protocol with MRI and endoscopy as an alternative to a TME resection [89]. Of note, the surveillance strategy can be modified based on the patient's disease, wishes, and recommendations of the multidisciplinary team as their disease evolves. Many patients chose the W&W strategy in order to avoid a permanent stoma or the long-term functional problems associated with TME surgery [99]. In 10–30% of patients, the tumor apparently had not disappeared completely, and a regrowth appears during surveillance, which is usually treated with delayed TME surgery [100]. In addition to the goal of increasing the QoL in operable patients, there is the clear additional benefit of avoiding major surgery in frail elderly patients and patients with substantial comorbidities. To further evaluate this hypothesis, Smith et al. used a model to compare three cohorts of men: 60-year-olds with mild comorbidities, 80-year-olds with minor comorbidities, and 80-year-olds with significant comorbidities (Charlson score >3). Patients with a complete clinical response after chemoradiotherapy were followed by a W&W protocol or offered radical surgery (TME). Absolute survival was similar in 60-year-old patients who underwent W&W or TME. However, in both fit 80-year olds and those with comorbidities, there was a 10·1% survival advantage at one year in those who underwent a W&W approach. There were no differences between groups in DFS or quality-adjusted life years (QALY). This model suggests elderly patients may have the most to gain from W&W after cCR [101].

Two large systematic reviews evaluate the available evidence on W&W after cCR. The meta-analysis and systematic review of Dossa et al. includes of 23 studies including 867 patients followed for 12–68 months. The 2-year regrowth rate was 15·7% (95% CI 11·8–20·1), with 95·4% percent of patients undergoing salvage treatment and only 1% of patients being technically unresectable. There was no difference in OS between the surgery and W&W groups, but DFS was superior in the surgery group, which was predominantly due to the regrowths (HR 0·47, 95% CI 0·28–0·78) [102]. Sammour et al. reviewed 15 studies with 920 patients and showed a pooled regrowth rate of 21·3% at a mean of 15·6 months. Surgical salvage was possible and performed in 93·2% of patients. Overall survival was similar (91·7% for W&W and 92·4% for TME surgery), and again DFS was lower in the W&W group (82·7%) than in the group that underwent surgery (87·5%) [103].

The International Watch and Wait Database (IWWD), a collaborative effort to pool information, has now data on more than 1000 patients [99]. Approximately half of the data are previously unpublished and it provides, therefore, provide an accurate reflection of the real-world risks and benefits of the W&W approach. Local regrowth was most frequently diagnosed in the first two years of follow-up, with a 2yr rate of 25·3%, and was located in the bowel wall in 96·7%. Nodal local tumor regrowth was very uncommon. The five-year overall survival was 84·6%, and five-year disease-specific survival was 93·8%. The risk of local unsalvageable disease was estimated to be smaller than 1·5% [104]. Together with the reviews of the published series, these data indicate that with a good surveillance schedule the risks of the W&W approach in clinical complete responders are low.

Dose escalation of radiotherapy can provide higher response rates, and a boost can be delivered by EBRT and/or by intraluminal CXB. Gerard et al. showed that higher radiation doses (>80Gy) administered via a combination of EBRT and CXB, resulted in local control of 85–90% of T1 tumors, 80% of T2 tumors, and 60% of T3 tumors [105]. More recently, Myint et al. evaluated 200 patients undergoing CXB alone (8·5%) or CXB with EBRT (91·5%) and showed that 72% (144/200) of patients had a cCR. Of those with residual tumor, 68% had an immediate salvage surgery. Eighty-six percent of patients maintained cCR and, overall, organ preservation was achieved in 62% of patients at a median of 2·7 years follow up [106]. Appelt et al. reported a complete clinical response in 40/51 patents with $T_{2\text{-}3}N_{0\text{-}1}$ tumors treated with 60Gy EBRT and a 5Gy endorectal brachytherapy boost [107].

Another possibility to increase the rate of cCR is by adding systemic chemotherapy either after the nCRT, consolidation chemotherapy, or preceding the nCRT, induction chemotherapy. Cercek et al. evaluated 61 patients who underwent 4 months of FOLFOX followed by chemoradiation. They showed a 27% pathologic complete response rate in their study [108]. Garcia-Aguilar et al. showed that adding 0, 2, 4 or 6 cycles of FOLFOX after nCRT resulted in pCR rates of 18%, 25%, 30% and 38% respectively [109]. However, this approach utilizes systemic chemotherapy including oxaliplatin, which has been shown to be more poorly tolerated in the elderly.

At the present time, the decision to pursue a W&W strategy can be considered after taking into account the goals and preferences of the patient, the short and long-term risks of proceeding with an oncologic resection (TME) versus risks of nCRT, and the likelihood of local control with nCRT. It should be again noted that, depending on the type of nCRT delivered, there will be a proportion of patients who require salvage treatment either because of an incomplete response or after a recurrence develops. This should be discussed with the patient before embarking on a treatment strategy.

Adjuvant chemotherapy

In rectal cancer, adjuvant chemotherapy is typically given following surgical resection with or without nCRT. In this context, the goals are presumably to eradicate micro-metastatic disease and prevent distant recurrence. There is controversy about whether the decision to give adjuvant chemotherapy should be based on the pre-op staging (imaging based), the post-operative pathology, or both. A number of studies have been performed to evaluate the benefits of adjuvant chemotherapy for rectal cancer.

Early studies showed decreased recurrence and improved survival with adjuvant chemotherapy. A Cochrane review in 2012 including 9221 patients across 21 trials spanning multiple decades with wide heterogeneity showed a small but statistically significant improvement in OS and DFS with adjuvant 5-FU based chemotherapy (HR for OS 0·88 (0·76–0·91), HR for DFS 0·75 (0·68–0·83) [110].

More recent studies failed to show a similar survival benefit. The EORTC 22921 trial was powered to show an absolute 10% survival benefit. However, with a 10·4-year median follow-up, there was no demonstrable difference in OS, DFS, or cumulative incidence of distant spread. Chemotherapy did decrease rates of local recurrence [111]. An Italian trial showed no difference in OS, local control, and distant spread [112]. More recently, Breugom et al. evaluated 470 patients, more than 80% of whom had stage III disease on

pathologic examination, and showed that addition of adjuvant chemotherapy demonstrated no difference in OS or DFS [113].

Two recent meta-analyses were performed. Breugom et al. evaluated four trials with 1196 patients and showed no difference in OS, DFS, or rate of distant recurrence. However, in a subgroup analysis, they did find improved DFS and decreased rate of distant recurrences in tumors between 10 and 15 cm from the anal verge [114]. Bujko et al. evaluated 5 randomized trials with a total of 2398 patients and showed no benefit for chemotherapy in improving OS or DFS [115].

Despite the largely negative results with the addition of adjuvant chemotherapy, the current NCCN guidelines recommend adjuvant chemotherapy after nCRT and surgery [116]. ESMO clinical practice guidelines state that it is '*reasonable to consider adjuvant chemotherapy { … } with yp Stage III and ('high risk' yp Stage II). The level of scientific evidence for sufficient benefit is much lower than in colon cancer and is probably limited to DFS rather than to OS. It should also be noted that elderly patients with colon cancer do not appear to derive the same benefit from the addition of oxaliplatin as their younger counterparts* [117]. In addition, the latest adjuvant data from the 'IDEA' collaborators in colon cancer may potentially influence future trial design in terms of the regimen used and the length of administration [118].

Hence, the decision on postoperative chemotherapy (fluoropyrimidine alone or combined with oxaliplatin) should be risk-balanced, taking into account both the predicted toxicity for a particular patient and the risk of relapse, and should be made jointly by the individual and the clinician' [119]. A similar, equally thoughtful and consultative approach should be taken in elderly patients with rectal cancer. As such, the SIOG consensus recommendations for CRC advocate for consideration of the risk of adverse events, the patient's risk of recurrence, and the physician's clinical judgment in choosing whether to give adjuvant chemotherapy [120]. In addition, one must not neglect to take into account the patient's wishes after an informed discussion has taken place.

Treatment strategies for synchronous metastatic liver disease

The vast majority of CRC liver metastases (CRLM) occur in the first 12 months from the primary diagnosis (synchronous or early metachronous). In a large population-based study, the incidence of synchronous liver metastases was 16% in patients aged 65–74 years and 11.7% in patients 75 and older. In patients older than 75 years, the five-year incidence of metachronous liver metastases was 12·5% [121]. Cross-sectional imaging by CT or MRI forms the foundation for detection of CRLM. It has been established that liver resection for CRLM should only be performed in the context of a curative process [122]. Despite the lack of Level 1 data, outcomes reported from the analysis of large databases and the International Liver Metastasis Registry (*LiverMetSurvey International Registry* [123]) show that liver resection for CRLM with curative intent (R0 resection) is feasible, safe and effective in elderly patients although perioperative risks are higher compared to young patients [124,125].

