

**UNIVERSITY OF MEDICINE AND PHARMACY
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**MORPHOLOGICAL
MODIFICATIONS INDUCED BY
NEOADJUVANT RADIOTHERAPY
IN RECTAL CANCER**

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KEYWORDS: rectal cancer, neoadjuvant radiation, carcinogenesis, surgical excision, pathology, statistical analysis, correlations.

INTRODUCTION

Colorectal cancer is a major problem in the pathology of malignant digestive tract and is a real challenge in developing diagnostic and therapeutic strategies. In this study we believe that the improvement of the pathological diagnosis by qualitative analysis using histological staining techniques, and objective, optical quantitative and ultrastructural analysis using computer-assisted morphometry techniques based on exploring both pieces excised from patients with non radiated rectal tumors and those radiated preoperatively can lead to a better assessment of the status of the tumor, thus improving the prognosis of these patients.

KNOWLEDGEMENT STATE

A proper diagnosis and staging is ideal as regards the choice of therapy. Distal tumors located to 15 cm or less from the anal portion (measured with rigid sigmoid scope) are classified as belonging to the rectum; over 15 cm are considered colon distal tumors.

Histopathology of primary tumor has proven negative prognostic significance only for special types of adenoarcinomas: mucinous carcinoma, squamous cell "signet ring" carcinoma, small cell carcinoma and scirrhous carcinoma [He Demellawy et al., 2007, Washington et al. 2009, Willett 2001, Nakahara et al., 1992].

For colon cancer classification are used multiple systems, the most satisfactory being considered classification / staging TNM (Tumor, Node, Metastases) - which is proposed by UICC (Union International Contre le Cancer) and AJCC (American Joint Commission of Cancer) and respects the main three components.

For patients with locally advanced cancer and especially those with fixed rectal cancers, preoperative conventional fractionation RT (45-50 Gy in 5.5-6 weeks) may reduce tumor size, thus facilitating resection.

Histological aspects of irradiated rectal tumors are similar to those of a sub acute-chronic inflammation because most tumors are resected after a break of a few weeks from the finish of preoperative treatment.

Significant regressive changes in the irradiated tumor could lead to the complete disappearance of the malignant cells of the tumor tissue and the replacement of this with fiber or fiber-inflammatory granulation tissue. You can see the signs of resorption and histiocytic reaction with macrophages loaded with hemosiderin and "sparkling" macrophages, cholesterol deposits, foreign body reaction and dystrophic calcifications [Damjanov and O'Neil 2009; Langer et al. 2009; Becker et al. 2003; Shia et al. 2004].

Tumor regression in irradiated tumors may follow a centrifugal model but even if the superficial tumor has regressed, residual tumor can be found in the deeper layers of the tumoral bed or in the periphery [Becker et al. 2003].

Non-neoplastic tissue in non irradiated patients may also suffer treatment-related changes such as inflammatory non-tumor ulcerations, submucosal edema and inflammation.

For patients with locally advanced cancer and especially for those with fixed rectal cancers, preoperative conventional fractionation RT (45-50 Gy in 5.5-6 weeks) may reduce tumor size, thus facilitating resection.

Surgical resection is the cornerstone of curative treatment. Superficially invasive cancers, small ones, can be managed effectively with limited surgical procedures such as local excision [Mirea et al., 2013]. However, most patients have deeply invasive tumors that require more extensive surgery such as abdominoperineal resection or proctectomy [Ionescu and Szabo, 1984, Radulescu and Belus, 1999 Willett, 1998]. There are currently discussions about what type of surgery must be performed in rectal cancer, the most important factor that determines the type of intervention being the height of the tumor related to the sphincter [Ionescu and Szabo, 1984 Angelescu et al., 2003].

PERSONAL CONTRIBUTIONS

OBJECTIVES OF THE RESEARCH

The topic is of great interest and concern, it is important to determine a correct therapeutic behavior conditioned by various clinical aspects and the morphology of rectal tumors that were or were not subjected to preoperative irradiation.

The major objective of the research project is to highlight the impact of neoadjuvant radiotherapy on clinical and morphological profile of rectal tumors and of the surrounding tissues compared to those cases of rectal tumors which have not undergone radiotherapy.

