

New perspectives in treatment decision for integrated management of rectal cancer: multimodal research for multimodal treatments

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SUMMARY: New perspectives in treatment decision for integrated management of rectal cancer: multimodal research for multimodal treatments.

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Rectal cancer management improved results in the last thirty-five applying new integrated treatment options. Preoperative radiochemotherapy or radiotherapy alone joined to the modern surgery gaining significant improvement of outcomes. Nevertheless, a definitive conclusion about superiority of one on the other in term of survival and toxicity is still lacking, and further improvement is in general required and seems obtainable. The need for a wide sharing of the

accumulated knowledge is represented by the consensus conferences that over the years summarizes the state of the art for the management of rectal cancer. One of the most promising opportunities comes from the attempt of characterization of the tumor heterogeneity. An always-increasing number of new parameters come from different sources including genomic, imaging, pathological features and many others. The need of new informatics technologies able to handle and continuously incorporate new inputs derived from the evidences is also imperative. The combined use of large shared databases and "learning models" could allow generating and rapidly testing new hypotheses, providing further survival improvement in the next years.

KEY WORDS: Rectal cancer - Multimodal treatment - miRNA - Ontology - Clinical management - Nomogram - Learning machines.

Rectal cancer management dramatically improved results in the last thirty-five years taking advantage from new integrated treatment options (1). It could be summarized that until the beginning of '80s, surgery was the only treatment option, potentially associated to adjuvant radiotherapy (RT) but gaining unsatisfactory outcome for local control (LC) and overall survival (OS). When Heald first proposed the introduction of the new and challenging surgical approach represented by the total mesorectal excision (TME), a new perspective for management of rectal cancer was opened (2). In the same period the first experiences of postoperative combination of RT with chemotherapy (CT) to radiosensitize tissues and improve results was proposed in the adjuvant setting obtaining a clear amelioration of survival outcomes (3). The progressive shift of the integrated approach in the preoperative setting was proposed either in the frame of radiochemotherapy (RTCT) in the pioneering trials by Butoker and Nigro (4) or in the setting of RT alone in the northern European approach, progressively introducing the multimodal integrated approach that nowadays represents the golden standard for most of the clinical presentations. These two RT approaches (long and short course) still face one each other, looking for definitive conclusions about superiority in term of outcome and toxicity, but also being representative of the differences of interpretation of the same standard approach among different scientific scenarios between North Europe on one side and North America or Middle Europe on the other one (5). TME-surgery continues to be a cornerstone of treatment management, but many technical innovations (for example the minimally invasive approaches) and new surgical managements are proposed for super-selected clinical pre-

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sentations, like the wait-and-see for very favorable response to preoperative treatments (6). Nevertheless an optimization of the results is needed to further improve survival outcomes. The feeling of the need for a wide sharing of the accumulated knowledge leading to a focus on the modern indications for the different treatment options is represented by the consensus conferences that over the years summarized the state of the art for the management of rectal cancer (7, 8). The last European consensus conference on colon and rectal cancer care, represented by the European Registration of Cancer Care (EURECCA), published some documents with the first aim to increase the homogeneity of clinical management in Europe for such malignancies, supporting clinicians of multidisciplinary teams for decision-making; the second aim was to enhance the quality of treatments by providing benchmarks defined among participants on the bases of audits and outcome analysis of the population-based registries (9). For clinicians and researchers the difficulty to handle the growing accumulation of knowledge is a central issue in oncology and within the specific field of rectal cancer in particular. If around '80s the most important prognostic and predictive parameters to take into account for treatment decision were represented by stage grouping through pathological features added to histological, demographic and anamnestic information, nowadays the number of parameters to take into account is constantly increasing. Also in other malignancies, for instance, it was demonstrated as TNM only partially includes all the prognostic determinants, highlighting the need for more complete evaluation of tumor heterogeneity (10).