De Liguori Carino et al. analyzed data from liver resections performed on 178 consecutive senior adult patients. The overall survival (OS) rate at 5 years was 31·5% [126]. Similar results were reported by Nagano et al. who reported 34·1% 5-year survival rate in 202 elderly patients undergoing surgery for CRC with liver metastatic disease [127]. Adam et al. compared 60-day postoperative complications and 3-year survival rates in a group of 999 > 70-year-old patients versus a control group of 6765 younger, consecutive patients who underwent liver resection for metastatic stage IV CRC. Elderly patients had a higher rate of postoperative mortality and morbidity; surprisingly, the 3-year survival rate was similar in the two groups (57·1% vs 60·2% respectively), but was statistically significantly different ($p < 0001$). Independent predictors of survival were more than three metastases, bilateral metastases, concomitant extrahepatic disease and no postoperative chemotherapy [122]. Again, a thorough assessment of the individual frailty, not age, should guide decision making, especially in light of the progressively declining complication rates reported in the literature for this subgroup of patients [128].

Unfortunately, data show that elderly patients with CRLM are not always offered the same treatment opportunities as younger patients [2]. It is strongly recommended that patients (of any age) with synchronous liver metastasis from rectal cancer must be assessed upfront in a dedicated MDT. The preferred strategy indicated by The European Society for Medical Oncology (ESMO) [129], the National Comprehensive Cancer Network (NCCN) and the National Institute for Health and Care Excellence (NICE) [130] guidelines is upfront neoadjuvant chemotherapy vs chemoradiation, if the primary rectal cancer is asymptomatic, followed by sequential resections (liver then rectum or vice versa). When nCRT is planned, liver resection is preferentially performed during the 8–12 week window after the completion of nCRT and before bowel resection (reverse approach) [131]. Simultaneous resection should be discouraged when the hepatectomy would be considered major surgery or when complex rectal surgery is planned due to a significantly higher mortality and morbidity.

Emergency treatment and palliation

Emergency surgery in the older adults is associated with an increased morbidity and mortality. Wilson et al. showed that elderly patients have a 38% in-hospital mortality after undergoing emergency surgery. Seventy percent of that cohort had at least one post-operative morbidity and they showed that a post-operative morbidity increased the likelihood of death during the same admission three-fold [132].

With the high rates of morbidity and mortality, prevention and early intervention are key in dealing with emergencies in elderly patients with rectal cancer. There are three emergencies encountered in rectal cancer patients: bleeding, obstruction, and perforation.

In evaluating elderly patients with emergent or urgent presentations, a multidisciplinary evaluation is preferable. Efforts should be made to involve the patient, their family, and primary care physician/geriatrician in the treatment decisions, if time allows. In addition, a determination should be made regarding the patient's frailty. In the emergent setting, the Flemish Triage Risk Screening Tool has been correlated with increased morbidity, mortality and length of stay in an elderly population undergoing emergency surgery [133]. The tool is a 5-question assessment that can be done quickly in the Emergency Department without the need for ordering additional testing. If the patient is unresponsive or has an altered mental status, a family member should be queried to ensure the results are as accurate as possible and reflective of the patient's true status. Finally, the degree of local and distant disease should be determined, typically by CT scan in this setting, before proceeding with a treatment plan, if possible.

In treating rectal bleeding associated with rectal cancer, the degree of bleeding should be quantified and history of past treatments considered. For clinically significant bleeding, if the patient is fit, resection can be considered. Otherwise, if the patient is unfit for surgery or has a significant disease burden, after being stabilized, radiation therapy or local bleeding control is preferred. For occult bleeding, local bleeding control can be considered first followed by radiation therapy for persistent bleeding.

The treatment approach for obstructive rectal cancer depends on the location. If the obstruction is located in the proximal rectum, colonic stents can be used as a bridge to resection in a fit patient with minimal disease burden [134] as an alternative to a Hartmann's procedure. Alternatively, in an unfit patient with a large disease burden, colonic stents can be utilized for palliation. Colonic stents are not recommended if patients are planned for chemotherapy without resection. A diverting stoma should be considered the treatment-of-choice in patients with obstruction that are not planned for resection or stenting for palliation. This will typically be the case in patients with mid/distal rectal tumors, which are not suitable for resection in the acute setting and not amenable to stenting.

Elderly patients present later than younger patients with signs of bowel perforation and the corresponding fecal contamination increases the incidence of post-operative complications. However, morbidity and mortality can be controlled if complications are managed early [135]. For free perforations, except in patients who are undergoing supportive/palliative care based on fitness or disease burden, exploration should be offered emergently with washout, diversion, and, possibly, resection. Resection of the rectal cancer will not typically be pursued in the emergent scenario, however, if the perforation is at the caecum secondary to large bowel obstruction, resection can be considered. For a contained perforation, conservative measures including antibiotics and percutaneous drainage can be employed. Close monitoring is required in such cases with prompt surgical management pursued in the case of concern for development of free perforation or failure to respond to conservative measures. A proximal diverting stoma could also be discussed with the patient.

A tailored treatment approach is required in the emergency setting due to the heterogeneity of this population and varying degrees of acuity of the emergency scenarios. Patient fitness, expectations and degree of disease burden should be taken into account in determination of an optimal treatment strategy. If possible, emergencies should be prevented or intervened on as quickly as possible to decrease morbidity and mortality.

Evaluation of pathologic differences in elderly patients

As pathology guides treatment, the question has arisen if histopathological features and biological behavior is different in young patients versus elderly patients presenting with CRC. To date, there is no specific data in rectal cancer, however, this issue has been evaluated in colon cancer patients. Patel et al. showed that in a 32,819 patient cohort, elderly patients had a higher incidence of right-sided tumors and, in fact, in the patient population 80 years of age and greater, 55% of the tumors were located in the ascending colon [136]. A Surveillance, Epidemiology and End Results (SEER) registry study evaluating 208,077 patients showed that the incidence of right-sided cancers proportionally increases with age. In addition, in this cohort, elderly patients were less likely to have adequate lymph node sampling (>12 lymph nodes), as demonstrated in other large database studies [137]. However, in patients who were adequately staged, elderly patients were less likely to have node-positive disease [138]. Amri et al. showed similar findings and demonstrated that patients younger than 50 years have greater incidence of metastatic disease, node-positive disease, and extramural vascular invasion than those patients older than 50 years [139].

A recognized pathway for development of CRC has been established where a tumor suppressor gene is silenced via hypermethylation of CpG islands at the promoter of genes. Tumors that arise via this pathway are classified as bearing the CpG island methylator phenotype (CIMP). CIMP tumors are most commonly seen in elderly patients, in females, in right-sided tumors, in microsatellite-stable tumors, in poorly differentiated tumors, and in tumors with mucinous histology [140]. Similarly, there may be a specific pathway for the development of rectal cancer in elderly patients, but this has yet to be identified.

Recent work has also focused on the effect of the microbiome on the development of CRC. Fusobacterium nucleatum has been shown to be associated with colon cancer. In addition, the presence of fusobacterium was more prevalent in older patients [141]. This may have a role in explaining the differences between older and younger cancer patients although the environment of a tumor may be more accommodating to multiplication of fusobacterium rather than fusobacterium being an actual causative agent in tumor development [142]. Further work is necessary to answer these questions.

Treatment outcomes

Enhanced recovery pathways

Enhanced recovery (ER) pathways include evidence-based alterations in preoperative, intraoperative, and postoperative care to reduce organ dysfunction and the stress associated with surgery and to promote rapid recovery. The well-known key elements of these pathways are: extended patient information and involvement in their own care; preservation of gastrointestinal function (carbohydrate solution before surgery, early oral feeding), minimizing organ dysfunction (goal-directed fluid therapy, avoidance of drains and nasogastric tube, minimally invasive surgery), active pain control (opioid-sparing anesthesia and analgesia, local anesthetic infiltration of incisions), and promotion of patient autonomy including early mobilization [143]. This multidisciplinary perioperative strategy requires a team approach involving surgeons, anesthesiologists, nurses, dieticians and physiotherapists, without forgetting the absolute importance of caregiver participation.

It has been deemed difficult for elderly patients to strictly adhere to the ER protocol and the effectiveness of these strategies in this subgroup of patients has been questioned. The additional challenges in adopting ER protocols in elderly patients revolve around their higher levels of comorbidities, increased possibility of frailty, and increased social care requirements [144]. However, modern literature suggests that elderly patients actually have an advantage in functional recovery, if enrolled in ER pathways.

