LOCALLY ADVANCED RECTAL CANCER
-MULTIDISCIPLINARY APPROACH-

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Preoperative staging of rectal neoplasms with endorectal ultrasonography

KEYWORDS: Rectum; Ultrasonography; Staging

Currently there are a variety of surgical options available when considering the management of the patients with rectal neoplasm. The choice of treatment will depend on height of tumor from the anal verge, stage, and degree of differentiation, presence of synchronous lesion, nature of underlying pathology, and operative risk factors.

In recent years, stage of tumor and associated lymph node involvement have generated considerable interest with regard to choice of treatment for many reasons. Firstly, survival is directly proportional to tumor stage. Secondly, local therapy is becoming increasingly popular for early rectal cancer and adjuvant radiotherapy with or without chemotherapy has emerged as a definitive treatment modality in certain types of rectal cancer. Furthermore, objective assessment of depth of wall invasion of a rectal neoplasm has provided a means by which local excisional techniques for small stage rectal cancers may be reported and compared objectively (1).

Endorectal ultrasonography (ERUS) provides accurate data on degree of wall penetration and pararectal lymph node involvement (2). ERUS provides several advantages over other diagnostic modalities, such as computed tomography and magnetic resonance imaging. ERUS is less expensive than these other two examinations, the ultrasound examination is relatively quick and is well tolerated by the patient. Moreover, the patient is not exposed to radiation during the examination. Because the equipment is portable, the examination can also be performed as an intraoperative procedure.

Using radial transducer from 10 MHz rectal wall is represented by concentric circles of alternating hyperechoic and hypoechoic bands on the ERUS. The majority of investigators agree on a 5-layer model of the rectal wall. In this model, the first (inner) hyperechoic line is mucosa without lamina muscularis mucosae, the first (inner) hyperechoic line is lamina muscularis mucosae, middle hyperechoic line is submucosa, second (outer) hypoechoic line is muscularis propria and third (outer) hyperechoic line is serosa. The crucial layer is the middle hyperechoic line, which if broken, implies invasion through the muscularis mucosae into submucosa (T1 stage). If there is widening of the outer hypoechoic line, but no break in the outer hyperechoic line, then tumor is confined to the muscularis propria (T2 stage). If there is a break in the outer hyperechoic line, the tumor has invaded the perirectal fat (T3 stage) (3).

The ERUS allows for visualisation of the immediate perirectal tissue, and therefore a search for enlarged lymph nodes should be routine step in the evaluation of a rectal tumor. One must be careful not to confuse blood vessels with enlarged lymph nodes. To make distinction between the two, a complete evaluation at different levels will show the serpiginous, branching, longitudinal nature of the blood vessel compared with the consistent round appearance of the lymph node. The differentiation between an inflammatory node versus a metastatic node can at times be difficult. However, an enlarged lymph node located adjacent or superior to the level of the tumor, having a round appearance with irregular borders, and of the same hypoechoic echogenicity as the primary tumor should be considered a metastatic node (4).

ERUS also provides an image of the organs adjacent to the rectum. In men the seminal vesicles are clearly observed and must be distinguished from lymph nodes. The prostate is also clearly observed, and any tumor invasion through Denonvilliers fascia can easily recognised (T4 stage).

ERUS is not free of errors in staging rectal tumors (5). Errors in interpretation which result in overstaging of a carcinoma may be caused by inflammatory changes, preoperative radiotherapy, possibly haemorrhage in the bowel wall such as immediately after biopsy. All of the previous errors commonly present as hypoechoic lesions, which may be confused with carcinoma. Peritumoral inflammatory changes at the leading edge of a tumor will thus be interpreted as tumor margin. Such a lesion is a risk of being overstaged. Understaging commonly occurs in the case of stenotic lesions, in which the entire tumor may not have been examined. A tumor in which lymph node involvement was not identified by ultrasound may also be understaged. Finally, understaging may also occur especially in tumors that are minimally invasive.

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Rectal cancer: diagnostic performance of magnetic resonance findings in local tumor extension

KEYWORDS: Rectal neoplasms; Magnetic resonance; Staging

INTRODUCTION

Rectal cancer is currently the second most common internal malignancy in Europe, United States, Australia and also in our country after bronchial cancer in males and breast carcinoma in females. The 5-year survival rates are 80%, 60% and 25%, respectively.

It is important to separate rectal from colon lesions and not mixed them as " colorectal cancer" while the local failure pattern and treatment strategies are different. (1,2)

The predisposing factors are adenoma, polyposis, ulcerative colitis, Crohn's colitis and a heredity disposition.

Clinical detection: Non-specific symptoms or occult bleeding appear in early phase. Clinical symptoms in the late stage are rectal bleeding, pain, change in bowel habits and stool caliber (dependent on size, rate of growth of the tumor).

Diagnostic procedures: Most cancers in this area can be detected by a simple digital examination, barium enema, and rectosygmoidoscopy or endorectal ultrasound. Once discovered, rectosigmoidoscopy should be followed with appropriate biopsy in order to verify pathohistological diagnosis.

Staging and classification: There are various systems of classification and staging for colorectal cancer (TNM classification, staging systems of the American Joint Committee (AJC), the Astler-Collier classification and the Dukes classification. The Duke's classification, as a surgical pathologic staging system for rectal cancer is the most widely used (3).

An aggressive diagnostic approach that includes pretherapy staging of advanced rectal malignancies can enable the most appropriate treatment regimen to be planed. Pretherapy staging is useful in patients in whom resection of the tumor is not immediately feasible but may become possible after irradiation; in patients with suspected advanced disease in whom a decision for or against extensive abdominal surgery needs to be made and in patients who may benefit from local endocavitary irradiation. (4)

Table 1. TNM classification

AJC	TNM Classification	DUKES	UICC
T1	Submucosa	A	T1/pT1 mucosa or submucosa only
T2	Muscularis	A	T2/pT2 muscle or serosa
T3	Subserosa/ nonperitonealized paracolic or perirectal issues	B	T3a/pT3a Extension to contiguous structures, No fistula T3b/pT3b with fistula
T4	Perforates visceral peritoneum Directly invades other organs	C	T4/pT4 Extension beyond contiguous structures
N1	1-3 pericolic/perirectal lymph nodes	C	N0 No regional node involvement
N2	≥4	C	
N3	Vascular trunk	C	
M1		D	

MATERIALS AND METHODS

MR diagnostic procedure was performed in 68 patients (40 men, 28 women; mean age 65), who were suspected of tumor infiltration of rectum at prior flexible rectosygmoidoscopy. They underwent pelvic examination on 1.5T MRI unit Siemens Magnetom SP 63-4000 by use of the routine protocol consisted of T1W axial and coronal planes, T2W axial and sagittal planes and axial or sagittal plane after application of Gd-DTPA. Forty-five per cent of the patients had previous barium enema examination. Computerized tomography (CT) examination was done in 47% of the cases.

RESULTS

Rectal cancer was found in 68 (100%) patients, male - female ratio1.5: 1 (40:28), with pathological-histological finding of adenocarcinoma.

Local tumor extent is particularly well shown on T1W images. Tumor tissue shows low signal intensity similar to musculature. T2W tumor tissue shows high signal intensity: however this is dependent on the type of tumor. Gadolinium application enabled clear demarcation between tumor tissue and surrounding tissue.

Dukes A or T1 stadium of the rectal cancer was not found in any of the patients; Dukes A/B or T2 was identified in 19 patients (27.9%); Dukes B or T3 N0 in 7 (10.3%); Dukes C or T3N1 in 12 (17.6%), Dukes C or T3N2 in 5 (7.3%); T3N3 in 2 (2.9%); Dukes C or T4 stage in 18 (28%), and Dukes D or M1 in 5 patients (7.3%).

Rectal MR and CT showed comparable accuracy for stages II to IV of the disease.

The lymph nodules were round and of variable size, having intermediate or low signal intensity on T1W and also on T2W images. Enlargement of lymph nodes were found in stage N1 in 15 patients (35.7%), in stage N2 in 18 (42.8%) and in N3 in 9 patients (21.4%).

Bone metastases (sacrum) were found in one patient (1.8%) and liver metastasis in 4 (5.8%) patients.

