Evidence and research perspectives for surgeons in the European Rectal Cancer Consensus Conference (EURECA-CC2)

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**PURPOSE: Although surgery remains the most important treatment of rectal cancer, the management of this disease has evolved to become more multidisciplinary to offer the best clinical outcome. The International Conference on Multidisciplinary Rectal Cancer Treatment: Looking for an European Consensus' (EURECA-CC2) had the due to identify the degree of consensus that could be achieved across a wide range of topics relating to the management of rectal cancer helping shape future programs, investigational protocols and guidelines for staging and treatment throughout Europe.
MATERIALS AND METHODS: Consensus was achieved using the Delphi method. Eight chapters were identified: epidemiology, diagnostics, pathology, surgery, radiotherapy and chemotherapy, treatment toxicity and quality of life, follow-up, and research questions. Each chapter was subdivided by topic, and a series of statements were developed. Each committee member commented and voted, sentence by sentence three times. Sentences which did not reach agreement after voting round # 2 were openly debated during the Conference in Perugia (Italy) December 2008. The Executive Committee scored percentage consensus based on three categories: "large consensus", "moderate consensus", "minimum consensus".
RESULTS: The total number of the voted sentences was 207. Of the 207, 86% achieved large consensus, 13% achieved moderate consensus, and only 3 (1%) resulted in minimum consensus. No statement was disagreed by more than 50% of members. All chapters were voted on by at least 75% of the members, and the majority was voted on by 85%.
CONCLUSIONS: This Consensus Conference represents an expertise opinion process that may help shape future programs, investigational protocols, and guidelines for staging and treatment of rectal cancer throughout Europe. In spite of substantial progress, many research challenges remain.**

Key words: rectal cancer, combined modality treatment, preoperative radiotherapy, intraoperative radotherapy, surgery, postoperative radiotherapy, chemotherapy, toxicity, research, treatment outcome

INTRODUCTION

In the last two decades we have seen important advances in the way patients with rectal cancer are investigated and treated. Several European randomized studies have been recently published analyzing different adjuvant approaches and pointing the implemented imaging contribute, histopathological assessment of the resected specimen and improvement in surgical techniques, as main characters of this multidisciplinary management[1]. In order to help shape clinical practice based on best scientific evidence from the literature, the International Conference on "Multidisciplinary Rectal Cancer Treatment: Looking for an European Consensus" (EURECA-CC2) was organized in Italy under the endorsement of European Society of Medical Oncology (ESMO), European Society of Surgical Oncology (ESSO), and European Society of Therapeutic Radiation Oncology (ESTRO). The goal of this consensus conference was to help shape future programs, investigational protocols, and guidelines for staging and treatment of rectal cancer throughout Europe[2].

The aim of this manuscript is to focus on the main recommendations addressed in this Consensus to support the daily practice of surgeons.

MATERIAL AND METHODS:

The conference[2] was organized with the endorsement of the three European Societies by the Radiation Therapy Department of the Catholic University of Rome and the Perugia's University, that have already organized the first

Consensus Conference[3] and are responsible for the development of an ESTRO Multidisciplinary Teaching Course managed with ESSO and ESMO. An Executive Committee was settled including two delegates from each of the three societies, two of the journal *Radiotherapy & Oncology,* a radiologist, an epidemiologist, and a pathologist who have already participated in the multidisciplinary ESTRO teaching course. Afterwards, the Executive Committee established, on majority vote, a Scientific Committee, with experts who were involved in the major European published trials.

Consensus was achieved using the Delphi method[4]. Version 1 was created by the Executive Committee. The document was available to all committee members as a web based document customized for the consensus process. Each member commented and voted, sentence by sentence. In addition, references to each sentence were presented and members were able to add additional ones. A consensus score was agreed between the experts. The outcome of each vote by web (% agree, % disagree, and new comments and references) was available to each member prior to the next vote. Another voting was performed during the conference in Perugia (Italy) from 11 December through 13 December 2008. The Meeting was open to everyone interested in the topic. Sentences which did not reach agreement after the previous voting were openly debated by attendees at each session and the audience had the opportunity to ask further questions. Following the conclusion of the Perugia meeting the voting of the final document occurred. The final text was reviewed and collated by 2 experts (without changing the outcome of the votes).

