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Review Article

Colorectal Adenocarcinoma in Precision Medicine

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Abstract

This review discusses colorectal adenocarcinoma, one of the most common cancers worldwide, with increasing diagnoses and high mortality rates despite therapeutic advancements. Precision medicine plays a crucial role in treatment, with a focus on genetic mutations such as KRAS, NRAS, and BRAF, and microsatellite instability. Targeted therapies and immune checkpoint inhibitors are tailored based on the tumor's molecular profile, significantly improving survival rates. Trifluridine/tipiracil, regorafenib, and fruquintinib are effective in advanced stages, though with limited response rates. The importance of genomics and personalized treatment is emphasized, with biomarkers like KRASG12 mutations affecting overall survival outcomes.

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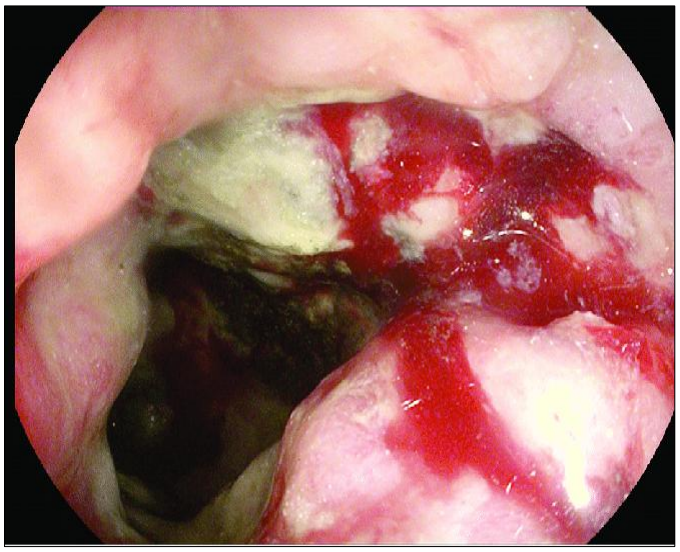
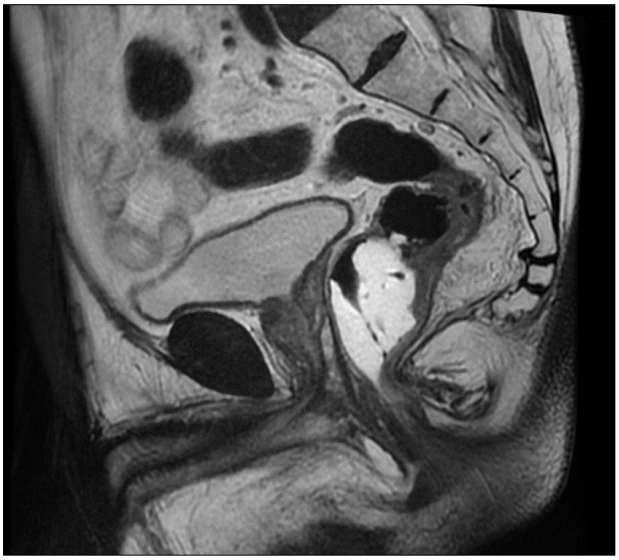
INTRODUCTION

Adenocarcinoma of the colon and rectum is one of the most frequent neoplasms along with breast, prostate, and lung cancer. In 2024, new diagnoses bring neoplasia to second place for frequency in both sexes, with an increase of 1.5% compared to 2020. Approximately 40% of affected patients develop secondary localizations from the first diagnosis after radical surgery; in this population with stage IV disease Cancer-related mortality remains high, despite therapeutic innovations and brings 5-year survival to 65% in men and 66% in women. When undertaking the treatment of metastatic colorectal cancer the lines guidance, including updated AIOM ones, recommend evaluation of the mutational status of KRAS, NRAS, and BRAF and of microsatellite instability. Somatic mutations in the KRAS and NRAS genes are present in 60% of tumors, while that of BRAF in 8-10%; both are well-known factors of resistance to