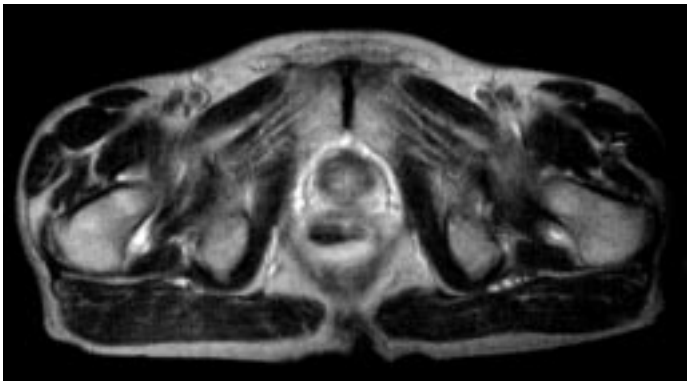

Figure 1. Rectal cancer /axial plane/ infiltration of muscularis propria

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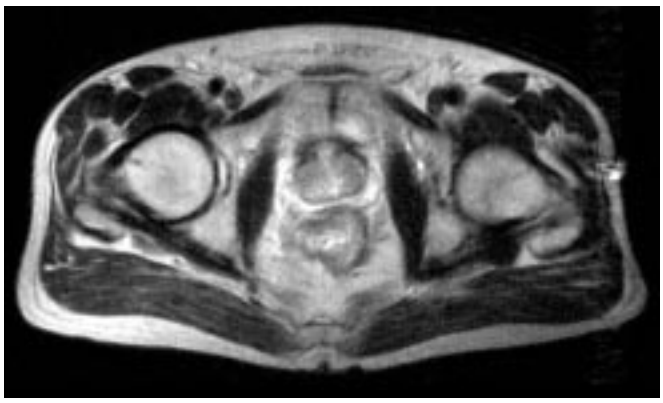

Figure 2. Rectal cancer /axial plane/ transmural extension in the surrounding fat tissue

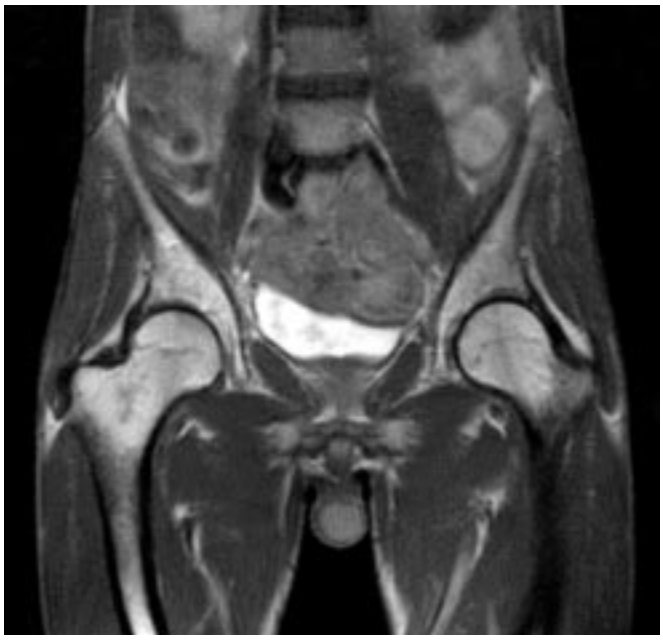

Figure 3. Rectal cancer /coronal plane/ infiltration of the bladder and small intestine

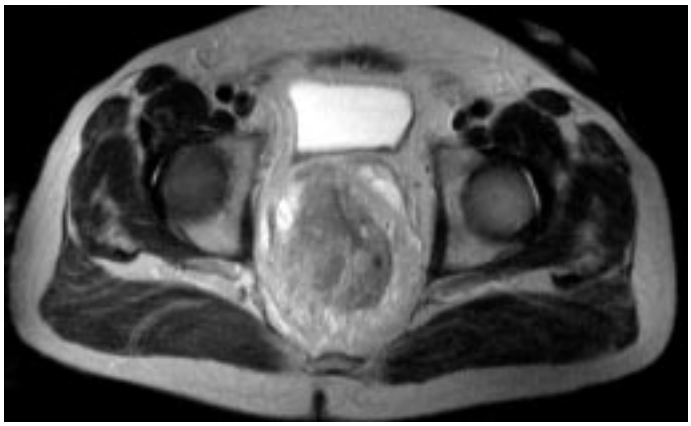

Figure 4. Rectal cancer /axial plane T2W/ infiltration of seminal vesicles

MR findings on infiltration of rectal lumen versus findings performed by rectoscopy were not statistically significant ($p>0.05$).

DISCUSSION

Specialized techniques are required to examine the rectal and perirectal area by MR, although MR is not appropriate diagnostic tool for mucosal lesions evaluation. The visualization of the primary tumor is essential for staging of the extension of the mucosal tumor into the bowel wall and adjacent structures (5,6).

Adenocarcinoma of the rectum generally appears on MR images as a lobulated, soft tissue mass or as well demarcated focal area of rectal wall thickening. Lesions of the rectum are seen as asymmetrical or circumferential thickening of the bowel wall with deformation and narrowing of the lumen, with obstruction. This study had some important limitations (e.g. small number of patients who underwent CT examination - 47%). However, comparing MR and CT results, both techniques staged rectal tumors equally, while perirectal extension is better delineated with MR (7,8). Large tumor may show a central T1W low signal intensity and T2W hyperintensity that represents necrosis (7). We found that high signal intensity on T2W sequences may indicate viable portion of tumor, tumor necrosis as well as edematous tissue. Rectal cancer invasion of the surrounding structures (bladder, prostate, seminal vesicles, urethra, ureters, vagina, small intestines, sacrum and surrounding nerves and vessels) are readily seen on MR. Invasion of adjacent organs is best demonstrated on sagittal (parasagittal) or coronal MR images. MR is therefore superior to CT in multiplanar rectal cancer evaluation. MR also seems to be more effective for staging process (9). MR is particularly useful in surgical planning since sagittal and coronal images can assess the relationship between tumor and rectal sphincter, allowing planning of sphincter saving operations. MR can reliably identify stage III and stage IV tumors, which require more extensive pelvic surgery. MRI is most useful method in patients who have not undergone radiation, biopsy or surgery because associated hemorrhage and edema can be mistaken for transmural invasion.

CONCLUSION

MRI is well-established diagnostic tool for the investigation of the primary rectal cancer. MR is superior to CT in rectal cancer evaluation since perirectal fat invasion may be easier to identify. MRI is the most sensitive noninvasive method available for the detection of metastatic lesions in the liver. We expect that new software programs and new gastrointestinal MR contrast agents will become available for clinical use during the next years as well as use of an endorectal oil which will allow more accurate staging of rectal cancer.

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The role of surgery in multimodal treatment of locally advanced rectal cancer

KEYWORDS: Rectal neoplasms; Treatment; Surgery; Radiotherapy

Though surgery is the main therapeutic modality for rectal cancer, preoperative radiochemotherapy (RCT) or radiotherapy (RT) alone during past decades, especially in 1990s, became an important part of the treatment. What are the goals of RCT/RT used before surgery? They can be defined in several clinical situations (1):

1. To lower local failure rates and improve survival in resectable cancer,
2. To allow surgery in primarily inextirpative cancers,
3. To facilitate a sphincter - preserving procedure in low lying rectal cancers,
4. To cure patients without surgery in those with either a very small cancer or in those at a very high surgical risk.

In this article we shall try to see what is the current status in the second of those situations.

In any stage of rectal cancer, except maybe stage IV, the goal of surgery is to lower the local recurrence (LR) rate as much as possible. LR after curative resection of rectum for cancer has a poor prognosis and is seldom cured (2, 3). But the comparison between the articles is still difficult (4). There are several items that can influence on the evaluation of the results (5):

* The lack of definition of LR (any recurrence occurring in the pelvis with or without extrapelvic /distant/ metastases or only pelvic recurrence),
* Large proportion of the patients with a short follow-up (recurrence is time dependent),
* Case mix of patients (particularly the stage distribution and distribution by distance of the tumor from anal verge),
* The number of patients in the study,
* The definition of curative surgery,
* The use of adjuvant therapies,
* The retrospective collection of data,
* The statistical calculations and expression of the results,
* Assessment that the pelvic disease is incurable may be difficult for the surgeon to determine at operation.
* The preoperative distinction between a primarily unresectable cancer (stage T4 with overgrowth to unresectable organs) and a clinically fixed and locally advanced tumor (stage T3 and certain T4's) (1).

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If we go further, the critical questions that should be asked to focus attention on the subgroup of rectal cancer patients most at risk for LR are what is the LR for:

* advanced stage
* mid and distal rectal cancers? (4).

Very often, in most of the articles we can not find an answer for this question. Moreover, the best criterion for a good operation is histopathologic report, where attention has been given to the circumferential margin because a positive circumferential margin increases the risk of having a LR (6). That enlightens a problem of the education of the surgeon, especially his knowledge in total mesorectal excision, which is a method of choice for the operation of a very low rectal cancer.