The total number of voted sentences was 207. Of the 207, 86% achieved large consensus, 13% achieved moderate consensus, and only 3 (1%) resulted in minimum consensus. The sentences with moderate or minimum consensus are identified in the text.

The literature update since the conference has not undergone the consensus process.

RESULTS:

Surgery remains the most important treatment of rectal cancer although it's proved that several adjuvant treatments can improve the outcome in particular stages[18,29,20,21]. Loco-regional tumor control in rectal cancer surgery has changed dramatically during the past 10–15 years. This started with discussions of the value of more exact surgery and precise procedures following embryonic planes. The role of the main surgical procedures for early, intermediate and locally advanced lesions is examined[5].

EARLY LOCALIZED TUMORS

Early tumors are neoplasms limited to the rectal wall (c/p T1-2 N0 M0). They represent 3-5% of rectal cancers, and include small, exophytic, mobile tumors without adverse pathologic factors (i.e., high grade, blood or lymphatic vessel invasion, colloid histology, or the penetration of tumor into or through the bowel wall) and can be adequately treated with a variety of local therapies.

The role of mucosectomy alone

With a moderate consensus it was agreed that early carcinomas limited to T1sm1, with well/good differentiated tumors, no evidence of blood or lymphatic vessel invasion and negative margins, can be safely and effectively resected by endoscopic mucosal resection (EMR)[6]. However, there is not enough evidence to recommend this procedure as standard treatment. After EMR, pathologic analysis of submucosa infiltration is essential to assess the completeness of the resection[6].

The role of local excision alone

Patients with T1 small, exophytic, mobile tumors without adverse pathologic factors (i.e., high grade, blood or lymphatic vessel invasion, sm[3]) can be adequately treated with local excision alone, preferably a Transanal Endoscopy Microsurgery (TEM) procedure[7,8]. In early localized tumors TEM may emerge as a technical reliable option to remove the full thickness rectal wall and to evaluate the completeness of the removed specimen[7,8].

With a minimum consensus it was agreed that technically, the use of local excision requires that there is a non obstructing tumour and its dimension is less than half of the lumen and/or size less than 4 cm of diameter[8].

The specimen after local excision has to be carefully analyzed to evaluate its integrity, the depth of invasion in the bowel wall, the absence of margin infiltration both laterally and deeply and the presence of adverse pathologic factors: high grade, blood or lymphatic vessel invasion.

When patients with early, localized tumor have undergone a local surgical procedure, they can be at risk for disease recurrence in the rectal wall or in the local nodes depending to the initial stage. Patients with pT1 tumors without adverse pathologic factors have a low rate of local failure (5-10%) and positive nodes (%) and usually do not need adjuvant therapy. However, there is a lack of evidence to demonstrate equivalent outcomes to radical surgery[9]. On the contrary, when adverse pathologic factors are present (involved margins, sm[3], poor differentiation, lymph vessel invasion) or the tumor invades into or through the muscularis propria (pT2-3), the local failure rate increases to at least 17% and the incidence of positive nodes to above 10% and adjuvant treatments are recommended[10,11].

Patients with pT1 tumors (after local excision) with any of the adverse pathologic factors mentioned above or with any doubt about quality of the local excision procedure have to undergo a resection of the entire rectum. Postoperative radio(chemo)therapy could be considered for compromised general conditions or if the patient refuses surgery[9,12].

The optimal treatment of a pT2 tumor after a local excision is not clear, since large randomized trials are not available. Local excision alone is insufficient and radical surgery is therefore recommended. Postoperative radio(chemo)therapy is a reasonable alternative when adverse prognostic factors (involved margins, poorly differentiated tumor and lymphovascular invasion) are absent and the patient has co-morbidity or refuses surgery. However, in se-

ries with long term follow-up, the pelvic failure rates are 18-25%[13], i.e. much higher than if radical surgery is done. Local excision is associated with less anorectal and genitourinary dysfunction and better quality of life compared with radical surgery. Salvage of local failures is possible after local excision. In half of the patients, with local failure after local excision +/- radio(chemo)therapy, local control can be achieved with salvage abdominoperineal resection (APR). Close follow up to detect early relapse and then perform curative resection is recommended. Local recurrence after local excision and postoperative radio (chemo)therapy tends to occur late (median about 5 years)

At least half of the patients who undergo salvage abdominoperineal resection (APR) for local recurrence after local excision and /or radiotherapy can be cured: however, if those patients had been offered definitive surgery as the first treatment, cure rates would be higher.