Many studies have demonstrated that ER pathways are safe, cost-effective, and that they shorten the length of hospital stay and decrease complication rates in patients undergoing colorectal resection [143–145]. The feasibility and efficacy of ER pathways in elderly patients has been the subject of 2 recent systematic reviews [144,145], including 16 studies (3 randomized trials). The quality of these studies was rated as 'fair' by the reviewers. Both reviews found statistically significant differences in favor of ER pathways with decreased length of hospital stay and fewer overall complications. They showed a 45% decrease in postoperative morbidity in favor of ER pathways. Compliance with the ER pathway measures was lower in elderly patients and postoperative morbidity rate was higher. However, the morbidity rate was statistically-significantly lower in the ER pathway group than in elderly patients undergoing "traditional care" [145]. Studies that include older patients probably contain an inherent selection bias; therefore, the results may not be transferable to all elderly patients since physically and mentally fit patients tend to be recruited more frequently. Nevertheless, the core elements of any ER pathway should be personalized and made available, whenever applicable, regardless of the patient's fitness.

While utility of some of the items included in ER pathways such as the use of epidural anesthesia and the absence of oral

antibiotics with mechanical bowel preparation have been questioned by the current literature [146,147], there are a core set of elements that can and should be applied to elderly patients. Discontinuation of intravenous fluids and early oral intake, timely removal of the urinary catheter (when possible given low pelvic dissection), and early mobilization may have a direct beneficial effect on elderly patients, by reducing general complications and perioperative mortality. Significant efforts must be made by the care team to actively involve both patients and caregivers in the protocol, in order to increase compliance and facilitate early recovery.

Functional recovery

Effectiveness of any oncologic treatment has been historically measured by several indicators, in order to define patient survival after the treatment. OS, DFS, or Progression-Free Survival (PFS) 5 years from the diagnosis have long been considered the best indicators to define cancer control. Unfortunately, indicators such as 5-year DFS only have limited value for 80-year-old patients undergoing rectal cancer surgery, due to the competing limited life expectancy. Therefore, functional recovery (FR) should be evaluated in elderly population as an equally important variable [148]. FR should not be confused with restoration of bowel function or time to oral food intake after surgery and is instead a multidimensional outcome. FR should be addressed regarding two main areas: organ-specific postoperative outcomes and individual ability to regain independence.

'Organ-specific' FR outcomes should include evaluation of urinary, sexual and bowel function, including both Low Anterior Resection Syndrome (LARS) and Fecal Incontinence (FI). Rates of elderly patients undergoing a diverting loop ileostomy (DLI) closure after sphincter-saving surgery should also be included as a FR outcome measure. The main recommendation in this field is first to use internationally validated and well-established instruments in order to measure specific function as objectively as possible. The International Prostate Symptom Score (IPSS), International Index of Erectile Function, and Female Sexual Function Index, the Cleveland Clinic Florida Fecal Incontinence Score and the LARS score are currently available examples.

Sexual needs of elderly patients should not be underestimated as about 26% of patients between 75 and 85 years of age report being sexually active [149]. Based on current data, care givers and patients should know that treatment of rectal cancer, above all in the elderly, comes with a substantial loss of function. About 60% of patients experience some degree of decline of sexual and urinary function. Sexual, urinary and bowel function have been shown to be negatively impacted by decreased tumor height in the rectum (with upper rectal cancer tumor being treated with better outcomes), the use of chemo-radiation and the occurrence of pelvic surgical complications; age has not been shown to be an independent risk factor [150]. While MIS and robotic surgery failed to provide significant improvement, providers should keep in mind that non-operative strategies, such as nCRT followed by W&W protocols, also come with detrimental functional effects (30% and 23% of patients respectively reported LARS and urinary function impairment). A recent publication from the W&W database showed no difference in sexual function of patients after nCRT followed by surgery compared to nCRT alone [151].

When reporting functional data on elderly patients undergoing restorative rectal surgery, attention should be paid to the rate of people completing their surgical pathway and ultimately being able to reverse their temporary stoma. Data from the Dutch Surgical Colorectal Audit group showed that only 67·7% of elderly patients in the age range of 71–80 reversed their DLI; data are even more dramatic when analyzing patients ≥81 years old, where only 59·8% had their stomas reversed [152]. Having a loop ileostomy and undergoing CRT are also independent factors influencing readmission rate. Approximately 13–21% of patients need to return as inpatients secondary to complications of their DLI and there is a 20–40% complication rate secondary to DLI closure. At the same time, data are available about higher ability of elderly patients to better adjust to sub-optimal functional outcomes and that they can tolerate a permanent colostomy equally well as a restorative procedure [153]. Thus, an inter-sphincteric APR, performed with only limited morbidity and the advantage of undergoing only one procedure, could be a better option in some of these patients.

The main message should not be to increase the number of non-restorative procedures, but instead to reach a better understanding of which patients will be able to complete their surgical journey successfully. Improved counseling of the side effects of having a 'permanent' DLI rather than a colostomy and an informed, two-way conversation is also advised in order to set patient expectations correctly, rather than unreasonably advertise a 'restorative procedure' that will never happen. Strong experience in Northern Europe about the use of diverting loop colostomy after LAR are also evolving and might offer a viable option to promote sphincter-sparing procedures, while not compromising FR with high-output ostomies [154].

Organ-specific FR outcomes have been widely reported in the literature but what remains less prominent, despite increasing interest from cancer patients, is FR as measured by regaining an active, independent life. Restoration of independence has been shown to be one of the most desired goals patients have when starting oncological treatment. From this perspective, the work of The International Consortium for Health Outcomes Measurement (ICHOM) has been crucial to making health specialists more aware of patients' 'real' goals and promoting a collection of outcomes that really matter to patients [155,156]. Regaining independence can be measured as a composite outcome including: cognitive status, ability to perform routine activities of daily leaving (ADL), ability to walk proficiently, and measurement of nutritional/inflammatory status.

Many instruments have been proposed and offered in order to gain data about these particular domains. Currently the most convincing data in the literature regard the use of ADL score, the MiniCog, TUG/6 min-walking test, and sarcopenia (defined as decreased muscle mass and function) [157–159]. The role of sarcopenia in evaluating functional ability of patients before and after surgery is rapidly increasing, because both sarcopenia and myosteatosis can be measured with a CT scan, which is routinely performed in cancer patients. Sarcopenia and myosteatosis will surely have amplified value in the future, since it has been demonstrated that they correlate with patients' endocrine function, including insulin resistance, nutritional status and state of chronic inflammation [158,159].

Surgical care in elderly patients with cancer must be tailored, focusing on the patients' FR and HRQoL rather than mere 5-year DFS. Promoting optimal oncological results is essential, but increasing emphasis on FR has been highlighted by both patients and by payers, who understand the key role of measuring and allocating resources in order to promote treatments that can generate better outcomes that are more germane to patients' needs.

Patient reported outcome measures

As with FR, PROM studies have been very slowly gaining attention comparing what patients really want vs. what we, as care providers, think that patients need. Global health systems are shifting toward value-based care to drive better outcomes in

the setting of rising health care costs. This shift requires a common definition of value, starting with the outcomes that matter most to patients. Questions like: 'Will I die of the cancer or my other conditions?' or 'Will I tolerate cancer treatment?' are more frequent in the minds of patients than 'What are the chances I'll survive 5 more years?' or 'What is the local recurrence rate for my condition?'.

Recent publications of the ICHOM standard sets in colorectal surgery have defined new HRQoL measure standards that should be included while designing a new study or optimizing our post-treatment care. This International group includes about 300 specialists, together with significant numbers of patient representatives, focused on the most frequent medical conditions experienced, with the goal of defining the minimum standard outcome sets and risk factors using a structured process. The international nature of this effort has demonstrated the global similarities of patient's needs and requirements, wherever they live. ICHOM working groups are developing consensus on the universal use of well-validated outcome measures, including PROMs. These standards position providers, payers, patients, and information technology vendors on a common path for tracking what needs to be evaluated and render implementation of outcome measurement easier and more efficient [155].

It should be acknowledged that PROMs, despite their complexity, are as crucial to record in real life. Examples from other surgical fields show that prospective, routine HRQoL measurement is possible, even in a busy surgical practice, and generate extremely valuable results [160,161]. Randomized control studies may not be the ideal approach for either elderly patients or PROMs. However, the role of good-quality trials based on clinical observation and rigorous prospective outcome measurement should be validated and implemented in order to achieve reliable results for HRQoL and FR.

Financial issues and health care cost

The global financial burden of almost any healthcare system (socialized or privatized) together with the ever increasing expense of treating cancer make the analysis of healthcare costs a pressing need with the goal of achieving sustainability. In this setting, there are only two options: to offer fewer services (reducing treatment options/delaying activities/selecting more 'profitable' patients) or to allocate resources to measures that have been proven to be cost-effective.