The other problem is the construction of the trial, is it a comparison with historical control group or is it a randomized trial? For example, in Uppsala trial they found a resectability rate after chemoirradiation of 71% compared with 34% in a historical control group treated with radiotherapy only (7). But when they constructed multiinstitutional randomised trial, resectabilty rates where high in both groups (85% vs. 75%, an insignificant difference), probably because of greater surgical experience and aggressiveness (1, 8).

In the following lines we shall quote some recent results published this year. Nissan et al. from Sloan-Kettering Memorial Cancer Center, New York were analised 292 abdominoperineal resections of rectal cancer, of which 123 patients received preoperative RT, 65 patents received postoperative RT and 94 patients were operated without RT. After 36 months of follow-up the LR rate was 5.9% for preoperative RT group, 6.4% for postoperative RT group and 9.2% for group without RT (9). They also found early postoperative complications significantly higher in the neoadjuvant radiotherapy groups compared with the non-radiotherapy group.

Mehta and colleagues from Stanford, USA analised 30 patients with T3 or T4 rectal cancer who received preoperative RT (10). They found 33% of specimens histologically without tumors postoperatively, two LR (after 6 and 20 months), one death, and all the other patients were alive (3-53 months of follow-up).

Tjandra et al. from Melbourne analised 42 patients with T3 or T4 rectal cancer preoperatively chemoirradiated (11). Four patients developed distant metastases before operation and 38 patients were operated. Complete tumor response was found in 6 patients, but they also found adverse effects on quality of life and anorectal function.

Medich et al. from Pittsburgh analised 60 patients with rectal cancer (TNM stages II, III and IV) and who received preoperative chemoirradiation (12). They found complete response to the therapy in 5 patients (8%) and downstaging or downsizing in 17 patients (28%).

In our preliminary trial (unpublished), which was conducted at our Institute as a preparation for the inclusion into the LARCS-A Nordic Multicentric Trial, 14 rectal cancer patients were treated (6 females and 8 males, age range 48-71, average distance of lower edge of the tumor from anal verge 6.5 cm). All patients received preoperatively 50 Gy in 25 fractions, two fields technique AP/PA with energy range 10-14 MV. Two patients (14.3%) developed diffuse liver metastases before surgery was performed. In two patients (14.3%) there was no effect of radiotherapy and tumors remained unresectable. In the rest 10 patients (71,4%) there was performed radical surgery (5 abdominoperineal resections and 5 low anterior resections - all with protective ileostomy). No LR has been registered up to now (1-11 months from operation). Postoperative complications were: one ileovaginal fistula (low anterior resection), one dehiscence of ileostomy closure, which was successfully reoperated, and one mild infection of perineal wound in the case of Miles operation.

In the conclusion we can say that though one should neither overestimate the positive effects of neoadjuvant therapy of locally advanced rectal cancer nor underestimate its adverse effects, it seems that it gives real hope in the improvement of our results. Still many unanswered questions in this area are opened.

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Neoadjuvant vs. adjuvant radio(chemo) therapy in locally advanced rectal cancer

KEYWORDS: Rectal Neoplasms; Neoadjuvant therapy; Adjuvant therapy

Radiotherapy can be applied in treatment of rectal cancer in following ways: as adjuvant therapy, therapy of the recurrent disease, palliative therapy and as primary therapy in early stages.

Meta-analyses in numerous studies confirmed that radiotherapy reduced local relapses, but, unfortunately, overall survival was not improved only with radiotherapy (1,2). The local control should not be either underestimated or overestimated, because, apart of the lethal outcome, relapses cause great problems in patient's quality of life.

Although radiotherapy is used in this field of oncology for years, numerous aspects of its administration should be better defined and answer the following: the selection of patients for combined therapy; whether the preoperative radiotherapy is superior than postoperative one and when it has to be delivered; how to select the most favorable cytostatic drugs for combined treatment, their dose and way of application as well as the role of radiotherapy after the large surgery interventions (total mesorectal excision).

Radiotherapy can be administered as an external beam therapy on the megavoltage machines (LINAC) as well as brachytherapy (endoluminal and/or interstitial) and combined therapy (3).

Radiotherapy can be combined with surgery as:

a) Preoperative radiotherapy
b) Postoperative radiotherapy
c) Intraoperative radiotherapy

Radiotherapy in combination with chemotherapy: simultaneous use of radio and chemotherapy (concomitant chemotherapy) most frequently demands tumor dose that ranges about 55 Gy on megavoltage machines.

Both preoperative and postoperative radiotherapies are used in numerous protocols. The advantages of preoperative radiotherapy are: potential of making possibility for radical surgery, reducing of tumor cell viability and dissemination. There are programs for short-term and protracted radiation as well as programs with median and high doses. Reducing of local relapse rate was statistically verified, but there is no evidence of prolonged survival (3).

Results of multicentric randomized postoperative trials show that the postoperative radiotherapy with chemotherapy reduces the percentage of local relapses, prolongs disease free survival, as well as the total survival with quite acceptable morbidity.

Patients who are not candidates for curative surgery can become opera-

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ble after preoperative radiotherapy. The types of operation influence the radiotherapy approach.

The patients with low anterior resection or APR and positive nodes (stage C1, C2, C3) and patients with tumor penetration into the bowel wall (B2, B3) have a great risk for local relapse and distant metastases. That is why radiotherapy, today combined with 5-FU has an important role in improvement of the prognosis. Tumors limited to the mucosa (stage A) or those that involve muscularis propria (Stage B1) have no indications for postoperative radiotherapy. Stage B1 can be an exception if the resection is not a radical one.

Radiotherapy today is conducted with megavoltage machines (X-rays) with at lest three fields with protection of normal tissues. The detailed operative finding is necessary, and, even marker places of risk. The initial volume covers the pelvis and lymph nodes. These are initial wide fields from 3-5 cm above and under the tumor, most frequently with 2 lateral and 1 posterior field or 4 crossed fields. If the patient is irradiated after the APR, any central shielding is prohibited. The total dose with pelvic fields is about 50 Gy, usually with a boost of 5-10 Gy. The daily dose is usually 1,8 Gy and during the last week of treatment, a special attention has to be maid to exclusion of small intestine curves.

There is no dilemma today whether preoperative or postoperative radiotherapy reduces local relapses or not. The fact that is also obvious is that in randomized studies combined therapy has not improved survival rate (radiotherapy and surgery).

The inclusion of chemotherapy in the combination improves treatment results.

Adjuvant therapy is introduced by facts that local recurrence rate is more than 30% in rectal cancer patients treated by surgery alone.

But, now, local recurrences are estimated to be about 10%. Improved surgical techniques improve survival and decrease local recurrence. If it is so, than the role of adjuvant therapies should be re-evaluated (4).

To individualize treatment for rectal cancer patients, we must be able to use the molecular biology, for each tumor that dictates prognosis, as well as specific prognostic factors related to resistance or sensitivity.

Now, preoperative therapy is widely used and provides the opportunity for prospective analyses of response to specific treatment and the influence of some molecular parameters on treatment outcome.

The translation of this information (from laboratory to the clinic) is very important to understand the objective and limitations (5). The treatment of rectal cancer has changed and undergoes transformation: more patients are treated with local modality radiation, chemotherapy or both. We need to identify prognostic (tumor biology) and predictive factors (treatment sensitivity and resistance) (5). The clinical use of one or more intracellular molecular markers for prognosis and therapeutic prediction has to be prospectively identified, and it will be soon.

Incidence of local failure is less than 10% in T1-T2 N0M0, increases to 15%-35% in stages T3N0M0 and T1N1N0, and is as high as 45% to 65% in stages T3-T4N1-2M0 (6). Local failure is severely debilitating; salvage therapy is with limited success. Decreasing the local failure is an important and - point in the treatment of rectal cancer.

Is adjuvant therapy necessary for patients who undergo TME (total mesorectal excision)? (6).

TME series are reported to decrease the local recurrence rate to 5%: but they include patients with T1-T2N0 disease. In N+ patients local failures rate is 23%. TME data: selection of patients, some patients received adjuvant therapy some papers exclude operative deaths, and some are associated with higher complications rates (7).

On the positive side, TME has increased the importance of careful surgical techniques and quality control. As with other cancer treatments, all end points need to be examined, such as local control, survival, sphincter preservation, surgical complications and quality of life. Preoperative adjuvant therapy (most commonly radiation combined with systemic chemotherapy) is an alternative to postoperative.

The primary advantages of preoperative therapy are sphincter preservation and a lower incidence of acute toxicity. The disadvantage of preoperative radiotherapy is the potential of overtreatment (early stage) or metastatic disease. As for the sphincter preservation, the advantage of preoperative radiotherapy is to decrease the volume (downsize) of the primary tumor, and when the tumor is located close to the dentate line, this decrease in volume may allow the surgeon to perform a sphincter - preserving procedure.