The role of standard resection

Patients who have received standard Total Mesorectal Excision (TME) surgery for an early, localized tumor do not need further therapy.

cT2 rectal cancers and cT1 with high risk factors are adequately treated with standard resection with TME alone providing the nodes are negative (N0).

When high risk predictive factors are present in operative specimen, a standard resection done a few weeks after a local excision, does not compromise the oncological results compared to patients who undergo a standard resection as the initial treatment. However, depending on the tumor location, this may compromise the ability to perform a sphincter sparing operation.

The role of radiotherapy alone

External radiotherapy alone in early rectal cancer might be a feasible alternative to local excision in patients with poor medical condition or who refuse any surgical treatment. However the evidence is limited and definitive recommendation requires further studies.

The role of preoperative radio(chemo)therapy

Preoperative radiotherapy in clinically operable cT2N0 rectal cancers 15 cm from anal verge results in an even lower risk of local failure, but is usually not indicated since the absolute risk of a local failure in these early tumors is very low, provided very high quality staging and surgery can be performed. Recommendation for its use depends on interdisciplinary decision making and institutional preferences.[14,15].

With a moderate consensus it was agreed that patients, who are either medically inoperable or refuse radical surgery, can receive preoperative radiation followed by local excision. Patient who not fit for prolonged radio (chemo) therapy can receive short course radiotherapy alone and delayed surgery. This approach is reported in only a few series and its use must be limited to only this subset of patients[16,17].

INTERMEDIATE STAGE (STAGE II-III RESECTABLE)

Intermediate tumors are defined as neoplasms extending beyond the rectal wall but without unresectable infiltration to surrounding organs (c/p t3-4 or n1-2 m0).

The role of the TME in the treatment of patients with intermediate resectable rectal cancer has been critical in the last 10-15 years changing dramatically the loco-regional control although an adjuvant treatment is recommended to reduce the local recurrence[18,19,20,21] and improve the overall survival[18,19].

The role of TME

Local relapses after TME alone for pT3-4 N1-2 of the medium or low rectal cancer still range between 15-21% in randomized trials[14,15].

The efficacy of TME is closely related to the training and the volume of cases per year of each surgeon. The surgeon represents one of the major prognostic factors for the treatment of rectal cancer[22].

Population-based registries show that improvements in outcome after TME occur mainly in younger patients. Furthermore, 6-month postoperative mortality is significantly increased in elderly patients (or = 75 years of age) compared with younger patients (75 years of age). For elderly patients who have good physical and mental status, the same treatment that is given to younger patients is appropriate. In contrast, for those with diminished physiological reserves and comorbid conditions, alternative treatments that keep surgical trauma to a minimum and optimize the use of radiotherapy might be more suitable[23,24].

With a minimum consensus it was agreed that, by using anterior resection with TME radical surgery can be achieved also in distal rectal cancer since rectal cancer rarely grows more than a few millimeters distally from the macroscopic margin in the bowel wall, indicating that a distal margin of 1 cm will probably be sufficient for local cure in terms of intramural spread. If such an approach is considered, frozen section (during surgical intervention) is mandatory.

In patients with tumors in the middle or distal third of the rectum, lymph nodes or other tumors deposits can be found in the mesorectum up to 4 cm distally from the tumor. Complete removal of mesorectum distally is always indicated in these tumors locations[25,26].

In tumors located in the upper rectum a Partial Mesorectal Excision (PME) extending 5 cm below lower tumor margin and sparing the distal part of the mesorectum is feasible. However, definitive evidence for this is not available.

The role of Radiotherapy

Two different treatment modalities can be used in patients with intermediate stage resectable rectal cancer. First of all a preoperative radio(chemo)therapy followed by surgery +/- postoperative chemotherapy and then an initial surgery followed by postoperative combined modality therapy, if the tumor is pT3-4 and/or N1-2.[1].