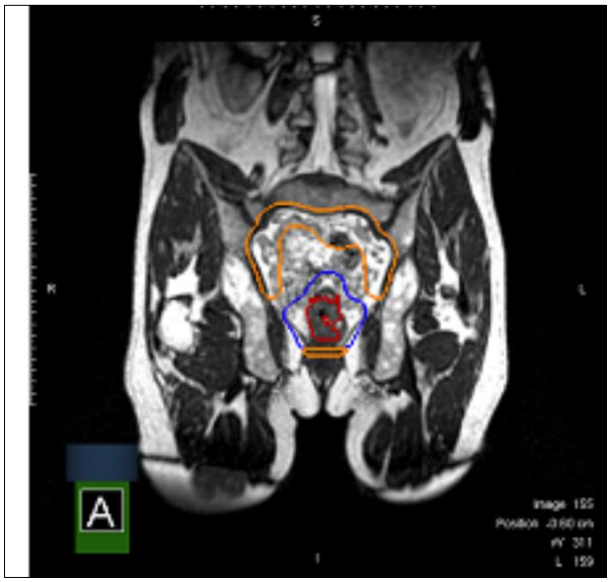
anti-EGFR monoclonal antibodies, while BRAF mutation. It also constitutes an important unfavorable prognostic factor. The instability of the microsatellites as well as the candidate the patient for an oncogenetic evaluation for the screening for Lynch Syndrome, however, constitutes a very strong predictive factor of response to immune checkpoint inhibitors. The molecular state of the tumor has important implications in the choice of first-line treatment. In the first line of patients with microsatellite stability, the use of is recommended combinations of fluoropyrimidines (administered by infusion, in the form of 5-fluorouracil and folinic acid with oxaliplatin and/or irinotecan, in combination with a monoclonal antibody against VEGF or anti-EGFR. Such combinations should be used in all patients in a condition to be treated with one polychemotherapy, reserving monochemotherapy strategies with fluoropyrimidine a elderly or frail patients. If microsatellite instability is found, the first choice consists of immune checkpoint inhibitors, in particular the pembrolizumab, waiting to see data on anti-anti-combinations PDL-1 and ANTI-CTLA4