The question of whether preoperative combined modality therapy is more effective than postoperative is under investigation in a randomized trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) in which Institute for Oncology and Radiology of Serbia participated.

Preoperative therapy allows sphincter preservation in approximately 75% of patients who had been judged clinically for APR.

Now, phase I/II trial is examining the used of newer agents such as Tomodex, UFT/leucovorin, CPT - 11, oxaliplatin, and capecitabin with preoperative radiation in rectal cancer treatment.

The future use of adjuvant or neoadjuvant therapy to treat rectal cancer is likely to emphasize selectivity regarding the patients who require the therapy; which types of therapy have a chance of benefiting individual patients, which patients do not require additional therapy, and which patients have a poor prognosis but for whom no effective therapy exists (8).

Two major factors are thought to influence local recurrence in rectal cancer:

1. Surgery related factors and
2. Tumor related factors.

Surgery related factors include: low anterior resection inadequacy of excision of the mesorectum, limited extend of lymphadenectomy, use of circular stapling, postoperative anastomotic leakage and tumor perforation during operation.

Tumor related factors that help to predict risk of local recurrence include: anatomic location of the tumor, histologic type, tumor grade, pathologic stage, status of radial resection margin, presence or absence of neural, venous, or lymphatic invasion, tumor border configuration, and host lymphoid response to tumor.

Tumor based molecular markers may help to further discriminate biologically aggressive tumors: p53, p21, p27, TS and VEGF alone or in combination with pathologic features (9). They may also help to predict response to treatment of adjuvant or neoadjuvant therapy for rectal cancer. Although several tissue based factors have been shown to have prognostic value for outcome and or predictive value for therapy their importance remains to be validated in statistically valid studies (9).

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Chemotherapy for rectal cancer - current status and future perspectives

KEYWORDS: Rectal neoplasms; Drug therapy; Drug, Investigational

Multidisciplinary approaches to the locoregional and systemic control of rectal cancer include the role of chemotherapy in adjuvant, locally advanced and metastatic setting. Surgery is the first line treatment for colorectal cancer, since only in patients where the tumor can be radically resected there is a possibility of long-term cure. At presentation, approximately three-quarters of patients diagnosed with colorectal cancer have operable disease, however, 50% of them will subsequently develop metastases.

Rectal cancer lies below the peritoneal reflection and because of the proximity of the surrounding structures the rates of local recurrence are higher than for colon cancer. Thus, the role of chemotherapy in adjuvant therapy for rectal cancer very often is considering together with radiotherapy. Historically, attempts to improve local and consequently systemic control of the disease were at first made by radiotherapy, and the role of chemotherapy has been discussed in context of radiation-drug interaction i.e. radiosensitization. Clinical studies from 70's failed to prolong survival in operated patients using 5FU and methyl-CCNU. Randomized trials performed in past two decades have shown that pre/postoperative radiotherapy can substantially decrease local failure rates, but without influence on overall survival. Introducing chemotherapy in combined regimens resulted in significantly improved survival, compared with surgery alone and postoperative radiotherapy (1,2,3,4). Moreover, a survival benefit was seen by postoperative chemotherapy alone without any radiotherapy in the famous trial (Protocol R-01) conducted by National Surgical Adjuvant Breast and Bowel Project (NSABP) in 1988. (3). The first meaningful consensus was reached in 1990 in USA where National Institutes of Health recommended postoperative radiochemotherapy for all patients with T3 and/or N positive rectal cancer (B2 and C stage) (5). Studies from 90`s have further questioned the role of radiotherapy as the part of postoperative therapy: in a follow-up trial by NSABP (R-02) all patients received chemotherapy whereas postoperative radiotherapy was randomly assigned to half of 694 patients. No survival advantage was seen in radiotherapy arm, although those patients had slightly reduced the cumulative incidence of locoregional relapse from 13% to 8% at five-year follow-up (6). Therefore, in contrast to NCI's recommendations, many European investigators feel that it is premature to advocate combined modality as routine therapy outside the clinical study setting.

In postoperative radiochemotherapy, superiority of protracted infusion of 5FU to bolus 5FU has been proved, in one large randomized trial from 1994 (7). Concerning 5FU modulation, on 1696 patients it was shown that adding of either leucovorin or levamisole have no advantage to 5FU alone, when combined with radiotherapy (8), contrary to results of chemotherapy in metastatic disease where modulation of 5FU with leucovorin stays as the standard in therapy (9).

Recent advances in molecular biology have led to better identifying patients (Dukes B and C) at high risk of recurrence that would benefit from adjuvant chemotherapy. Genetic alterations (mutations of the K-ras oncogene, loss of tumor suppressor gene p53 and DCC) can serve as markers for diagnosis and prognosis. PCR techniques for detecting micrometastases in lymph nodes could improve prognosis of patients in Dukes B stage (10) as well as the level of thymidylate synthetase (TS) expression in patient samples following surgery (high level - worse prognosis) (11). A substantial benefit was seen in NSABP R-01 study for patients with high TS intensity that received adjuvant chemotherapy, contrary to high TS level in advanced disease, where it predicts 5FU resistance, and low TS levels were associated with 52% response (12). The role of monoclonal antibodies in adjuvant therapy was investigated in the study of Reithmuller, using 17-1A antibody (murine IgG class 2A that detects tumor associated antigen CO17-1A). In this randomized study (observation only vs. treatment with 17-1A) on 189 resected Dukes C patients, after 7 years follow-up, treatment reduced mortality by 32% and recurrence rate by 23% (13).

The liver as a common site of metastases in colorectal cancer was the target of intra-portal adjuvant therapy (via portal vein) in a randomized study reported by Taylor, on 257 patients, where after surgical resection of primary tumor a 7-day portal infusion of 5FU 1g/24hours x 7 days was applied (14). He reported significantly improved survival ($p=0.002$) for intraportal arm, but more recent Swiss study has tempered conclusions that this kind of adjuvant treatment can improve prognosis of radically resected patients. Swiss Group for Clinical Cancer research (SAKK) presented on 769 patients randomized to receive either no adjuvant treatment, intraportal 5FU+Mitomycin C perioperatively 7 days or the same chemotherapy via a central vein an equivalent DFS or OS rates for all treatment arms. This study suggests that perioperative treatment is of no value when optimal surgery has been performed (15).

Radiochemotherapy is also widely accepted in the treatment of locally advanced rectal cancer. Combination of radiotherapy and chemotherapy (predominantly 5FU, administered as IV bolus, infusional or peroral, unmodulated or biochemically modulated) given preoperatively has been regarded as "standard" therapy. This approach is supported by results of numerous phase II studies, but the scientific evidence does not fulfil the highest levels. Better results have been reported in 90's: the resectability rate has become greater, as well as the pathological complete remission rate (up to 30% of specimens). Even if we accept that the preferred sequencing of modalities is preoperative radiotherapy plus chemotherapy followed by maximal resection (this manner provides higher antitumor activity without substantially increased toxicity), we have still to wait for the results of randomized trials to establish which schedule is the best. Having in mind that the incidence of systemic failure is more than 50%, and local failures after irradiation still occur, especially when a gross total resection is not surgically feasible, it's clear that we need more efficient chemotherapy during and after external irradiation.

For more than 30 years chemotherapy of advanced colorectal cancer was a "one drug show". 5FU still represents the "gold standard", but in the last decade a number of new active drugs were identified, as well as the novel targets with increased tumor selectivity. The activity of 5FU (10-20% response rate) and its toxicity profile depend on dose and mode of administration. Adding of folinic acid (FA) to 5FU represents a classical advantage to response rate and tumor-related symptoms (16); infusional 5FA(FA is more active than bolus with respect to response rate and time to progression, exhibiting a more favorable toxicity profile (less mucositis, neutropenia and

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diarrhea, but can cause hand-foot syndrome) (17), but all that interventions produce a little effect on overall survival. High-dose 5FU(FA regimens (weekly, continuous infusion over 24h with MTD of 5FU 2.6 g/m2 and over 48h MTD 3.5 gr/m2) with dose-limiting toxicity being non-hematological, also failed to achieve significant survival advantage over standard, bolus 5FU/FA Mayo regimen.

Playing an essential role in de novo synthesis of thymidylate and subsequently DNA synthesis, enzyme thymidylate synthase (TS) has been recognized as a target for cancer chemotherapy in the development of fluoropyrimidines. 5FU is converted intracellularly into its active metabolite 5-fluorodeoxyuridine (5FdUMP) which is very potent inhibitor of TS. On the other hand enzyme dihydropyrimidine dehydrogenase (DPD) which catabolizes 5FU initially can affect both the toxicity and antitumor efficacy of 5-fluorouracil (tumors expressing a high level of DPD are resistant to 5FU and conversely, patients who are deficient in DPD have been observed to experience severe side-effects). It's already mentioned above that high TS level in tumor predicts 5FU resistance, and to overcome these problems, a new generation of TS inhibitors, folate-based, were designed.