MATERIAL AND METHODS

The study was composed from a group of 59 patients admitted to the Emergency County Hospital Craiova, in the I - II - III Departments of Surgery, in 2013 - study aiming to be a prospective one.

Tumor tissue fragments were subjected to conventional histological processing techniques (fixation and paraffin embedding) after which serial sections were made from each block and they were stained with the classic staining methods.

RESULTS

Clinical Profile

Analysis of results from the assessment of clinical parameters in both groups of patients with rectum malignant tumors suggested the outlining of different profiles in the two tumor types.

Rectal carcinomas studied, both non-irradiated and irradiated were far more common in men, their number is over two times higher than in women, a situation found in other international studies [Purim et al., 2013 Toyoda et al., 2009, Debucquoy et al., 2009, WIEGERING et al., 2014].

The distribution of patients according to age periods showed a higher proportion of cases in VIth-VIIIth decade of life in both groups, with a mean age of 66.32% in the no irradiated group and 63.48% in the irradiated group, data are similar to those obtained in other international studies [WIEGERING et al., 2014 Debucquoy et al., 2009].

The distribution of patients by the way of admission is different between the two groups, meaning that the cases preoperatively irradiated are hospitalized particularly elective while the non-irradiated patients are particularly emergency hospitalized.

In the group of patients undergoing preoperative radiotherapy clinical signs were more "gentle", dominated by rectal bleeding; there were very few cases in which the complex picture was present, consisting of combinations of main evocative clinical symptoms but also alarming ones. In patients who did not receive preoperative radiotherapy, the clinical picture was either a complex one containing at least a evocative sign of intestinal obstruction syndrome or it was represented by intestinal obstruction syndrome.

Greater share of surgery in the group with irradiated patients was the rectum amputation, due to the location of the rectal tumors in the middle and lower rectal segments. For tumors located at the rectal-sigmoid junction and in the superior rectum, the most common surgery was rectosigmoidian anterior resection described by Dixon. Hartmann resection was practiced to the patients emergency hospitalized or debilitated.

Postoperative complications, in the group of patients who did not receive preoperative radiotherapy, were nearly two times more common than in the group of patients who underwent preoperative radiotherapy. Dynamic postoperative ileuses had the largest share (56.25% of cases with abdominal complications), which occurred mainly on patients with emergency surgery and on patients with elective surgery but with a poor performance status.

In the studied cases, postoperative death was encountered only in the group of patients who did not receive preoperative radiotherapy, respectively at five patients representing 8% of total number and 14.7% of patients who did not receive preoperative radiotherapy.

Macroscopic evaluation

In the group of patients who did not receive preoperative radiotherapy, tumors were most commonly met in the upper segments of the rectum, at the rectal-sigmoid an junction and then in the upper segment of the rectum. In the group of patients who underwent preoperative radiotherapy, nearly 90% of the tumors were located in the lower rectal segment - more than half of the cases, and in the medium rectal segment - another third of cases.

In the group of patients who did not receive preoperative radiotherapy dominated vegetable and ulcerated tumors followed by ulcerated and infiltrative forms, with or without ulceration, while in the group of patients who underwent preoperative radiotherapy, the ratio changed for ulcerated forms, followed by vegetable and ulcerated forms and the infiltrative ones with or without ulceration.

Rectal submucosa and muscle tunica surrounding the irradiated tumors were generally thicker than those of the rectal wall surrounding non-irradiated tumors. This phenomenon can be explained by the fact that the fibrosis, occurred as a result of the irradiation action on tumor tissue, can also be found in the healthy tissue around the tumor.

Regarding tumor proliferation, its diameter, maximum height and height of the ulcer crater, if it existed, showed lower average values than similar measurements made in tumors which were not preoperatively irradiated . Also, tumoral migration under healthy mucosa both proximal and distal tumor pole was less in the irradiated ones than in the others.

An interesting phenomenon observed at microscopic tumor fragments evaluation was the presence of tumor growth under normal mucosa. It was evaluated in both groups at proximal and distal poles and side areas of the tumor.

The situation of the tumor migration under normal mucosa which surrounds the tumor was seen both in the group of tumors which have not been subjected to pre-operative radiotherapy and as well as in the group subjected to pre-operative radiotherapy meanwhile the phenomenon of tumor proliferation in normal mucosa from the base vegetable tumor proliferation or from the protrusion edges into the lumen of the ulcerated tumor proliferation predominantly with ulcerated aspect was present only in the group of tumors which have not been subjected to pre-operative radiotherapy.