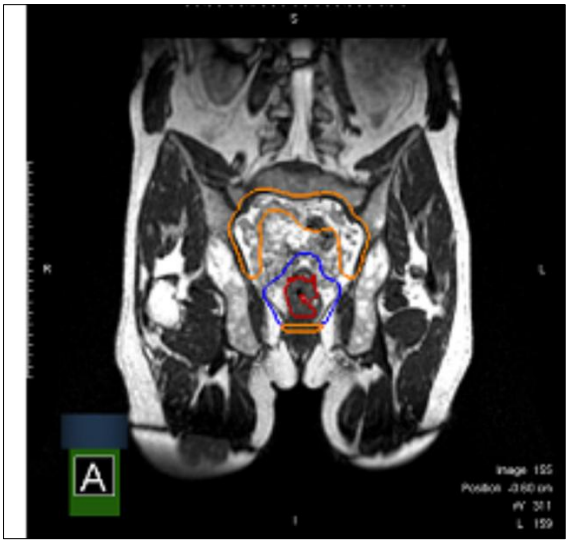
The combination most supported by efficacy data is a doublet (different from the one used in the first line) associated with bevacizumab, while patients with BRAF-mutated tumors should receive targeted treatment with encorafenif e cetuximab. In the third and fourth line, the treatment is aimed at disease control the therapies that have demonstrated a benefit in studies randomized trials (trifluridine/tipiracil, regorafenib, fruquintinib) are characterized by limited response rates, which however translate into approximately 1-year survival 25% of patients. The AIOM guidelines support the use of trifluridine/tipiracil in already treated patients with all cytotoxic and biological therapies in previous lines, independently by the mutational status of RAS and BRAF and by the instability of the microsatellites. Trifluridine/tipiral is recommended in the third line in fit patients with intensive chemotherapy at the beginning of their treatment path and in the second line in unfit patients if not candidates for other available therapies. The toxicity profile of trifluridine/tipiral is characterized by adverse events manageable hematological and non-hematological conditions were not reported in clinical trials cardiac toxic events which, although rarely, have been encountered in treatment infusional with 5-fluorouracil and capecitabine and different from these two drugs, the metabolism of trifluridine/tipiracil is not affected by polymorphisms of DPYD. The availability of numerous therapeutic options has made it possible to prolong life expectancy from around 15 months when only therapies were available cytotoxic at 37 months in patients treated with 6-7 drugs. Numerous pieces of evidence show that although the contribution given by the single drug in advanced line is of limited entity, the benefit is incremental and the improvement in survival is evident in patients who have been able to receive multiple lines of therapy and in particular Trifluridine/tipiracil or regorafenib in late lines. In this collection of experiences from daily clinical activity, they examined important aspects to offer patients suffering from colorectal adenocarcinoma metastasis the maximum survival benefit through administration of therapy with trifluridine/tipiracil in advanced line. All cases examined subjective of trifluridine/tipiracil excellent tolerability is objective, they are both crucial for maintaining a good quality of life PF and good health OS. Toxicity in most cases requires postponing the cycle. Furthermore, its tolerability spectrum allows for the treatment of fragile patients and those with significant comorbidities, including renal failure. In an international study on genomic biomarkers using the analysis of the whole genome of 37 patients with metastatic colon cancer mCRC treated with chemotherapy Trifluridine/Tipiracil, mutations of the codon G12 of KRAS (KRASG12) were identified and revealed to be a potential biomarker of resistance. As in the results of the RECOURSE study on 800 patients, the mutations KRASG12 were found to be predictive biomarkers for a reduced benefit in terms of overall survival, with potential implications for approximately 28% of patients with mCRC. These data are a huge confirmation of how genomics is the basis of precision medicine and how, according to the specific risk revealed for the patient during the selection phase, one or more services are required provided by the Precision Medicine Center, including MIFAR (integrated metabolism of drugs) I° and II°, Pharmacogenomic analysis and TDM. The study of single nucleotide polymorphisms on known and unknown genes (PDL-1, ALK, MET, ROS, CTLA-4, FGFR4, HLA) will allow us shortly to obtain fundamental data useful to the patient to be started on a specific personalized treatment. We will be able to define early the variability in the response to therapies, chemotherapy and/or immunotherapy and target therapy, in the gastrointestinal, genitourinary, pulmonary, breast, melanoma areas to anticipate toxicities and serious adverse effects in adequate and effective times, representing a real challenge in Oncology.