The development of oral fluorinated pyrimidines has become a very popular area of research. Some of them have been introduced to inhibit the degradation of orally given 5FU: UFT (uracil plus tegafur in a fixed 1:4 ratio) competitively blocks the action of DPD through uracil, enuracil is a direct inhibitor of DPD, and S1 also inhibits DPD through its component 5-chloro-2,4-dihydroxypyridine. Capecitabine is an example of selective 5FU prodrug that can be absorbed intact through the gastrointestinal tract, and then converted to 5FU by three enzymatic steps, in tumor tissue. The most clinical experiences could be derived from studies about capecitabine and UFT. Their efficacy is comparable to parenteral 5FU-LV, in terms of response rate, median time to progression and median survival. Oral fluoropyrimidines have a favorable toxicity profile with lower rates of stomatitis and neutropenia, except palmar-plantar erythema similar to that observed with CI of 5FU (mechanism of action of oral 5FU prodrugs might mimic continuous infusion of 5FU). Oral fluoropyrimidines represent an attractive and creative pharmacological advance valid enough to find their place in therapy of advanced colorectal cancer, combining with other novel cytotoxic drugs. Their role in adjuvant setting is still investigational.

Irinotecan and oxaliplatin are another two promising drugs, apart from numerous fluoropyrimidine family. Topoisomerase I inhibitor, irinotecan (CPT-11) has demonstrated its activity in previously 5FU treated patients (RR 13-15%), and also in chemotherapy untreated patients (RR 24-29%). Two large multicentre trials (in Europe and USA) consistently reported that the addition of irinotecan into infusional or bolus 5-FU/FA regimens is superior to 5FU/FA alone, in terms of overall response, duration of progression-free survival and overall survival (18,19). Based on these data, combination irinotecan/5-FU/FA may be considered as the new reference in first line chemotherapy of advanced colorectal cancer Oxaliplatin as a representative of third generation of platinum compounds has proven to be more active in therapy of colorectal cancer (21% RR in chemo-naive patients) than other platinum drugs. In randomized studies when combined with 5-FU/FA, oxaliplatin has shown significantly better response rate and progression-free survival compared with 5-FU/FA alone, but differences in survival were marginal (20,21).

Thus, after failure on standard Mayo regimen (bolus 5-FU/FA) a several second-line approaches may be offered patients in good performance status: weekly infusional 5FU-FA, irinotecan, oxaliplatin, some of oral 5FU prodrugs, alone or in combination. Moreover, some US study groups are presently comparing weekly 5FU/FA with irinotecan or oxaliplatin combined with weekly 5FU/FA as adjuvant therapy after the resection of stage II or III colon cancer.

In the case of liver metastases only, intrahepatic administration of chemotherapy (HAI - hepatic arterial infusional chemotherapy) may be considered in selected centers and within clinical trials. A meta-analysis indicated that this treatment resulted in higher response rate, but without survival prolongation, compared to systemic chemotherapy (22). Two relatively small recent trials reported that following resection of hepatic metastases a combination of HAI and systemic chemotherapy may prolongs survival (23,24).

In parallel with development of new cytotoxic drugs, advances in the field of molecular biology and immunology have led to definition of new targets providing the basis for the treatment with increased tumor selectivity. The first of these tumor-specific targets involve the process of cancer cell growth regulation: K-ras oncogene is mutated in up to 50% of colorectal cancers and several agents that interfere with the constitutive activation of p21ras (inhibitors of farnesyl protein transferase) are currently investigating in phase I and phase II clinical trials; the overexpression of growth factor receptors on cell surface (EGFR and HER2/neu) may be targeted by monoclonal antibody against HER2/neu (trastuzumab) or inhibitors of EGFR tyrosine kinase (ZD1839-Iressa); mutated p53 genes are found in 75% of all colorectal cancer, and numerous efforts are underway to introduce wild-type p53 into cancer cells and to promote apoptosis, using adenoviruses as vectors and requiring local administration through hepatic artery in patients with liver metastases (26). Targeting host response to cancer, both cellular (CD8 cytotoxic T-cell response) and humoral (monoclonal antibodies) immunity are used: initially, vaccine therapy for adjuvant therapy was prepared of irradiated autologous tumor-cell homogenates and BCG as vaccine adjuvant, and failed to prolong survival in stage II and III colon cancer patients; in another approach a virus is genetically engineered to express a tumor antigen (CEA for example) and testing of this viral vector vaccine is planned in a setting of minimal residual disease; it is mentioned above that murine monoclonal antibody 17-1A against 34-kd glycoprotein antigen commonly expressed on adenocarcinomas given patients in stage II and III colon and rectal cancer resulted in prolonged survival compared to surgery alone (13), but confirmatory trials failed to repeat such results. The third target is the interaction between tumor cells and their microenvironment: to inhibit angiogenesis as the fundamental process in tumor growth, a family of degradative enzymes, matrix metalloproteinases (MMPs) has been identified and their inhibitors were designed; also, a recombinant humanized antibody against VEGF(vascular endothelial growth factor) is in clinical development, in randomized phase II study that compares 5FU/FA with 5FU/FA plus anti-VEGF monoclonal antibody in metastatic colorectal patients. In designing clinical trials with these rather cytostatic than cytotoxic agents, regression of measurable disease may not be the most appropriate surrogate for activity: gross tumor shrinkage could not be expected. Thus, an alternative end points are needed like time to progression. How to integrate these new treatments with classic cytotoxic agents as well as how to optimally design clinical trials to demonstrate effectiveness it will be the great challenge for laboratory and clinical investigators in forthcoming years.

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Chemotherapy of locally advanced rectal cancer

KEYWORDS: Rectal neoplasms; Antineoplastic agents, Combined; Survival rate

A great number of patients with rectal cancer (RC) can be cured, so they can normally reach their potential life span. The cure of RC can be defined only by complete eradication of total tumor burden from the body. This eradication is possible mainly by radical surgical resection, but also sometimes by irradiation of small localized tumors. RC is chemoresistant neoplasm. The results of the chemotherapy (CHT) for RC are not spectacular, but CHT can often obtain an important benefit for a patient (1).

Therapeutic approach in RC is established and accepted by medical community for stages of locally disease and of advanced disease. About the borderline entity, the locally advanced rectal cancer, still there is no consensus related to the best combination of complementary therapeutic modalities (2).

Advanced rectal cancer (metastatic and/or unresectabe RC): all therapeutic modalities are mainly palliative, but often can obtain good quality of life during considerable span of time. Exceptionally can be performed the operation with intention to cure, including both metastasectomy and resection of primary RC (3). In most cases the role of surgery is limited to by-pass colostomy and sometimes to debulking of pelvic tumor mass; there is often a chance for cryosurgery to obtain a good local control by repeated debulking procedures. Irradiation can obtain pain relief and also temporary local control. Although with limited impact, the CHT has an important role too.

Standard CHT in advanced RC is based on intravenous 5-fluorouracil and folinic acid (FU/FA) regimens and can provide only a moderate (20-30%) objective remission rate (CR and PR). The main reason of this ineffectiveness is the small growth fraction (2-4%) in RC tissue (4). In spite of a low objective response rate, more than a half of the patients have some benefit from the CHT. Even the temporary stopping of progression is also very important result of CHT, so the overall antitumor activity (including PR, MR and NC) can be achieved in 60-85% patients, with a delay of progression of 6-7 months, resulting in overall survival of 8-12 months or more (5). There is also the effect on the quality of life, primarily on the pain relief in the great proportion of patients. The same effects express orally FU analogues (capecitabine, tegafur) and although more expensive, they are more convenient than intravenous regimens. The new agents (oxaliplatin, irinotecan, and raltitrexed) used alone or in combination with FU/FA can potentially enhance the effectiveness of CHT (3,6).

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Localized rectal cancer: Standard treatment is radical resection, and in selected cases irradiation, both with intention to cure. Depending of the postoperative histopathological assessment of the stage of the disease, the adjuvant postoperative irradiation is recommended for more advanced tumors. There are some evidences that adjuvant CHT can reduce the rate of distant metastatic disease, and also that CHT administered alone or in combination with postoperative radiotherapy can reduce the rate of local recurrences. The adjuvant CHT and RT after potentially curative resection of RC, for TNM stages II and III (Dukes B2 and C) was recommended as the standard treatment in USA from 1990 by National Institute of Health Consensus conference (7). The standard adjuvant CHT is based on FU/FA or FU-levamisole combinations. Novel agents mentioned above, as well as specific antibody I7-1A (8) can also be considered for adjuvant setting, but still in investigation clinical studies.