Elderly patients seem to embody the perfect financial storm. The unique mix of high incidence of (expensive) cancers associated with individual disabilities, the lower socioeconomic status, and the limited productivity all make QALY analysis extremely challenging. Healthcare systems experience the expanding burden of cancer care in the elderly, where the patient has to face not only the dramatic occurrence of cancer, but also, in certain countries, the significant risk of financial loss due to high medical costs.

In the United States 62·1% of all bankruptcies in 2007 were for medical reasons [162] with people being 2·5 times more likely to file for bankruptcy after a cancer diagnosis [163]. Given the SEER data showing that, among people diagnosed with CRC, there is a consistent, positive association between filing for bankruptcy and earlier mortality it seems appropriate to consider *financial toxicity* of cancer in the elderly patient [164].

A deeper analysis of costs highlights two areas where efforts should be focused in order to promote a healthier and more sustainable system: early diagnosis and screening for frailty. It has been shown that excess costs per survival/year were approximately three-fold greater for Stage IV CRC than for Stage III and double for Stage IV vs. Stage II. Compared with costs for colon cancer, costs for rectal cancer are overall similar for early stages while somewhat higher for Stages II to III. Across all stages, excess costs per year of survival are highest among the oldest patients. Secondly, it has been shown that higher costs are related to complications in CRC surgery with 31% of total hospital cost spent on complications, with adverse events 17 times more likely to happen in the elderly. By showing that frailty is the most important risk factor in predicting postoperative complications, it would follow logically to invest in systems that are able to screen for individual vulnerability [165]. Emergency surgery should be avoided as much as possible not only from the healthcare viewpoint of patients and surgeons, but also from a financial perspective.

Cost analysis of surgical treatment strategies showed an advantage (about $4200 per case) of laparoscopy vs. open surgery with increased QALY by lowering postoperative incisional hernia rates [166]. Robotic surgery has so far failed to demonstrate value delivery for patients; the increase in cost is not associated with any improvement in QoL [167]. In all of the modeled patient cohorts, W&W is both less costly and more QALY-effective, whenever clinically pursuable [168]. The increased expenses of adjuvant treatments do not appear to have a corresponding gain in QALYs and should be reconsidered and avoided. Even more crucial is to highlight that for CRC, about 30% of total care costs, approximately $5 billion, are spent in the last year of life. This again corresponds to expensive and largely ineffective chemotherapy administered in the last few months of patients' lives [169].

'*Achieving high value for patients must become the overarching goal of health care delivery, with value defined as the health outcomes achieved per dollar spent […] If value improves, patients, payers, providers, and suppliers can all benefit while the economic sustainability of the health care system increases*' [170]. Unfortunately, value in health care remains largely unmeasured and misunderstood. Establishment of more virtuous and value-based systems would be advisable.

Conclusions

The majority of rectal cancer patients are elderly. The aim of physicians is not to control a disease but to care for patients. While efforts are ongoing to generate centers of excellence worldwide, it is incumbent on the physician/healthcare professional to ensure that the key element to treating these patients correctly is through personalization of their care based on individual frailty. We should mandate that a standardized frailty screening/assessment becomes part of every MDT discussion on elderly cancer patients, at the same level as the preoperative staging or the histopathology results. We cannot treat rectal cancer without understanding the individual surrounding the rectum.

Despite the fact that the majority of rectal cancers affect elderly patients, we still have very limited specific knowledge about this large group of individuals, who are usually treated based on treatment protocols adapted from studies on younger patients. Treating rectal cancer with the best possible multimodal approach is necessary for every fit elderly patient, regardless of his/her age. Personalized strategies can be pursued once frailty is recognized. Helping senior adults to overcome rectal cancer must revolve around pursuing their FR as much as their DFS. It is mandatory to become aware that treatment outcomes cannot merely be measured by DFS, length of hospital stay or financial cost; results must always be patient-centered and consistent with the expectations of the individuals we care for.

These expert recommendations present a robust framework to assist rectal cancer specialists in providing precision treatment that ensures patient-centered care, thus positioning the needs of older rectal cancer patients at the core of a personalized care pathway.

Funding

No funding was received for the drafting of the manuscript, neither any author received any form of compensation from any public institutions or private companies to participate on this project.

Conflicts of interest

All authors decline any conflict of interest regarding to the specific topic of this manuscript.

Acknowledgement

Authors are highly grateful for the crucial help from the volunteers and the staff members at the Istituto Oncologico Romagnolo, for their support of this project and the enthusiasm they showed embracing it with the common goal to improve cancer care in the elderly.

Authors would also like to acknowledge the fruitful collaboration with the taTME International Registry group who graciously provided interim data on elderly rectal cancer patients from the registry.