Elements for characterization of the tumor heterogeneity come from many different sources: some of whom let to better evaluate the tumor presentation and features related to prognosis, while others can also be used to improve treatment outcomes. Imaging represents a perfect example: many imaging modalities as Magnetic Resonance (MR) or Positron Emission Tomography (PET) aid the modern routine clinical practice for rectal cancer. In the last years a new step forward was made by these imaging modalities. For example, the prognostic role of circumferential resection margin involvement was progressively established for treatment outcome after radical treatment for rectal cancer (11) and how to take it into account for selection of treatment modality was debated (9). On the other hand there are consistent evidences that MR can properly predict survival outcomes through the correct evaluation of the involvement of mesorectal fascia, thus opening the filed of treatment individualization in this regard (12). Also PET provides always more useful information to be kept into account for treatment personalization, over the integration of the TNM staging. Recent evidences suggest that sequential PET data can accurately predict pathological complete response (pCR) and can be used as a decision support tool for surgery after prospective validation (13). More in general, a new paradigm of approach to information derived by imaging was proposed, named radiomics (14). It is based on the concept that through high-throughput extraction of large amounts of image features from radiographic images can lead to obtaining novel sources of data to individuate the specific heterogeneity of clinical presentation and personalize the treatments. The importance of genetic and molecular profiling and definition of mutation status to properly select population for ones most likely to benefit by new drug administration in rectal cancers is consolidated (15). Genetic profilings are always more widely adopted for rectal cancer, not only being representative of the different baseline presentations from less to more advanced (16), but also predictive of response to RTCT (17) and potentially exploited in decision making processes by clinicians. That issue is object of growing interest also due to the new and promising approach of the so-called "liquid biopsies". Tumor cells release circulating free DNA (cfDNA) into the blood: by new technological advantages it is possible to detect cancer-associated alleles and develop wide evaluation of the genetic and epigenetic aberration related to the specific clinical presentation (18). A new frontier in this frame is represented by the promising role of microRNA (miRNA) in the oncological field of interest. MiRNA represent a class of small non-coding RNA with the role of regulation in many different cellular pathways. They are also responsible of the reaction to ionizing radiations, thus strongly affecting tumor response to RT or RTCT (19, 24). With the potential aim to manipulate the radioresistance determined by miRNA by artificial restoration of under-expressed miRNA or, conversely, by blocking overexpressed miRNA, some promising studies were addressed on rectal cancer. Recent studies determined a specific profiling signature of different regulations of some miRNA that is associated to the outcome in term of pathological response after preoperative RTCT (20) and in a close future will be object of attempts to further individualize the clinical perspective of multimodal treatments.

Finally, also some classic treatment-related issues as the toxicity reported during neoadjuvant

RTCT were found to be potentially associated to specific features of response to treatment and survival outcome (although with conflicting preliminary results), making them appealing to optimize treatments and important to be handled by the clinicians to tailor the therapy (21).

The modern trend of treatment's individualization and the increasing amount and complexity of available medical data, determines a growing need for the development of clinical decision-support systems based on prediction models of treatment outcome (22). Attempts were made for rectal cancer in this direction proposing a nomogram to help clinicians in the selection of treatment options, on the basis of the evidences reported by the main randomized trials available in literature (23). The rapid and continuous accumulation of new evidences on such an amount of different issues (imaging, genetic, clinical, trial results, etc) determines the urgency for solutions able both to quickly interpret the evidences derived from new data and to confirm on independent and wide confirmatory datasets the upcoming results of new hypotheses derived from research. The use of large and shared databases for data-mining added to implementation of new technologies applied to data interpretation could be a valid option. A fundamental requirement for developing large database to run rapid learning models and apply standardized data collection, is the definition of a common language about the specific features to investigate in each single research field. The "Ontology" (a compound word derived from ancient Greek) represents knowledge as a set of concepts within one or multiple domains, and the relationships between those concepts. Ontologies describe how information can be structured, and could be used as a sort of dictionary where all the information, related in this case to rectal cancer, are searchable. Through definition of ontologies for different research and clinical issues it will be possible to simultaneously incorporate plenty of data from several different large datasets in models able to keep into account each feature and its relative interaction with the other ones, providing a high personalization of treatment and possibly a major improvement in survival outcomes. The need to properly and continuously analyze the load of data derived from large databases, support the implementations of "learning machines": software able to update and proceed to implementation of the models created by evidences, along with the progressive adding of new evidences. The combined use of large shared databases and "learning models" could allow a continuous update of the models by incorporation of new evidences from different sources and joined Centers having each database in different parts of the world.

The role of high quality, large randomized trials, and consequent systematic reviews and meta-analyses, leading to consensus-based international guidelines will not to be replaced, but it will be addressed and confirmed by such new approaches.

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