Locally advanced rectal cancer is term used for RC, which is unresectable due to extensive local spread (9). However, these lesions are potentially curable. Although unresectable at presentation, they may be downsized by preoperative tumor debulking procedures. These procedures cause tumor regression to such an extent that the cancer can be resected radically, with a curative intent (2,10).

The treatment used prior to surgery, with intention to make its results more favorable is named primary, or neoadjuvant therapy. Moderate chemosensitive tumors, e.g. breast cancer, laryngeal cancer etc, can become more convenient for resection after chemotherapy (11). Due to chemoresistance of RC, irradiation is standard neoadjuvant treatment used for downsizing of locally advanced RC. During many years there were also trials with FU used as "radiosensitizer" which could enhance the effect of irradiation.

The use of nowadays-available cytostatics for primary (neoadjuvant) treatment, as an attempt for downsizing advanced RC, can only exceptionally be successful because of chemoresistance of this type of neoplasm. Therefore, CHT could be applied only in combined-modality therapy, as a supplement of the proven irradiation treatment. The role of chemoradiotherapy has been extensively studied but the most favorable scheduling is not yet known (2).

Except its contribution in reducing of tumor burden, there could exist also some additional benefits of neoadjuvant CHT, e.g. activation of tumor specific cytotoxic T-cells and angiogenesis inhibition (12).

Considering a high risk of advanced RC for local recurrence and/or metastatic spread, adjuvant CHT is also recommended. Also could be considered application of monoclonal antibody 17-1A in combination with CHT, as an attempt to destroy dormant cells too (8).

In conclusion, treatment of locally advanced CRC still remains under the investigation and participation in clinical trials should be obtained for all eligible patients (9).

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CEA negative values in metastatic colorectal carcinoma

KEYWORDS: Colorectal neoplasms; Neoplasms, Metastases; Tumor markers, Biological; Prognosis

Although CEA was discovered more than 35 years ago, (1) some controversies still surround its best applicability and optimal clinical utility in the management of colorectal cancer. Increased preoperative values, although not always corespondent with Dukes stage has predictive role in colorectal cancer outcome, usually reflecting higher tumor burden and often, confirming micrometastases. (2). Increased postoperative CEA, represents overt or occult metastases in 60-94% of patients, (3) and sometimes can be indication for second look operations. (4, 5). Decreasing CEA values during chemotherapy usually confirms better therapy response. (6, 7, 8), while increased values predict and even precede poor response. (9) On the other hand, despite decades of experimental and clinical research, biological functions of CEA are not yet completely understood. It is generally accepted that only well-differentiated tumors can produce CEA, while less differentiated, meaning more aggressive tumors, remains CEA negative. (10,11) Therefore, it could be assumed that patients with CEA within normal range during metastatic disease have more aggressive tumors. Since there are reports of better chemotherapy response and longer survival in patients with CEA within normal range at the time of metastatic disease diagnosis, those data seems to be confusing. (12) Does the hypothetical patient with CEA within normal range at the time of metastases development, have more or less aggressive colorectal carcinoma, worse or better prognosis? Reviewing the literature we could not find data about CEA negative metastatic colorectal cancer patients. Therefore, the primary endpoint of this study is to determine prognostic and predictive influence of initially CEA negative values in metastatic colorectal carcinoma patients.

PATIENTS AND METHODS

Patients

During 4 years 250 patients with metastatic colorectal carcinoma, previously untreated except with adjuvant chemotherapy, were included in three consecutive 5-FU based chemotherapy trials. CEA was randomly determined in 114 patients: before therapy initiation, after two cycles and at the time of estimated best response and only the initial CEA values were considered. According to initial tumor marker level, patients were stratified in three groups: CEA negative: CEA < 5 ng/ml (n=22); CEA positive: CEA >5 < 100 ng/ml (n=33); and "extremely" high CEA: CEA > 100 ng/ml (n=59). Twenty patients in the later subgroup (33,8%) had CEA higher than 1000 ng/ml, range 1000-40.000 ng/ml.

Statistical Methodology

Cox proportional hazard model was used to assess prognostic significance of CEA levels and survival. Univariate and multivariate log regression analysis was used to determine the probability for achieving response in correlation to CEA levels, and Kaplan- Meier for survival curves.

RESULTS

Statistical Consideration

Univariate and multivariate log regression statistical analysis confirmed that the probability to achieve chemotherapy response probability to achieve better response was clearly dependent upon CEA level (p=0.0035).

The probability to achieve complete response was again extremely statistically dependent of CEA levels (Fisher p=0.0001) i.e. the higher CEA values, the smaller is the probability to achieve CR. achieve complete responseThe same statistical correlation was confirmed for survival that is Survivalstrongly dependent upon CEA level (p=0.001), and was shortest in a group of patients with "extremely" increased levels of CEA. The survival was shortest in the subgroup of patients with higher CEA levels (Kaplan-Maier, log-rank p=0.0007)

Response in correlation to CEA level

Among 114 patients who had determined CEA values, 112 patients were evaluable for response upon WHO criteria. (13). Responses were 7 complete (CR= 6.1%), 22 partial (PR= 19.2%), 45 stable disease (SD= 39.4%) and 38 progressive disease (PD= 33.3%), while 2 patients were not evaluable for response. The median value of CEA in the subgroup of patients that achieved CR was 1.45 (range 0.24-18 ng/ml). In the PR subgroup median values of CEA were 50.10 (range 0.52-3580 ng/ml). In the SD subgroup median CEA were 66.0 (range 1,4-40.000 ng/ml). In the PD subgroup median values were 158.0 (range 1.19-40.000 ng/ml). Among 7 CR, 6 were observed in CEA negative group, while only one CR was achieved in a CEA positive patient. The percent of CR is 6.1 that is remarkably higher than usually reported. But, for unclear reasons, all CR were observed in a CEA determined group of patients and none in a CEA unknown group of patients. The percent of CR calculated in all 250 treated patients, is 2.8%, which correlates with literature data. Achievement of CR was rapid, median after three cycles and long-lasting median 24 months, range 10-37. Median age for patients with CR was 55 years. Among 7 patients that achieved CR, 5 were female, median age 48 years. Median survival of patients with CR was 32 months (11-46m+) while one female patient is still alive, almost 4 years after metastatic disease was first diagnosed. All complete responders, as the patient with increased CEA that normalized after second chemotherapy cycle, remained CEA negative through whole treatment and follow up period until disease recurrence. Eventually, recurrence occurred in all patients and was accompanied with increment of CEA, except in one patient that again, had CEA within normal range and another patient that had unknown CEA status at the time of relapse.

DISCUSSION

Almost 50% of operated colorectal cancer patients will develop metastases and die, despite chemotherapy within 9-14 months (14,15). As far as we know, there are no permanent cures of metastatic colorectal carcinoma with chemotherapy. Approximately 3% of complete responses are far too small to have greater influence on the overall survival. Resection of liver metastases can result with permanent cure or at least five to ten years' survival in approximately 10% well-selected patients (16,17,18). The characteristics of patients that could be effectively treated with resection of liver metastases are well recognized, while characteristics of patients capable to achieve CR with chemotherapy, are not defined. In fact, due to small percent of CR it

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is not clear could the prospective identification of patients who are most likely to achieve CR be possible at all. The correlation of CEA values and capability to achieve CR is also undefined. More that 85% of metastatic colorectal carcinomas are accompanied with increased values of CEA and it is still unclear whether the increased CEA is a consequence or maybe, even a cause of metastases or combination of both that makes fatal *circulus viciosus* for the patient (19). It is usually accepted that CEA simply represents tumor burden, the higher CEA, the bigger tumor volume and metastases. On the other hand, between 5-15% of patients have normal values of CEA even during overt metastatic disease. Does these patients has different course of disease and if they do, than why, remains undefined. More than a decade ago it was recognized that CEA is a member of immunoglobulin gene superfamily (20, 21). Some experimental data suggests that modulating intercellular adhesion and functions, CEA act as a promoter of cellular aggregation thus affecting metastatic potential of malignant cells (22). Also, it was suggested that CEA might inhibit host defense mechanisms and enhance intercellular adhesion. It was also, postulated that immunotolerance to CEA could play a significant role in metastases development. That hypothesis was basic for promising anti-CEA antigen immunotherapy with ultimate goal to disrupt the supposed immunotolerance to CEA (23). Indeed, specific anti-CEA idiotype T-cell response was confirmed in most patients with recurrent colorectal carcinoma during treatment with antidiotypic monoclonal antibody. Seventy percent of the treated patients developed active humoral and cellular immunity to CEA (24). In our group of patients clear benefit was observed for response, especially complete response, duration of response and survival in-patients who had initial CEA within normal range. Only one patient with increased CEA achieved complete response, while the other 6 complete remissions were achieved in CEA negative patients. Correlation between initial CEA and probability to achieve response proved to be highly statistically significant. Therefore, it is our impression that metastatic colorectal cancer patients with initial CEA within normal range have more favorable prognosis. In fact, these patients seem to represent that rare subset, capable to achieve durable complete response, remaining CEA negative through remission period.