Four meta-analyses about the value of radio (chemo) therapy (pre- or postoperatively) report partly conflicting results[18,19,20,21]. All of them reveal a decrease in local recurrence rates. The analysis by Camma et al.[18] and the Collaborative Colorectal Cancer Group[19] reported a survival advantage, whereas the analysis by Munro and Bentley[20] did not. The Swedish Council of Technology Assessment in Health Care (SBU) performed a systematic review of radiation therapy trials[21] and reported that survival is improved by about 10% using preoperative radiotherapy at adequate doses. The partly conflicting results are at least partly due to inabilities to recognize overlaps between some of the trials.

Preoperative and postoperative therapies have been compared in randomized trials[14,27,28]. The German Rectal Cancer Trial[27] showed fewer local recurrences and less acute and late toxicity, but no survival benefit with preoperative therapy. A preoperative short-course of radiation therapy was compared in two different trials with a long-course RT alone[28] and with a long-course chemoradiation[14], respectively. More favorable results for the subsets with a high-risk of recurrence were seen in the preoperative groups.

At the present time, given the improved local control, and acute and long-term toxicity profile, patients with cT3 rectal cancer who require additional therapy to surgery (chemoradiation or short course radiotherapy) should receive it preoperatively[14,21,27,28].

The APR planes

Pathological studies of the CRM at the level of the anorectal junction and anal sphincters show high risk of tumor involvement[29].

The quality of surgery in the levator/anal canal area below the mesorectum varies between surgeons who may operate in different surgical planes: intrasphincteric/ submucosal plane, sphincteric plane and levator plane[1,30,31].

With an APR there are two planes: one for the mesorectum and one for the anal canal. It is crucial to have the correct strategy when an APR is performed. The dissection from above has to be stopped before entering the levator plane. The next step is to dissect from below outside the sphincteric plane and by doing so finally divide the levators from below. With this technique a waist in the specimen, ar an "apple core" just at the place of the tumor, can be avoided and prevent the specimen from having positive CRM[25,31,32,33].

The value of sphincter/organ saving treatment

Sphincter preservation is usually considered when tumor is found in the lower third of the rectum. Since the mesorectum decreases in size close to the top of the anal canal, tumors arising in this area can easily invade surrounding structures, such as the internal and external sphincters and the levator muscles. This is common if the depth of invasion is beyond T2. Consequently, it is crucial to ensure that the pelvic floor is free from tumor if a locoregional curative procedure, with the sphincters intact, is to be performed in very low rectal cancers.

A non-significant improvement in sphincter saving surgery was reported in a French study which randomized patients to surgery within 2 weeks after completion of radiation therapy, compared with 6 to 8 weeks. The long interval between preoperative irradiation and surgery provided increased tumor down staging with no detrimental effect on toxicity, but did not result in significant differences in long-term local control or survival[34]. None of the other randomized trials nor meta-analyses of the trials support the idea of increased possibilities for sphincter preservation after radio(chemo)therapy[21,35,36].

Sphincter preservation without good function is of questionable benefit. Based upon reports, most patients are considered to have an acceptable to good function but as many as 20% will be more or less incontinent, not only for flatus or loose stool but also for solid stool. For some elderly and immobile patients a stoma can even be preferable to a preserved but moderately functioning sphincter. Based upon questionnaire studies stoma patients, as a group, do not have a worse quality of life than patients treated with sphincter preservation.

Cultural differences are significant. For example a stoma may be more or less disastrous for the patient than a local failure in southern parts of Europe and the Arabic world. Therefore, many patients from the Mediterranean areas will accept poor bowel function in preference to a stoma, and will also accept using diapers[37].

T4 UNRESECTABLE RECTAL CANCER

Locally advanced tumors are defined as neoplasms extending beyond the rectal wall with unresectable infiltration to surrounding organs or structures, and/or perforation of the visceral peritoneum (c/p T4 N0 -2 M0).