References

[1] Lawler M, Selby P, Aapro MS, Duffy S. Ageism in cancer care: time to change the mindset. BMJ 2014;348. g1614.
[2] De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. EUROCARE-5 Working Group. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5 – a population-based study. Lancet Oncol 2014;15:23–34.
[3] National cancer intelligence Network. Major resections by cancer site, in England; 2006 to 2010. National cancer intelligence Network short report. http://www.ncin.org.uk/about_ncin/major_resections [Accessed March 13, 2018].
[4] Lawler M, Alsina D, Adams RA, Anderson AS, Brown G, Fearnhead NS, et al. Critical research gaps and recommendations to inform research prioritisation for more effective prevention and improved outcomes in colorectal cancer. Gut 2018 Jan;67(1):179–93.
[5] http://seer.cancer.gov/csr/1975_2014/ [Accessed March 13, 2018].
[6] www.cijfersoverkanker.nl The Netherlands cancer registry [Accessed March 13, 2018].
[7] Speelman AD, van Gestel YR, Rutten HJ, de Hingh IH, Lemmens VE. Changes in gastrointestinal cancer resection rates. Br J Surg 2015 Aug;102(9): 1114–22.
[8] van Gestel YR, Lemmens VE, de Hingh IH, Steevens J, Rutten HJ, Nieuwenhuijzen GA, et al. Influence of comorbidity and age on 1-, 2-, and 3-month postoperative mortality rates in gastrointestinal cancer patients. Ann Surg Oncol 2013 Feb;20(2):371–80.
[9] Papamichael D, Audisio RA, Glimelius B, de Gramont A, Glynne-Jones R, Haller D, et al. Treatment of colorectal cancer in older patients: international Society of Geriatric Oncology (SIOG) consensus recommendations 2013. Ann Oncol 2015 Mar;26(3):463–76.
[10] Balducci L. Aging, frailty, and chemotherapy. Cancer Contr 2007;14:7–12.
[11] Hamaker ME, Wildes TM, Rostoft S. Time to stop saying geriatric assessment is too time consuming. J Clin Oncol 2017;35(25):2871–4.
[12] Fagard K, Casaer J, Wolthuis A, Flamaing J, Milisen K, Lobelle JP, et al. Value of geriatric screening and assessment in predicting postoperative complications in patients older than 70 years undergoing surgery for colorectal cancer. J Geriatr Oncol 2017;8(5):320–7.
[13] Fagard K, Leonard S, Deschodt M, Devriendt E, Wolthuis A, Prenen H, et al. The impact of frailty on postoperative outcomes in individuals aged 65 and over undergoing elective surgery for colorectal cancer: a systematic review. J Geriatr Oncol 2016 Nov;7(6):479–91.
[14] Jones TS, Dunn CL, Wu DS, Cleveland Jr JC, Kile D, Robinson TN. Relationship between asking an older adult about falls and surgical outcomes. JAMA Surg 2013;148(12):1132–8.
[15] Baitar A, Van Fraeyenhove F, Vandebroek A, Droogh E, Galdermans D, Mebis J, et al. Evaluation of the Groningen Frailty Indicator and the G8 questionnaire as screening tools for frailty in older patients with cancer. J Geriatr Oncol 2013;4(1):32–8.
[16] Robinson TN, Wu DS, Pointer LF, Dunn CL, Moss M. Preoperative cognitive dysfunction is related to adverse postoperative outcomes in the elderly. J Am Coll Surg 2012;215(1):12–7.
[17] Huisman MG, van Leeuwen BL, Ugolini G, Montroni I, Spiliotis J, Stabilini C, et al. "Timed up & Go": a screening tool for predicting 30-day morbidity in onco-geriatric surgical patients? A multicenter cohort study. PLoS One 2014;9(1):e86863.
[18] Extermann M, Aapro M, Bernabei R, Cohen HJ, Droz JP, Lichtman S, et al. Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). Crit Rev Oncol Hematol 2005 Sep;55(3):241–52.
[19] Lawler M, Le Chevalier T, Banks I, Conte P, De Lorenzo F, Meunier F, et al. European cancer concord (ECC). A Bill of rights for patients with cancer in Europe. Lancet Oncol 2014;15(3):258–60.
[20] Lawler M, Le Chevalier T, Murphy Jr MJ, Banks I, Conte P, De Lorenzo F, et al. A catalyst for change: the European cancer Patient's Bill of Rights. Oncologist 2014;19(3):217–24.
[21] Junejo MA, Mason JM, Sheen AJ. Cardiopulmonary exercise testing for preoperative risk assessment before hepatic resection. Br J Surg 2012;99(8): 1097–104.
[22] West MA, Lythgoe D, Barben CP, Noble L, Kemp GJ, Jack S, et al. Cardiopulmonary exercise variables are associated with postoperative morbidity after major colonic surgery: a prospective blinded observational study. Br J Anaesth 2014;112(4):665–71.
[23] Moran J, Wilson F, Guinan E, McCormick P, Hussey J, Moriarty J. Role of cardiopulmonary exercise testing as a risk-assessment method in patients undergoing intra-abdominal surgery: a systematic review. Br J Anaesth 2016;116(2):177–91.
[24] Pecorelli N, Fiore Jr JF, Gillis C, Awasthi R, Mappin-Kasirer B, Niculiseanu P, et al. The six-minute walk test as a measure of postoperative recovery after colorectal resection: further examination of its measurement properties. Surg Endosc 2016;30(6):2199–206.
[25] Keeratichananont W, Thanadetsuntorn C, Keeratichananont S. Value of preoperative 6-minute walk test for predicting postoperative pulmonary complications. Ther Adv Respir Dis 2016;10(1):18–25.
[26] Moran J, Wilson F, Guinan E, McCormick P, Hussey J, Moriarty J. The preoperative use of field tests of exercise tolerance to predict postoperative outcome in intra-abdominal surgery: a systematic review. J Clin Anesth 2016;35:446–55.
[27] Mayo NE, Feldman L, Scott S, Zavorsky G, Kim DJ, Charlebois P, et al. Impact of preoperative change in physical function on postoperative recovery: argument supporting prehabilitation for colorectal surgery. Surgery 2011;150:505–14.
[28] Brunet J, Burke S, Grocott MP, West MA, Jack S. The effects of exercise on pain, fatigue, insomnia, and health perceptions in patients with operable advanced stage rectal cancer prior to surgery: a pilot trial. BMC Cancer 2017;17(1):153.
[29] http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-exercise-to-help-recovery-after-bowel-cancer-surgery-prepare-abc [Assessed March 3, 2018].
[30] Carli F, Charlebois P, Stein B, Feldman L, Zavorsky G, Kim DJ, et al. Randomized clinical trial of prehabilitation in colorectal surgery. Br J Surg 2010;97:1187–97.
[31] Minnella EM, Awasthi R, Gillis C, Fiore JF, Liberman AS, Charlebois P, et al. Patients with poor baseline walking capacity are most likely to improve their functional status with multimodal prehabilitation. Surgery 2016;160(4): 1070–9.
[32] West MA, Loughney L, Lythgoe D, Barben CP, Sripadam R, Kemp GJ, et al. Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study. Br J Anaesth 2015;114(2):244–51.
[33] Gillis C, Loiselle SE, Fiore Jr JF, Awasthi R, Wykes L, Liberman AS, et al. Prehabilitation with whey protein supplementation on perioperative functional exercise capacity in patients undergoing colorectal resection for cancer: a pilot double-blinded randomized placebo-controlled trial. J Acad Nutr Diet 2016;116(5):802–12.
[34] Huisman MG, Veronese G, Audisio RA, Ugolini G, Montroni I, de Bock GH, et al. Poor nutritional status is associated with other geriatric domain impairments and adverse postoperative outcomes in onco-geriatric surgical patients - a multicentre cohort study. Eur J Surg Oncol 2016;42(7):1009–17.
[35] Sandrucci S, Beets G, Braga M, Dejong K, Demartines N. Perioperative nutrition and enhanced recovery after surgery in gastrointestinal cancer patients. A position paper by the ESSO Task Force in collaboration with the ERAS Society (ERAS Coalition). Article in Press. Eur J Surg Oncol 2018;S0748–7983(18):30041–6. https://doi.org/10.1016/j.ejso.2017.12.010.
[36] Santa Mina D, Clarke H, Ritvo P, Leung YW, Matthew AG, Katz J, et al. Effect of total-body prehabilitation on postoperative outcomes: a systematic review and meta-analysis. Physiotherapy 2014;100:196–207.
[37] Li C, Carli F, Lee L, Charlebois P, Stein B, Liberman AS, et al. Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: a pilot study. Surg Endosc 2013;27:1072–82.
[38] Rutten HJ, den Dulk M, Lemmens VE, van de Velde CJ, Marijnen CA. Controversies of total mesorectal excision for rectal cancer in elderly patients. Lancet Oncol 2008;9(5):494–501.
[39] Walter LC, Covinsky KE. Cancer screening in elderly patients: a framework for individualized decision making. JAMA 2001;285(21):2750–6.
[40] Chen K, Cao G, Chen B, Wang M, Xu X, Cai W, et al. Laparoscopic versus open surgery for rectal cancer: a meta-analysis of classic randomized controlled trials and high-quality Nonrandomized Studies in the last 5 years. Int J Surg 2017;39:1–10.