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Histopathological and molecular parameters in prognostication and treatment response of colorectal cancer

KEYWORDS: Histopatology; Prognosis; Tumor markers, Biological; Colorectal Neoplasms

The basis for all staging systems of colorectal cancer is clearly related to the degree of penetration of the tumor through the bowel wall and the presence or absence of nodal involvement. Furthermore, vascular invasion and negative radial resection margin status have strong impact on prognosis. The presence of extramural and extranodal microscopic cancer foci discontinuous with primary lesion in colorectal cancer exhibits additional prognostic significance and our own results also proved significant rise of recurrence in cases with cancer microinvolvement of mesorectal fat as well as micrometastases in perirectal lymph nodes. In our series of 23 cases, those greater than 200 microns correlated closely with large tumor nodules and metastatic lymph nodes. Elevated pretreatment serum levels of carcinoembryonic antigen (CEA) have a negative prognostic significance. Many other prognostic markers have been evaluated retrospectively in the prognosis of patients with colon cancer, although most, including allelic loss of chromosome 18q (DCC gene allelic loss) or thymidylate synthase expression, have not been prospectively validated. Microsatellite instability (MSI-H), also associated with hereditary nonpolyposis colon cancer, has been shown to be associated with improved survival independent of tumor stage. Because of the frequency of the disease, the identification of high-risk groups, the demonstrated slow growth of primary lesions, the better survival of patients with early-stage lesions, and the relative simplicity and accuracy of screening tests, screening for colon cancer should be a part of routine care for all adults starting at age 50 years, especially for those with first-degree relatives with colorectal cancer. Following treatment of colon cancer, periodic evaluations may lead to the earlier identification and management of recurrent disease. A review of the use of CEA suggests: that this tumor marker is not a valuable screening test for colorectal cancer due to the large numbers of false-positive and false-negative reports and that postoperative CEA testing should be restricted to patients who would be candidates for resection of liver or lung metastases. Advances in understanding the biology of colon cancer have progressed rapidly over the last several years and include replication errors, mutations of oncogenes and tumor suppressor genes and expression of tumor specific antigens and cytokeratins. Some of them seem to be potential markers not only of prognostic value but also important as screening tools and therapeutic molecular targets. For instance, there are encouraging experimental results with cyclo-oxygenase-2 (COX-2) inhibitors, such as nonsteroidal anti-inflammatory drugs (NSAIDs), which effectively prevents colon cancer progression by induction of apoptosis and inhibition of angiogenesis and/or improves radiation response. In addition, antiapoptotic bcl-2 protein and apoptotic indices could also be examples of potential prognostic markers in predicting response of colorectal cancers to anticancer drugs and irradiation.

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Why evidence-based oncology? Commentary on the article "Palliative chemotherapy for advanced colorectal cancer: systematic review and meta-analysis"

KEYWORDS: Evidence-based medicine; Colorectal neoplasms; Drug therapy

Most doctors would argue that our goal in oncology (or in medicine) should be to attempt to learn the truth and act according to the state of events that provided the ground for that belief. Philosophers of the positive movement believed that once we learn the truth and act according to it, all of the evils of the world would disappear. Bertrand Russell wrote: "A habit of basing convictions upon evidence, and of giving to them only that degree of certainty which evidence warrants, would, if it became general, cure most of the ills from which word is suffering".

The lesson for oncology is clear, we would do the best for our patients by administering a diagnostic test or applying a treatment according to the published scientific evidence. What then is the reason that many of our management practices are based not on the evidence, but rather on personal experience, habits or authority? (1). The main reason for this appears to lie in the nature of the interpretation of evidence. On one hand, clinical medicine has always remained an interpretative discipline. Different observers can interpret result of a study differently. That is, evidently, the standards of clinical medicine will have to rely on the subjective value of personal knowledge. On the other hand, it is self-evident that not all evidence is created equal and that certain findings are closer to the truth than others. There must exist some rational system to determine if the results of one study are more believable than that of another. If this is the case, than how should evidence be evaluated and how should the compromise between "objective truth" and the subjective nature of the interpretation of evidence be accomplished?

David Hofstadter, an artificial intelligence researcher, believes that it is not possible to lay down laws to precisely define what is evidence, but that truth can be approached with guidelines whose development should rely not only on the principles of logic and reasoning, but also on intuition and common-sense (2). In sharing this view, we believe that the sensible combination of scientific principles for the identification and evaluation of evidence and common-sense approach can bring us closer to the truth. The principle of interpretation of evidence forms the basis of evidence-based oncology.

Evidence-based oncology has emerged as a powerful problem-oriented practice of oncology that seeks to:

1. Convert clinical issues regarding patient care into answerable questions,
2. Search, with maximum efficiency, for the best evidence with which to answer these questions,
3. Critically appraise that evidence for its precision (power), validity (closeness to the truth), and relevance (applicability in the practice),
4. Summarize and integrate this appraisal with clinical experience and expertise in order to apply the results in practice,
5. Evaluate performance and the impact of the process on clinical practice.

For example of evidence-based analysis, regarding current open questions in the treatment of advanced colorectal cancer, we are presenting our commentary and ranking score on the article "Palliative chemotherapy for advanced colorectal cancer: systematic review and meta-analysis" by the Colorectal Cancer Collaborative Group (3), published in Evidence-based Oncology Journal (4).

COMMENTARY

The medical treatment of advanced colorectal cancer (ACRC) has met major challenges in the last decade. The most important has been to establish the effectiveness of chemotherapy. As a result of randomizing trials, there is growing evidence that people with ACRC benefit from chemotherapy in terms of survival and quality of life. The quality of life gain does not appear to be restricted to patients with objective tumor response only, as twice as many patients achieved a disappearance or relief of tumor related symptoms. Several regimens are widely employed as first-line therapy but none is established as a universally accepted standard treatment (5). Existing trials comparing chemotherapy with supportive care are not widely known. For example, a leading oncology text only refers to one study on this topic (6). This results in uncertainty for both patient and physician envisaging chemotherapy.

Colorectal Cancer Collaborative Group has performed an important meta-analysis to determine whether chemotherapy compared to supportive care alone can provide meaningful benefit for patients with ACRC. As reported, the meta-analysis provides convincing evidence based on time to disease progression and survival data that chemotherapy is superior. Are there weaknesses in this meta-analysis? Probably not regarding criteria for selecting studies, search strategy, review procedures and statistical methods, which were used in the meta-analysis. Despite that, the present meta-analysis could not weight the benefit of chemotherapy against treatment toxicity and affect the quality of life. Assessment of treatment related toxicity and quality of life are fundamental in determining the acceptability of chemotherapy as a palliative treatment.

The observation concerning equal chemotherapy effectiveness in the elderly and in the young could be debatable because the elderly patients included are likely to be highly selected and thus not characteristic of patients in this age group. Participants in analyzed trials were of generally high performance status. One cannot necessarily generalize these results to patients in poorer general condition. Finally, in interpretation of the meta-analysis data some caution is advised because of publication bias (the existence of missed unpublished negative studies), which cannot be completely excluded.

This report is supported by another meta-analysis reported in literature. Jonker et al.(7), performed a meta-analysis of seven randomized controlled trials comparing chemotherapy with either observation or supportive care alone in people with ACRC. Again, chemotherapy significantly prolonged 1-year survival. These reports provide high-level guidance to physicians to offer

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chemotherapy to anybody with disease who can tolerate the relatively mild toxicity of treatments. Future studies and systematic review should address previously mentioned unanswered questions. New drug development and new insights in molecular markers of prognosis can assist in the individualization of treatment and improvement of the outcome for people with ACRC.

Ranking score (scale 1-4): relevance 4; validity 2; applicability 3; feasibility 3; impact 3; knowledge context 2.

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Evaluation of rectal cancer response after preoperative radiotherapy by spiral computed tomography

KEYWORDS: Rectal neoplasms; Radiotherapy; Computed tomography

The main aim of our study was to show the effectiveness of preoperative radiotherapy of locally advanced rectal cancer (T3NoMo and T4NoMo stage) by spiral computed tomography.