Correlations

Comparative analysis of lots of rectal tumors revealed several important aspects to be taken into account for the final evaluation of a patient with rectal cancer.

The type of surgery in patients with non irradiated rectal tumors is dictated by the location and by the extension tumor degree, complex cases, admitted through the emergency criteria can suffer post-operative complications, most commonly dynamic ileuses that can require some of them, in turn, recorection surgery and which may lead to death of the patient in very rare cases.

As a general histopathological type, non irradiated rectal tumors are especially biphasic. In single-phase, in principle, they are poorly differentiated adenocarcinoma forms or mucinous carcinomas. In biphasic cases, architectural appearance of superficial areas of the tumor is usually papillary and in depth evolve more often to poorly differentiated or mucinous forms. They are constantly accompanied by a lymphoplasmacytic inflammatory reaction especially moderate or severe as intensity and are usually headquarters intratumoral necrosis areas.

Irradiated tumors are aggressive tumors that are caught in advanced stages of rectal wall invasion, most often surpassing by burgeoning phenomena at the invasion front and tumor deposits sometimes with extension to regional lymph nodes to more than half of the cases and remote extension in 20% of cases. All these make the tumors to be rarely captured in the first TNM stage when they are discovered.

Aggression is more tempered in irradiated tumors. Tumors that exceed the rectal wall are found in a lower percentage than in the other group, new morphological prognostic markers (tumor budding site and deposits) being observed with a lower frequency, nodal invasion is absent from a significant contingent by patients so that one third of patients are caught in an early stage or converted to a lower level.

As a consequence of alterations in irreversible cells phenomenon, it occurs a regression of proliferative malignant glandular structures and the phenomenon by mucus formation of lacquers. In particular, in the studied group, by quantifying morphological degradation of all these parameters, tumor regression score most frequent, established by Dworak's method, was "1".

CONCLUSIONS

Our study which includes a detailed and comparative analysis of a significant clinical and morphological parameters has reached to some conclusions which could lead to an important usage in the future rectal carcinoma in medical practice:

Presurgical neoadjuvant radiotherapy modifies clinical profile of the patients with rectal cancer and the postsurgical clinical evolution, by remodelating the tumor and her surroundings.

Thus, neoadjuvant radiation therapy produce a complex set of morphological changes as in the malignant epithelial proliferations and to the normal rectum tissue structures or at its junction with the colonic segment from the vicinity of the tumor.

The measurements of the tumor and of its various components highlighted in the irradiated cases compared with the non irradiated ones, a reduction of tumor base, of the transverse diameter and of the height rather the tumor was ulcerated or not and a reduction of the depth of the ulcer crater if it existed.

It has not been observed a reduction in area and in depth of parietal invasion in irradiated tumors compared with no irradiated ones, perhaps because in practice, the peak in wall invasion is established where malignant cellular elements are identified, even if they have or no items degeneration.

Morphometric analysis demonstrated a normal bowel wall layers remodeling, remodeling quartered especially in the sub mucosal and muscular layers, which, under the influence of radiation, become the headquarters of a process of fibrillogenesis which leads to increased density of collagen fibers in the gap of the two parietal layers, leading to thickening there of them.

The presence of tumor proliferation under the healthy mucosa can have two distinct aspects: one is the actual migration of the tumor outside the base tumor beneath the normal mucosa. The second is the presence of tumor growth under the mucosa to the lumen driven by the development of the tumor.

Actual migration tumor growth outside the tumor base to the sub mucosa may be considered, along with microscopic aspects of temporal "budding" to front invasion and the presence of tumoral deposits in the surrounding rectal tissue remote from the tumor has a reserved prognosis factor.

Comparative qualitative and quantitative evaluations of these prognostic parameters showed that neoadjuvant radiotherapy in tumors caused a reduction in the frequency and extent of these parameters.

Finally, the results of comparative evaluation of the main clinical and morphological parameters of the non irradiated tumors with those with preoperative irradiation, especially quantitative morphometric evaluations can be a strong argument in favor of the real benefits brought by neoadjuvant radiotherapy treatment algorithm of rectal cancer, the most important of them being the reduction of these local extension of the tumor.

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