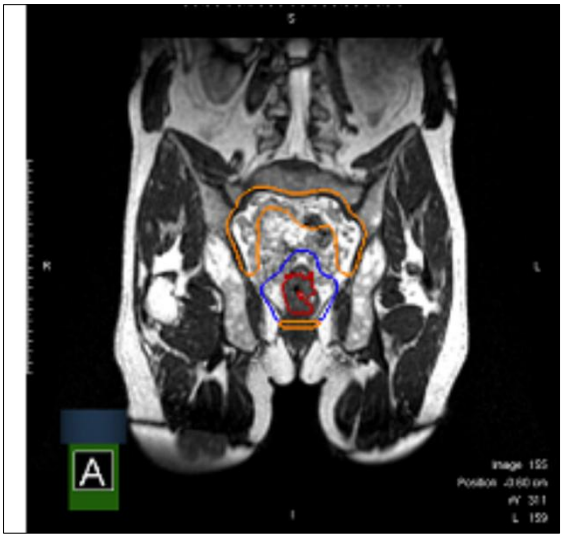


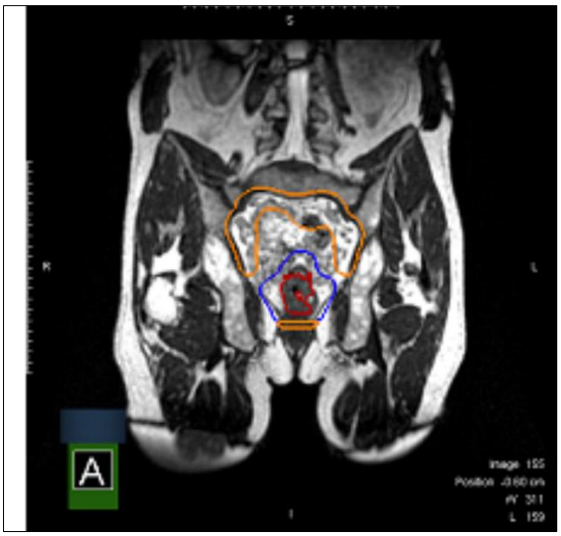


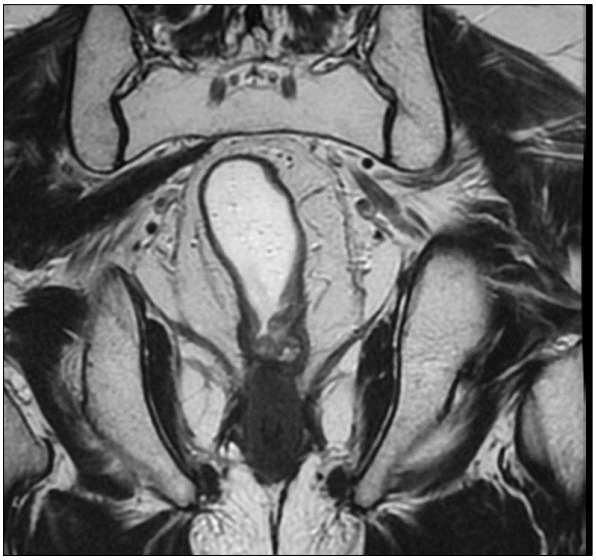
Start of RTCT with Capecitabine 1650 mg/m2

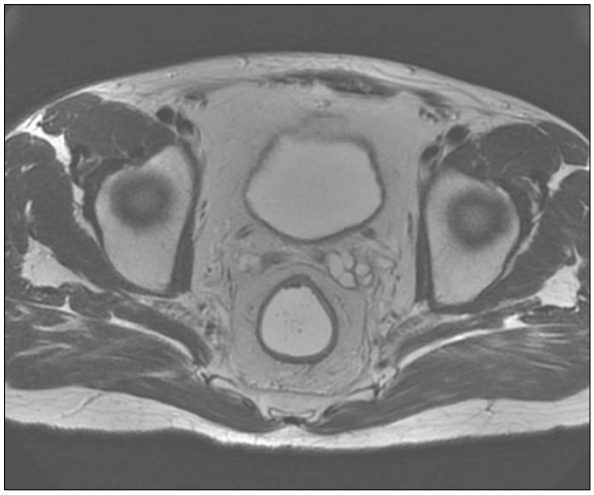












CONCLUSION

The availability of diverse therapeutic options has significantly extended life expectancy for metastatic colorectal cancer patients. While single-drug benefits are limited, combination therapies yield incremental improvements in survival. Biomarkers, such as KRASG12 mutations, are crucial for predicting treatment responses, highlighting the importance of genomics in precision medicine. Future advancements in pharmacogenomic analysis and biomarker identification will further refine personalized treatments, improving both survival rates and quality of life.

Ethics and Funding Disclosure

Ethical approval was obtained by institutional guidelines. Patient consent was acquired before genomic analysis. This study was supported by internal funding from La Sapienza University of Rome.

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