[41] Bonjer HJ, Deijen CL, Abis GA, Cuesta MA, van der Pas MH, de Lange-de Klerk ES, et al. COLOR II Study Group. A randomized trial of laparoscopic versus open surgery for rectal cancer. N Engl J Med 2015;372(14):1324–32.
[42] Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, et al. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicenter, randomised controlled trial. Lancet 2005;365:1718–26.
[43] Nelson H, Sargent DJ, Wieand HS, Fleshman J, Anvari M, Stryker SJ, et al. Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med 2004;350(20):2050–9.
[44] Jeong SY, Park JW, Nam BH, Kim S, Kang SB, Lim SB, et al. Open versus laparoscopic surgery for mid-rectal or low-rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): survival outcomes of an open-label, non-inferiority, randomised controlled trial. Lancet Oncol 2014;15(7):767–74.
[45] Vennix S, Pelzers L, Bouvy N, Beets GL, Pierie JP, Wiggers T, et al. Laparoscopic versus open total mesorectal excision for rectal cancer. Cochrane Database Syst Rev 2014;4. CD005200.
[46] Zheng J, Feng X, Yang Z, Hu W, Luo Y, Li Y. The comprehensive therapeutic effects of rectal surgery are better in laparoscopy: a systematic review and meta-analysis. Oncotarget 2017;8(8):12717–29.
[47] Fleshman J, Branda M, Sargent DJ, Boller AM, George V, Abbas M, 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):1346–55.
[48] Stevenson AR, Solomon MJ, Lumley JW, Hewett P, Clouston AD, Gebski VJ, et al. Effect of laparoscopic-assisted resection vs open resection on pathological outcomes in rectal cancer: the ALaCaRT randomized clinical trial. JAMA 2015;314(13):1356–63.
[49] Koedam TWA, Bonjer HJ, Lacy AM. Pathologic outcomes of laparoscopic vs open mesorectal excision for rectal cancer. JAMA Surg 2017;152(10):986.
[50] Fleshman J, Branda ME, Sargent DJ, Boller AM, George VV, Abba MA, et al. Disease-free Survival and local recurrence for laparoscopic resection compared with open resection of stage II to III rectal cancer: follow-up results of the ACOSOG Z6051 randomized controlled trial. Ann Surg 2018, Aug 3. https://doi.org/10.1097/SLA.0000000000003002 [Epub ahead of print].
[51] Li Y, Wang S, Gao S, Yang C, Yang W, Guo S. Laparoscopic colorectal resection versus open colorectal resection in octogenarians: a systematic review and meta-analysis of safety and efficacy. Tech Coloproctol 2016;20(3):153–62.
[52] Lee L, Dietz DW, Fleming FJ, Remzi FH, Wexner SD, Winchester D, et al. Accreditation readiness in US multidisciplinary rectal cancer care: a survey of OSTRICH member institutions. JAMA Surg 2017 Dec 13. https://doi.org/10.1001/jamasurg.2017.4871.
[53] Monson JR, Probst CP, Wexner SD, Remzi FH, Fleshman JW, Garcia-Aguilar J, et al. Consortium for Optimizing the Treatment of Rectal Cancer (OSTRiCh). Failure of evidence-based cancer care in the United States: the association between rectal cancer treatment, cancer center volume, and geography. Ann Surg 2014;260(4):625–31.
[54] Archampong D, Borowski D, Wille-Jørgensen P, Iversen LH. Workload and surgeon's specialty for outcome after colorectal cancer surgery. Cochrane Database Syst Rev 2012;3:CD005391.
[55] Beets G, Sebag-Montefiore D, Andritsch E, Arnold D, Beishon M, Crul M, et al. ECCO essential requirements for quality cancer care: colorectal cancer. A critical review. Crit Rev Oncol Hematol 2017;110:81–93.
[56] Jayne D, Pigazzi A, Marshall H, Croft J, Corrigan N, Copeland J, et al. Effect of robotic-assisted vs conventional laparoscopic surgery on risk of conversion to open laparotomy among patients undergoing resection for rectal cancer: the ROLARR randomized clinical trial. JAMA 2017;318(16):1569–80.
[57] Kim MJ, Park SC, Park JW, Chang HJ, Kim DY, Nam BH, et al. Robot-assisted versus laparoscopic surgery for rectal cancer: a phase II open label prospective randomized controlled trial. Ann Surg 2018;267(2):243–51.
[58] Adamina M, Buchs NC, Penna M, Hompes R. St. Gallen Colorectal Consensus Expert Group. St. Gallen consensus on safe implementation of transanal total mesorectal excision. Surg Endosc 2017 Dec 12. https://doi.org/10.1007/s00464-017-5990-2 [Epub ahead of print].
[59] Penna M, Cunningham C, Hompes R. Transanal total mesorectal excision: why, when, and how. Clin Colon Rectal Surg 2017;30(5):339–45.
[60] Simillis C, Hompes R, Penna M, Rasheed S, Tekkis PP. A systematic review of transanal total mesorectal excision: is this the future of rectal cancer surgery? Colorectal Dis 2016;18(1):19–36.
[61] https://tatme.medicaldata.eu/ [Accessed January 22, 2018].
[62] http://www.lorec.nhs.uk [Accessed January 22, 2018].
[63] Bach P, Hill J, Monson JR, Simson JN, Lane L, Merrie A, et al. Association of Coloproctology of Great Britain and Ireland Transanal Endoscopic Microsurgery (TEM) Collaboration. A predictive model for local recurrence after transanal endoscopic microsurgery for rectal cancer. Br J Surg 2009;96(3):280–90.
[64] Kawachi H, Eishi Y, Ueno H, Nemoto T, Fujimori T, Iwashita A, et al. A three-tier classification system based on the depth of submucosal invasion and budding/sprouting can improve the treatment strategy for T1 colorectal cancer: a retrospective multicenter study. Mod Pathol 2015;28(6):872–9.
[65] Martin-Perez B, Andrade-Ribeiro GD, Hunter L, Atallah S. A systematic review of transanal minimally invasive surgery (TAMIS) from 2010 to 2013. Tech Coloproctol 2014;18(9):775–88.
[66] Hallam S, Messenger DE, Thomas MG. A systematic review of local excision after neoadjuvant therapy for rectal cancer: are ypT0 tumors the limit? Dis Colon Rectum 2016;59(10):984–97.
[67] Smith FM, Ahad A, Perez RO, Marks J, Bujko K, Heald RJ. Local excision techniques for rectal cancer after neoadjuvant chemoradiotherapy: what are we doing? Dis Colon Rectum 2017;60(2):228–39.
[68] Perez RO, Habr-Gama A, São Julião GP, Proscurshim I, Scanavini Neto A, Gama-Rodrigues J. Transanal endoscopic microsurgery for residual rectal cancer after neoadjuvant chemoradiation therapy is associated with significant immediate pain and hospital readmission rates. Dis Colon Rectum 2011;54(5):545–51.
[69] Borstlap WA, Coeymans TJ, Tanis PJ, Marijnen CA, Cunningham C, Bemelman WA, et al. Meta-analysis of oncological outcomes after local excision of pT1-2 rectal cancer requiring adjuvant (chemo)radiotherapy or completion surgery. Br J Surg 2016;103(9):1105–16.
[70] Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345:638–46.
[71] Bosset JF, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, Daban A, et al. Enhanced tumoricidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results – EORTC 22921. J Clin Oncol 2005;23:5620–7.
[72] Gérard JP, Conroy T, Bonnetain F, Bouché O, Chapet O, Closon-Dejardin MT, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol 2006;24(28):4620–5.
[73] Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. German Rectal Cancer Study Group. Preoperative vs postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731–40.
[74] Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet 2009;373:811–20.
[75] Aschele C, Cionini L, Lonardi S, Pinto C, Cordio S, Rosati G, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Oncol 2011;29(20):2773–80.
[76] Gerard JP, Glynne-Jones R, Blackstock W, Aschele C, van de Velde C. Radiochemotherapy in rectal cancer: the role of oxaliplatin. Colorectal Dis 2003;5(3):29–35.
[77] Rödel C, Grabenbauer GG, Papadopoulos T, Hohenberger W, Schmoll HJ, Sauer R. Phase I/II trial of capecitabine, oxaliplatin, and radiation for rectal cancer. J Clin Oncol 2003;21:3098–104.
[78] Deng Y, Chi P, Lan P, Wang L, Chen W, Cui L, et al. Modified FOLFOX6 with or without radiation versus fluorouracil and leucovorin with radiation in neoadjuvant treatment of locally advanced rectal cancer: initial results of the Chinese FOWARC multicenter, open-label, randomized three-arm phase III trial. J Clin Oncol 2016;34(27):3300–7.
[79] Schmoll H-J, Haustermans K, Price TJ, Nordlinger B, Hofheinz R, Daisne J-F, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in locally advanced rectal cancer: first results of the PETACC-6 randomized trial. Proc Am Soc Clin Oncol 2014;32. abstract 3501.
[80] Nilsson PJ, van Etten B, Hospers GA, Påhlman L, van de Velde CJ, Beets-Tan RG, et al. Short-course radiotherapy followed by neo-adjuvant chemotherapy in locally advanced rectal cancer–the RAPIDO trial. BMC Cancer 2013;13:279.
[81] Ngan SY, Burmeister B, Fisher RJ, Solomon M, Goldstein D, Joseph D, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol 2012;30(31):3827–33.
[82] François E, Azria D, Gourgou-Bourgade S, Jarlier M, Martel-Laffay I, Hennequin C, et al. Results in the elderly with locally advanced rectal cancer from the ACCOR12/PRODIGE 2 phase III trial: tolerance and efficacy. Radiother Oncol 2014;110(1):144–9.
[83] https://clinicaltrials.gov/ct2/show/NCT02551237 [Accessed December 18, 2017].
[84] Monson JR, Weiser MR, Buie WD, Chang GJ, Rafferty JF, Buie WD, et al. Standards practice task force of the american society of colon and rectal surgeons. Practice parameters for the management of rectal cancer (revised). Dis Colon Rectum 2013;56(5):535–50.
[85] Lefevre JH, Parc Y. Tiret E French research group of rectal cancer surgery (GRECCAR). Increasing the interval between neoadjuvant chemoradiotherapy and surgery in rectal cancer. Ann Surg 2015;262(6):e116.
[86] Pach R, Kulig J, Richter P, Gach T, Szura M, Kowalska T. Randomized clinical trial on preoperative radiotherapy 25 Gy in rectal cancer – treatment results at 5-year follow-up. Langenbeck's Arch Surg 2012;397(5). 801–710.
[87] Frykholm GJ, Påhlman L, Glimelius B. Combined chemo- and radiotherapy vs. radiotherapy alone in the treatment of primary, nonresectable adenocarcinoma of the rectum. Int J Radiat Oncol Biol Phys 2001;50(2):427–34.
[88] Appelt AL, Pløen J, Vogelius IR, Bentzen SM, Jakobsen A. Radiation dose-response model for locally advanced rectal cancer after preoperative chemoradiation therapy. Int J Radiat Oncol Biol Phys 2013;85(1):74–80.