PATINETS AND METHODS

In the Institute for Oncology and Radiology of Serbia during a period from March 1996 to December 1999, a clinical prospective non-randomized study was performed in a total of 55 patients with locally advanced rectal cancer. All patients were treated by preoperative radiotherapy with a tumor dose of 45-50 Gy applied during 5 weeks on a linear electronic accelerator with technique of 3-4 fields. With an aim to initially stage and plan adequately preoperative radiotherapy examinations of all patients were performed on CT (HeliCAT II, ELSCINT Israel). The initially scan of abdomen and pelvis were made on a flat surface in prone position with the previous preparation of patients (30 ml 76% urographine contrast diluted in 1-1.5 liter of water which the patient drank 1.5 hours before the examination, with intravenously application of 60-120 ml of Telebrix 380 contrast during the examination), and also insufflations per recti 200-300 ml of diluted water soluble contrast. After adequate preparation patient was placed on specially designed flat table, which had at the middle metal mark made of special material for purpose to reduce artifacts. Patients lay in prone position, which was of great importance for radiotherapy planning. On initial CT examination we calculated volume V1, and after radiotherapy volume V2. Both volumes were calculated from three diameters: anteroposterial, transversal and longitudinal.

RESULTS

Tumor volume before radiotherapy was calculated from tumor diameters established during the CT examination: longitudinal (length of rectal segment invaded by tumor), transversal and anteroposterial diameter (AP). Volume V1 was calculated for every patient and than for the whole group. Average value was calculated for every diameter, than median, standard deviation, range (min- max), volume in millimeters and centimeters (Table 1).

Average value of longitudinal diameter for whole group was 61.66 mm,

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for transversal 40.86 mm, for anteroposterial diameter 27.64 mm, average

Table 1. Values of diameters and tumor volumes V1 for whole group

	DLONG1 (mm)	DTRANS1 (mm)	DAP1 (mm)	V1 (mm^3)	V1 (cm^3)
Number of patients	55	55	55	55	55
Average value	61.156	40.865	27.644	93087.509	93.0875
Median	60.000	40.000	25.000	66600.000	66.6000
Std. Deviation	22.790	15.608	12.986	112944.28	112.9443
Range	124.0	69.5	71.0	627480.0	627.48
Minimum	21.0	18.5	9.0	4200.0	4.20
Maximum	145.0	88.0	80.0	631680.0	631.68

volume value was V1 93.09 cm3.

One month after applied radiotherapy control CT examination was conducted. Patient was placed in supine position but all other criteria (slice thickness, table increments, etc.) examination was performed same as initially. The same parameters were tested as we did for volume V1. The radiotherapy was interrupted in one patient because of complications. Calculated values are shown in Table 2.

For whole group of patients values of diameters and volumes were: average value for tumor longitudinal diameter 38.97 mm, transversal 23.63 mm,

Table 2. Values of diameters and tumor volumes V2 for whole group

	DLONG2 (mm)	DTRANS2 (mm)	DAP2 (mm)	V2 (mm^3)	V2 (cm^3)
Number of patients	54	54	54	54	54
Average value	38.970	23.630	14.333	26318.804	26.3188
Median	40.000	20.000	11.000	9050.000	9.0500
Std. Deviation	21.770	15.071	9.664	40808.570	40.8086
Range	80.0	70.0	40.0	224000.0	224.00
Minimum	0.0	0.0	0.0	0.0	0.00
Maximum	80.0	70.0	40.0	224000.0	224.00

anteroposterial 14.33 mm and tumor volume V2 26.318 cm3. Maximal values were for: longitudinal tumor diameter 80mm, transversal diameter 70mm, anteroposterial 40mm, and tumor volume V2 224 cm3.

Tumor volume V1 and volume V2 , (before and after radiotherapy) were compared by Wilcoxons test of range. Important statistical difference was established (p= 0.00), which pointed out the positive effects of preoperative radiotherapy on tumor volume decrease (tumor downstaging) (Table 3).

Evaluation of tumor response after radiotherapy was based on results we got from spiral computed tomography examinations and rectoscopy, accord-

Table 3. Volumes values V1 and V2 for whole group

	Number of patients	Average value	Std. Deviation	Minimum (cm^3)	Maximum (cm^3)
V1CM	55	93.0875	112.9443	4.20	631.68
V2CM	54	26.3188	40.8086	0.00	224.00

ing to the recommendations of WHO (World Health Organization). The condition without any signs of tumor was denoted as complete regression. The decrease of tumor more than 50% in comparison to pretherapy size was denoted as partial regression. Complete and partial regression makes the response rate (RR). In case without any changes before and after therapy was registered as no change (NC) and locoregional and distant dissemination as disease progression.

In the group we studied, out of a total 55 patients, complete regression (CR) was detected in 5 patients or 9.3%, partial regression (PR) in 28 patients or 51.9% and no-change (NC) in 21 patients of 38.9%. Disease progression did not appear in any of the patients. In one patient or 2.08% the response to performed radiotherapy was not assessed. The response rate (RR) in the studied group was 61.2% i.e. it was detected in 33 patients (Chart 1). CR- complete regression, PR- partial regression, NC- no change, PD- progression of the disease.

CR- complete regression, PR- partial regression, NC- no change, PD- progression of the disease.

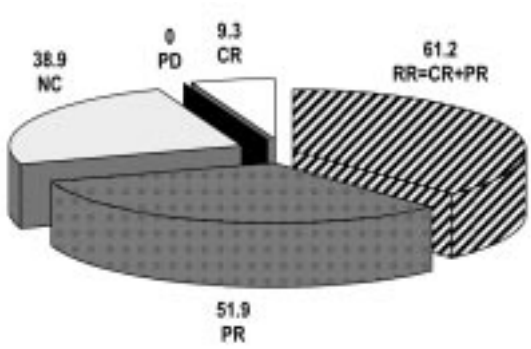

Figure 1. Tumor regression after performed radiotherapy

DISCUSSION

Studies of many authors have shown that preoperative radiotherapy has a great influence on primary tumor regression and also better resectability. Gerard and al. /1/ (EORTC) have achieved complete tumor regression in 5 patients or 3% in whole group of 166 patients after preoperative radiotherapy with 34.5 Gy, applied in 15 fractions, with 2.3 Gy per fraction. Reis Neto and al. (2) have published results of preoperative radiotherapy in group of 34 patients with tumor dose of 40Gy applied in 20 fractions, with 2Gy per fraction. Tumor regression (over 70%), was diagnosed by rectoscopy and digital examinations, in 26 patients or 76.4%, and over 90% in 6 patients or 17.6%. Minsky and al. (3) in their study have shown after applied preoperative radiotherapy with 46.8Gy which was given during a period of 5 weeks, with 1.8Gy per fraction, complete regression of the disease in 3 patients or 10% in whole group of 30 patients. Guarneri and al. (4) achieved complete tumor sterilization after preoperative radiotherapy in 5 patients among 65 patients which means in 7.6% of cases. Mermeshtain and al. (5) achieved complete tumor regression after preoperative chemoradiotherapy in 4 patients or 8.7% in whole group of 23 patients.

CT examinations that had been performed after radiotherapy were used only for evaluation of decrease in tumor diameters and volume, because changes in surrounding perirectal fat tissue caused by radiotherapy unabled correct locally staging. Comparison of our results with results of other studies (6-8) shown that in our study CT had greater accuracy in estimation of tumor diameters 82.05 % (average value of longitudinal diameter after radiotherapy was 3.9 cm, and histopathological was 3.2 cm).

Analyzing results of our clinical prospective nonrandomized study in a group of 55 patients with rectal cancer (T3NoMo and T4NoMo stage) after examination on spiral computed tomography, we concluded that preoperative radiotherapy has great influence on tumor downstaging, and that spiral computed tomography has high accuracy in estimation of tumor diameters and volumes.

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Modalities of surgical treatment of advanced rectal cancer

KEYWORDS: Rectal neoplasms; Surgery; Anus praeter naturalis

Surgery plays the most important role in the treatment of advanced rectal cancer. With an appropriate surgical operation the best chances for longer survival and better conditions for adjuvant therapy - radio and/or chemotherapy can be obtained. The objective of this overview is that applied surgical method depends on tumor distance from anocutan line and on T factor. Examined and evaluated patients were under surgical treatment in last four years at the Institute. A total of 50 of 190 operated patients with colorectal cancer had advanced disease (T3/T4). Positive lymph nodes had 21 patients and distance metastasis 16 patients. The results showed that in advanced rectal cancer the most often surgical approach was Milles operation - 27 patients (54%), *anus praeter naturalis* - 16 patients (32%), Dixon operation - 4 patients (8%) etc. 34 patients (68%) had tumor located from 2 to 6 cm from anocutan line (proctoscopically measured). In all cases resection edges were without malignancy marks. The treatment was respected by Institutes' protocol. From our results comes that in advanced rectal cancer the most important factor for selection of operation type is tumor distance from anocutan line.