The role of long-course pre-operative radio(chemo)therapy

All patients with primarily unresectable disease should receive preoperative chemoradiation. This includes radiation in the range of 50–54 Gy plus 5FU-based chemotherapy with the goal of increasing the chances of R0 resectability[21,38]. Compared to the same radiotherapy alone, chemoradiation improved in a randomized trial local and systemic tumor control38. Given the limitation of the total radiation dose which can be delivered to the bulky tumor in the pelvis and the frequent problem of local recurrence, the surgeon should be "aggressive" and not risk leaving microscopic residual tumor. Extended surgery to the infiltrated organ(s) should be considered even if there is a favorable response after preoperative therapy[38].

An alternative strategy under clinical evaluation for patients who are not medically able to receive long-course chemoradiation is short-course RT followed by delayed surgery[16,17].

The role of radiotherapy intensification (altered fractionation, IORT)

Although 50-90% of patients will be able to undergo a resection with negative margins, depending on the degree of tumor fixation, many still develop a local recurrence.

To reduce this concomitant or sequential boosts can be delivered in the preoperative setting with the goal of increasing the dose. However, doses above about 50 Gy may be associated with a higher complication rates. Positive evidence of the role of higher doses is still to be confirmed in randomized studies[39,40,41.42]

To increase local control of unresectable rectal cancer a large single dose (10 - 20 Gy) of radiation by electron beam or brachytherapy (Intraoperative RT or IORT) can be delivered to the tumor bed. Many North American and European single institution studies suggest a favorable local control rate in patients who also have positive margins or microscopic residual disease[43,44]. However, not all series show a benefit.[45]

The results (and recommended dose) of IORT depend on whether the margins of resection are negative or whether there is microscopic or gross residual disease. IORT does not compensate a suboptimal surgery. IORT-related toxicity increases with IORT doses 18-20 Gy.

The role of extended surgery

A rectal cancer is defined as unresectable if a potentially curative surgical resection is not feasible. The evaluation of resectability depends on the extent of the operation the surgeon is able to perform as well as the degree of morbidity the patient is willing to accept.

The heterogeneity of the presentation and a definition of resectability based on clinical rather than objective criteria make it difficult to compare between series[46].

It is important for the surgeon to recognize preoperatively the extent of tumor invasion into other organs and/or the pelvic sidewall for documentation prior to preoperative radiation and to establish a plan for *en bloc* resection[47].

From the surgical point of view, R0 resection represents the most important parameter to achieve the best long-term outcome in T4 rectal cancer in terms of overall survival, DF-SVV and local control.

After total pelvic exenteration, the morbidity rate is higher than 50% and includes: pelvic abscess or fistulas, sepsis, leak of the perineal suture, anastomotic leak, perineal wound infection, intestinal obstruction and pulmonary disease. Physiological age and absence of co-morbidities appear to be more acceptable when selecting patients for exenteration than chronological age[48].

When partial resection of involved organs enables removal of all tumor (*en bloc* resection), a limited resection (without total pelvic exenteration) could be performed[47]

With a minimum consensus it was agreed that when the trigone of bladder or the prostate is involved, Total Pelvic Extenteration is recommended for all patients, irrespective of the response to preoperative treatment. This involves the removal of the rectum, bladder, lower ureters, internal genital organs and bilateral internal iliac vessels en bloc to achieve a negative margin and complete clearance of lymphatics[47].

A R0 total pelvic exenteration is potentially curative operation for patients with advanced pelvic cancer: 5-year overall survival is acceptable (52%-60%)[48], but it has high morbidity and impaired quality of life.

Even if radical resection includes an extended lymphadenectomy with high ligation of the inferior mesenteric artery and lateral nodes dissection, the role of lateral lymphadenectomy has yet to be determined. Surgery extended to lateral pelvic nodes is associated with significant morbidity[47,49,50,51].

The role of adjuvant chemotherapy

The high incidence of metastases in these patients is the rationale for the use of adjuvant chemotherapy after chemoradiation and surgery. However the definitive study in patients with rectal cancer is not available[38,52,53].

RESEARCH SCENARIO

In this time of changing therapeutic approaches, a common standard for large heterogeneous patient groups will likely be substituted by more individualised therapies. It will depend on new evidence of more tailored diagnosis, surgery, radiotherapy and chemotherapy. The main questions addressed by ongoing research in these different fields are outlined.