[89] Habr-Gama A, Sabbaga J, Gama-Rodrigues J, São Julião GP, Proscurshim I, Bailão Aguilar P, 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):1109–17.
[90] Gerard JP, Chapet O, Ortholan C, Benezery K, Barbet N, Romestaing P. French experience with contact X-ray endocavitary radiation for early rectal cancer. Clin Oncol (R Coll Radiol) 2007;19(9):661–73.
[91] Papillon J. Intracavitary irradiation of early rectal cancer for cure. A series of 186 cases. Cancer 1975;36:696e701.
[92] Gerard JP, Chapet O, Romestaing P, Favrel V, Barbet N, Mornex F. Local excision and adjuvant radiotherapy for rectal adenocarcinoma T1-2 N0. Gastroenterol Clin Biol 2000;24(4):430e5.
[93] Frin AC, Evesque L, Gal J, Benezery K, François E, Gugenheim J, et al. Organ or sphincter preservation for rectal cancer. The role of contact X-ray brachytherapy in a monocentric series of 112 patients. Eur J Cancer 2017;72:124–36.
[94] Papillon J. Present status of radiation therapy in the conservative management of rectal cancer. Radiother Oncol 1990;17. 275e83.
[95] Gerard JP, Chapet O, Ramaioli A, Romestaing P. Long-term control of T2eT3 rectal adenocarcinoma with radiotherapy alone. Int J Radiat Oncol Biol Phys 2002;54(1). 142e9.
[96] https://clinicaltrials.gov/ct2/show/NCT02505750 [Accessed January 11, 2018].
[97] nice.org.uk/guidance/ipg532 Low energy contact X ray brachytherapy (the Papillon technique) for early stage rectal cancer [Accessed January 11, 2018].
[98] Corner C, Bryant L, Chapman C, Glynne-Jones R, Hoskin PJ. High-dose-rate afterloading intraluminal brachytherapy for advanced inoperable rectal carcinoma. Brachytherapy 2010;9(1):66–70.
[99] Beets GL, Figueiredo NL, Habr-Gama A, van de Velde CJ. A new paradigm for rectal cancer: organ preservation: introducing the international watch & wait database (IWWD). Eur J Surg Oncol 2015 Dec;41(12):1562–4.
[100] Habr-Gama A, Gama-Rodrigues J, Sao Juliao GP, Proscurshim I, Sabbagh C, Lynn PB, 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;88:822–8.
[101] Smith FM, Rao C, Oliva Perez R, Bujko K, Athanasiou T, Habr-Gama A, et al. Avoiding radical surgery improves early survival in elderly patients with rectal cancer, demonstrating complete clinical response after neoadjuvant therapy: results of a decision-analytic model. Dis Colon Rectum 2015;58(2):159–71.
[102] Dossa F, Chesney TR, Acuna SA, Baxter NN. A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2017;2(7):501–13.
[103] Sammour T, Price BA, Krause KJ, Chang GJ. Nonoperative management or 'watch and wait' for rectal cancer with complete clinical response after neoadjuvant chemoradiotherapy: a critical appraisal. Ann Surg Oncol 2017;24(7):1904–15.
[104] van der Valk MJM, Hilling DE, Bastiaannet E. Registry of 1009 patients in the International Watch & Wait database (IWWD) for rectal cancer: Results of clinical complete responders. Submitted.
[105] Gerard JP, Romestaing P, Chapet O. Radiotherapy alone in the curative treatment of rectal carcinoma. Lancet Oncol 2003;4(3):158–66.
[106] Sun Myint A, Smith FM, Gollins SW, Wong H, Rao C, Whitmarsh K, et al. Dose escalation using contact X-ray brachytherapy (Papillon) for rectal cancer: does it improve the chance of organ preservation? Br J Radiol 2017;90(1080):20170175.
[107] Appelt AL, Pløen J, Harling H. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. Lancet Oncol 2015 Aug;16(8):919–27.
[108] Cercek A, Goodman KA, Hajj C, Weisberger E, Segal NH, Reidy-Lagunes DL, et al. Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. J Natl Compr Cancer Netw 2014;12(4):513–9.
[109] Garcia-Aguilar J, Chow OS, Smith DD. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. Lancet Oncol 2015 Aug;16(8):957–66.
[110] 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;3. CD004078.
[111] Bosset JF, Calais G, Mineur L, Maingon P, Stojanovic-Rundic S, Bensadoun RJ, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. Lancet Oncol 2014;15(2):184–90.
[112] Sainato A, Cernusco Luna Nunzia V, Valentini V, De Paoli A, Maurizi ER, Lupattelli M, 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(2):223–9.
[113] Breugom AJ, van Gijn W, Muller EW, Berglund A, van den Broek CB, Fokstuen T, et al. Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomized phase III trial. Ann Oncol 2015;26(4):696–701.
[114] Breugom AJ, Swets M, Bosset JF, Collette L, Sainato A, Cionini L, et al. Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. Lancet Oncol 2015;16(2):200–7.
[115] Bujko K, Glimelius B, Valentini V, Michalski W, Spalek M. Postoperative chemotherapy in patients with rectal cancer receiving preoperative radio(-chemo)therapy: a meta-analysis of randomized trials comparing surgery ± a fluoropyrimidine and surgery + a fluoropyrimidine ± oxaliplatin. Eur J Surg Oncol 2015;41(6):713–23.
[116] NCCN clinical practice guidelines in Oncology rectal cancer 3. 2017. Available at: http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. [Accessed 29 December 2017].
[117] McCleary NJ, Meyerhardt JA, Green E. Impact of age on the efficacy of newer adjuvant therapies in patients with stage II/III colon cancer: findings from the ACCENT database. J Clin Oncol 2013;31(20):2600–6.
[118] Shi Q, Flowers CR, Hiddemann W. Thirty-Month complete response as a surrogate end point in first-line follicular lymphoma therapy: an individual patient-level analysis of multiple randomized trials. J Clin Oncol 2017;35(5):552–60.
[119] Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rödel C, Cervantes A, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28(suppl_4):iv22–40.
[120] Papamichael D, Audisio RA, de Gramont A, Glynne-Jones R, Haller D. Treatment of colorectal cancer in older patients: international Society of Geriatric Oncology (SIOG) consensus recommendations 2013. Ann Oncol 2015;26(3):463–76.
[121] Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. Epidemiology and management of liver metastases from colorectal cancer. Ann Surg 2006;244(2):254–9.
[122] Adam R, de Gramont A, Figueras J, Kokudo N, Kunstlinger F, Loyer E, et al. Managing synchronous liver metastases from colorectal cancer: a multidisciplinary international consensus. Cancer Treat Rev 2015;41(9):729–41.
[123] https://livermetsurvey-arcad.org/ Accessed December 20, 2017.
[124] Adam R, Frilling A, Elias D, Laurent C, Ramos E, Capussotti L, et al. Liver resection of colorectal metastases in elderly patients. Br J Surg 2010;97:366–76.
[125] Albertsmeier M, Engel A, Guba MO, Stintzing S, Schiergens TS, Schubert-Fritschle G, et al. Synchronous colorectal liver metastases: focus on the elderly: an Effectiveness Study from Routine Care. Langenbeck's Arch Surg 2017;402(8):1223–32.
[126] De'Liguori Carino N, van Leeuwen BL, Ghaneh P, Wu A, Audisio RA, Poston GJ. Liver resection for colorectal liver metastases in older patients. Crit Rev Oncol Hematol 2008;67:273–8.
[127] Nagano Y, Nojiri K, Matsuo K, Tanaka K, Togo S, Ike H, et al. The impact of advanced age on hepatic resection of colorectal liver metastases. J Am Coll Surg 2005;201:511–6.
[128] Cook EJ, Welsh FSK, Chandrakumaran K, John TG, Rees M. Resection of colorectal liver metastases in the elderly: does age matter? Colorectal Dis 2012;14(10):1210–6.
[129] Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016;27:1386–422.
[130] http://www.nice.org.uk/guidance/cg131/chapter/guidance National institute for health and care excellence. Colorectal cancer: the diagnosis and management of colorectal cancer. Accessed December 29, 2017.
[131] Pathak S, Nunes QM, Daniels IR, Smart NJ, Poston GJ, Påhlman L. Rectal cancer with synchronous liver metastases: do we have a clear direction? Eur J Surg Oncol 2015;41(12):1570–7.
[132] Wilson I, Paul Barrett M, Sinha A, Chan S. Predictors of in-hospital mortality amongst octogenarians undergoing emergency general surgery: a retrospective cohort study. Int J Surg 2014;12(11):1157–61.
[133] Zattoni D, Montroni I, Saur NM, Garutti A, Bacchi Reggiani ML, Galetti C, et al. Frailty screening in emergency general surgery. Effectiveness of the Flemish version of Triage Risk Screening Tool (fTRST) in predicting early and long-term morbidity and mortality among elderly patients. Submitted to the Journal of the American Geriatrics Society.
[134] Cirocchi R, Farinella E, Trastulli S, Desiderio J, Listorti C, Boselli C, et al. Safety and efficacy of endoscopic colonic stenting as a bridge to surgery in the management of intestinal obstruction due to left colon and rectal cancer: a systematic review and meta-analysis. Surg Oncol 2013 Mar;22(1):14–21.
[135] Han EC, Ryoo S, Park BK, Park JW, Lee SY, Oh HK, et al. Surgical outcomes and prognostic factors of emergency surgery for colonic perforation: would fecal contamination increase morbidity and mortality? Int J Colorectal Dis 2015;30:1495–504.
[136] Patel SS, Nelson R, Sanchez J, Lee W, Uyeno L, Garcia-Aguilar J, et al. Elderly patients with colon cancer have unique tumor characteristics and poor survival. Cancer 2013;119(4):739–47.
[137] Baxter NN, Virnig DJ, Rothenberger DA, Morris AM, Jessurun J, Virnig BA. Lymph node evaluation in colorectal cancer patients: a population-based study. J Natl Cancer Inst 2005;97(3):219–25.
[138] Khan H, Olszewski AJ, Somasundar P. Lymph node involvement in colon cancer patients decreases with age; a population based analysis. Eur J Surg Oncol 2014;40(11):1474–80.
[139] Amri R, Bordeianou LG, Berger DL. The conundrum of the young colon cancer patient. Surgery 2015;158(6):1696–703.

[140] Jover R, Nguyen TP, Pérez-Carbonell L, Zapater P, Payá A, Alenda C, et al. 5-Fluorouracil adjuvant chemotherapy does not increase survival in patients with CpG island methylator phenotype colorectal cancer. Gastroenterology 2011;140(4):1174–81.
[141] Tahara T, Yamamoto E, Suzuki H, Maruyama R, Chung W, Garriga J, et al. Fusobacterium in colonic flora and molecular features of colorectal carcinoma. Cancer Res 2014;74(5):1311–8.
[142] Amitay EL, Werner S, Vital M, Pieper DH, Höfler D, Gierse IJ, et al. Fusobacterium and colorectal cancer: causal factor or passenger? Results from a large colorectal cancer screening study. Carcinogenesis 2017;38(8):781–8.
[143] Forsmo HM, Erchsen C, Rasdal A, Körner H, Pfeffer F. Enhanced recovery after Colorectal Surgery (ERAS) in elderly patients is feasible and achieves similar results as in younger patients. Gerontol Geriatr Med 2017;3:1–8.
[144] Bagnall NM, Malietzis G, Kennedy RH, Athanasiou T, Faiz O, Darzi A. A systematic review of enhanced recovery care after colorectal surgery in elderly patients. Colorectal Dis 2014;16:947–56.
[145] Launay-Savary MV, Mathonnet M, Theissen A, Ostermann S, Raynaud-Simon A, Slim K. Are enhanced recovery programs in colorectal surgery feasible and useful in the elderly? A systematic review of the literature. J Vis Surg 2017;154:29–35.
[146] Halabi WJ, Kang CY, Nguyen VQ, Carmichael JC, Mills S, Stamos MJ, et al. Epidural analgesia in laparoscopic colorectal surgery: a nationwide analysis of use and outcomes. JAMA Surg 2014;149(2):130–6.
[147] Chen M, Song X, Chen LZ, Lin ZD, Zhang XL. Comparing mechanical bowel preparation with both oral and systemic antibiotics versus mechanical bowel preparation and systemic antibiotics alone for the prevention of surgical site infection after elective colorectal surgery: a meta-analysis of randomized controlled clinical trials. Dis Colon Rectum 2016;59(1):70–8.
[148] Banks E, Byles JE, Gibson RE, Rodgers B, Latz IK, Robinson IA, et al. Is psychological distress in people living with cancer related to the fact of diagnosis, current treatment or level of disability? Findings from a large Australian study. Med J Aust 2010;193:S62–7.
[149] Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. N Engl J Med 2007;357(8):762–74.
[150] Battersby NJ, Juul T, Christensen P, Janjua AZ, Branagan G, Emmertsen KJ, et al. Predicting the risk of bowel-related quality-of-life impairment after restorative resection for rectal cancer: a multicenter cross-sectional study. Dis Colon Rectum 2016;59(4):270–80.
[151] Hupkens BJP, Martens MH, Stoot JH, Berbee M, Melenhorst J, Beets-Tan RG, et al. Quality of life in rectal cancer patients after chemoradiation: watch-and-wait policy versus standard resection - a matched-controlled study. Dis Colon Rectum 2017;60(10):1032–104.
[152] Jonker FH, Tanis PJ, Coene PP, Gietelink L, van der Harst E. Dutch Surgical Colorectal Audit Group. Comparison of a low Hartmann's procedure with low colorectal anastomosis with and without defunctioning ileostomy after radiotherapy for rectal cancer: results from a national registry. Colorectal Dis 2016;18(8):785–92.
[153] Orsini RG, Thong MS, van de Poll-Franse LV, Slooter SD, Nieuwenhuijzen GA, Rutten HJ, et al. Quality of life of older rectal cancer patients is not impaired by a permanent stoma. Eur J Surg Oncol 2013;39(2):164–70.
[154] Rullier E, Le Toux N, Laurent C, Garrelon JL, Saric Parneix M. Loop ileostomy versus loop colostomy for defunctioning low anastomoses during rectal cancer surgery. World J Surg 2001;25(3):274–7.
[155] Zerillo JA, Schouwenburg MG, van Bommel ACM, Stowell C, Lippa J, Bauer D, et al. Colorectal cancer working group of the international Consortium for health outcomes measurement (ICHOM). An international collaborative standardizing a comprehensive patient-centered outcomes measurement set for colorectal cancer. JAMA Oncol 2017;3(5):686–94.
[156] http://www.ichom.org/ [Assessed December 7, 2017].
[157] Audisio RA, Pope D, Ramesh HS. Shall we operate? Preoperative assessment in elderly cancer patients (PACE) can help. A SIOG surgical task force prospective study. Crit Rev Oncol Hematol 2008;65(2):156–63.
[158] Huisman MG, Audisio RA, Ugolini G, Montroni I, Vigano A, Spiliotis J, et al. Screening for predictors of adverse outcome in onco-geriatric surgical patients: a multicenter prospective cohort study. Eur J Surg Oncol 2015;41(7):844–51.
[159] Pędziwiatr M, Pisarska M, Major P, Grochowska A, Matłok M, Przęczek K, et al. Laparoscopic colorectal cancer surgery combined with enhanced recovery after surgery protocol (ERAS) reduces the negative impact of sarcopenia on short-term outcomes. Eur J Surg Oncol 2016;42(6):779–87.
[160] Jaklitsch MT. "How am I doing? Just ask me!" the usefulness of patient self-reported quality of life in thoracic surgery. J Thorac Cardiovasc Surg 2015;149(3):663–4.
[161] Fernando HC, Landreneau RJ, Mandrekar SJ, Nichols FC, DiPetrillo TA, Meyer BF, et al. Analysis of longitudinal quality-of-life data in high-risk operable patients with lung cancer: results from the ACOSOG Z4032 (Alliance) multicenter randomized trial. J Thorac Cardiovasc Surg 2015;149:718–26.
[162] Himmelstein DU, Thorne D, Warren E, Woolhandler S. Medical bankruptcy in the United States, 2007: results of a national study. Am J Med 2009;122(8):741–6.
[163] Ramsey S, Blough D, Kirchhoff A, Kreizenbeck K, Fedorenko C, Snell K, et al. Washington State cancer patients found to be at greater risk for bankruptcy than people without a cancer diagnosis. Health Aff (Millwood) 2013;32(6):1143–52.
[164] Lang K, Lines LM, Lee DW, Korn JR, Earle CC, Menzin J. Lifetime and treatment-phase costs associated with colorectal cancer: evidence from SEER-Medicare data. Clin Gastroenterol Hepatol 2009;7(2):198–204.
[165] Lin HS, Watts JN, Peel NM, Hubbard RE. Frailty and post-operative outcomes in older surgical patients: a systematic review. BMC Geriatr 2016;16(1):157. 31.
[166] Jensen CC, Prasad LM, Abcarian H. Cost-effectiveness of laparoscopic vs open resection for colon and rectal cancer. Dis Colon Rectum 2012;55(10):1017–23.
[167] Ramji KM, Cleghorn MC, Josse JM, MacNeill A, O'Brien C, Urbach D, et al. Comparison of clinical and economic outcomes between robotic, laparoscopic, and open rectal cancer surgery: early experience at a tertiary care center. Surg Endosc 2016;30(4):1337–43.
[168] Rao C, Sun Myint A, Athanasiou T, Faiz O, Martin AP, Collins B, et al. Avoiding radical surgery in elderly patients with rectal cancer is cost-effective. Dis Colon Rectum 2017;60(1):30–42.
[169] Näppä U, Lindqvist O, Rasmussen BH, Axelsson B. Palliative chemotherapy during the last month of life. Ann Oncol 2011;22(11):2375–80.
[170] Porter ME, Teisberg EO. Redefining health care: creating value-based competition on results. Boston: Harvard Business School Press; 2006.