Organ preservation

After preoperative chemoradiation a variable percentage of pathological complete response (pCR) specimens is reported. Although some series show no correlation, many series report that patients who achieve a pCR following preoperative chemoradiation have improved long-term outcomes in terms of excellent local control rates, independent of their initial clinical T and N stage, even if the different pCR rates in chemoradiation arms did not affect the final outcome in the randomized studies. These data support the concept of heterogeneity among rectal cancers and the need to identify reliable markers to detect favorable patients who could be cured with less surgical therapy.

Organ preservation represents one of the ongoing topics of surgical research: the experience with preoperative chemoradiation followed by local excision is being investigated. Most series are limited to highly selected patients with cT3 disease who are either medically inoperable or refuse radical surgery. Since most series limit this approach to those patients who responded to preoperative therapy there is a need to identify prognostic and predictive factors to better define patients who are suitable for limited surgery. Trials are ongoing.

It is questioned if a local excision can be avoided if the tumor has regressed completely following radiotherapy. Intensive follow-up with the "wait-and watch" philosophy has been advocated by one group with impressive results, similar to those seen after radiotherapy for anal carcinoma[54,55]. This treatment policy has been adopted in patients where an APR has been the alternative procedure. However, it must be emphasized that this is an investigational approach and the standard of care remains surgery.

Laparoscopy surgery

Laparoscopic rectal cancer surgery seems to offer less blood loss, less pain, earlier return of bowel function and shorter hospitalization. The long-term impact on oncological endpoints awaits the findings from large on-going randomized trials[56].

Cylindric APR

Pathological studies of the CRM at the level of the anorectal junction and anal canal show a high risk of tumor involvement. A waist is often created by the surgeon where the mesorectum terminates and the levator (m. puborectalis) inserts into the sphincter complex. The quality of surgery in the levator/anal canal area below the mesorectum varies between surgeons who may operate in different surgical planes. Prospective studies on the reliability of the levator plane to reduce CRM+ are under clinical evaluation[25,57].

SUMMARY

DOKAZI I PERSPEKTIVE ISTRAŽIVANJA ZA HIRURGE PO EVROPSKOJ KONSENZUS KONFERENCIJI ZA KARCINOM REKTUMA (EURECA-CC2)

Cilj: Iako hirurgija ostaje najbitniji tretman karcinoma rektuma, lečenje ove bolesti je evoluiralo u multidisciplinarniji pristup da bi se ponudilo najbolje kliničko rešenje. Internacionalna konferencija "Multidisciplinarni tretman karcinoma rektuma: Traži se evropski konsenzus" (EURECA-CC2) imao je za zadatak da odredi stepen konsenzusa koji bi se mogao dostići kroz širok dijapazon tema u vezi sa tretmanom karcinoma rektuma, a u cilju oblikovanja budućih programa, protokola i vodiča za odredjivanje stadijuma i tretman u celoj Evropi.

Materijali i metode: Konsenzus je postignut korišćenjem Delphi metode. Osam poglavlja je identifikovano: epidemiologija, dijagnostika, patologija, hirurgija, radioterapija i hemioterapija, toksičnost tretmana i kvalitet života, praćenje i pitanja za istraživanje. Svako poglavlje je podeljeno po temama i serija izvoda je razvijena. Svaki član se obavezao i glasao, rečenicu po rečenicu tri puta. Rečenice oko kojih nije postignut dogovor posle drugog kruga glasanja su otvoreno diskutovane na Konferenciji u Perudji (Italija) decembra 2008. Izvršni komitet ocenjivao je procentualno konsenzus baziran na tri kategorije: "visoki konsenzus", "srednji konsenzus" i "minimalni konsenzus".

Rezultati: Ukupan broj rečenica za koje se glasalo je iznosio 207. Od tih 207, 86% je dostiglo visok konsenzus, 13% je dostiglo srednji konsenzus i samo 3 (1%) rezultovao je minimalnim konsenzusom. Ni na jednu izjavu nije bilo neslaganja preko 50% članova.

Zaključak: Konsenzus konferencija predstavlja proces ekspertize mišljenja koja može pomoći u oblikovanju budućih programa, protokola i vodiča za odredjivanje stadijuma i tretman karcinoma rektuma u celoj Evropi. Ipak, uprkos značajnom progresu ostaju mnogi izazovi za buduća istraživanja.

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