Purpose: Radiotherapy has been the standard treatment of anal canal carcinoma for the last three decades. However, there are still many open questions such as optimal radiation technique, adequate boost dose or best chemotherapy regimen. Besides cure and local control, other important goals are sphincter salvage and avoidance of a permanent colostomy, i.e. morbidity minimization.

Material and methods: At the Institute for Oncology and Radiology of Serbia, between March 1997 and May 2004, patients with anal canal carcinoma were treated with combined external beam radiotherapy and brachytherapy boost as primary treatment modality. Initially, external beam radiotherapy was applied with two opposed parallel fields and dose ranged from 40-50 Gy and after that patient continued the treatment with brachytherapy boost (intraluminal or interstitial) with doses ranged from 10-25 Gy. Total tumor dose in combined radiotherapy treatment ranged from 55-70 Gy.

Results: Out of 21 patients, acute complications were registered in 15 patients (71.4%) and the most frequent was dermatitis. Complete response after radiotherapy was registered in 17 patients (81%). In the median follow up time of 42 months, five-year overall survival was 71% and disease free survival was 61%. Late sequelae were registered in 14 patients (66.7%), but they were low grade.

Conclusions: Our study shows results using external beam radiotherapy and brachytherapy boost as single modality treatment, but we need more randomized trials to improve better local control and minimize toxicity.

Key words: anal canal cancer, radiotherapy, brachytherapy

BACKGROUND

Carcinoma of the anal canal is a rare disease, more common in women aged sixty to eighty years. The most frequent prognosis depends on the size of tumor. Five-year overall survival is 80-90% and local control is 80%, when the greater diameter of tumor is less than 4 cm. Five-year survival in larger tumors than 4 cm falls to 50%, and the local control to 40%. Papillon’s pioneer study in the mid-seventies and other smaller and bigger randomized studies indicated significant role of radiotherapy with, or without chemotherapy in treatment of anal canal carcinoma. Good local control is achieved by applying these treatment modalities, with greater chance of preservation of anal sphincter function for about 75% related to surgery, while improvement of total survival has not been proved yet.

Applying high dose external beam radiotherapy, overall three-year survival is over 75%, while applying only brachytherapy, local control of disease is 40-50%. Combining external beam radiotherapy and brachytherapy, two thirds of the patients survive 5 years with adequate function preservation of anal canal. Today, radiotherapy is standard and the first line treatment of anal canal carcinoma. There are still controversies regarding optimal irradiation techniques, application of boost dose and adequate concomitant chemotherapy regimen.

The aim of our study is assessment of treatment results, treatment tolerance, incidence and late post irradiation sequelae in patient treated with combined radiotherapy, external beam and brachytherapy boost dose.

MATERIAL AND METHODS

Patients with anal canal carcinoma were treated with radiotherapy, as primary treatment modality at Institute of Oncology and Radiology of Serbia. Inclusion criteria for the study were as follows: pathohistologically confirmed diagnosis of planocellular anal canal carcinoma; tumor of...
any T stage, or any N disease stage, according to TNM classification from 2002\textsuperscript{12}, absence of diagnosed distant metastases; without previous treatment of the anal canal carcinoma and good general condition with Karnofsky index 80%.

The following diagnostic examinations were performed within pretherapy assessment: clinical and rectal examination, rectoscopy (endoscopy), biopsy with pathohistological verification, abdominal and pelvic ultrasound, chest X-ray, gynecological examination, peripheral blood count and serum biochemistry and liver function tests. All patients were irradiated with external beam radiotherapy on linear electronic accelerators (energy 6, 10 and 18 MeV).

Irradiation volume initially included primary tumor, lower third of the rectum and regional lymph nodes. The upper field limit was at the level of lower sacroiliac joint margin, or L5-S1 intravertebral space, and lower border of the field included perineal skin. Lateral field borders included external iliac and inguinal lymph nodes. The patients were irradiated from two parallel fields: anteroposterior and posteroanterior (AP/PA), pelvico-ingvinal widened fields, with dose ranged from 40-50 Gy, applied in 20-25 fractions, 1.8-2 Gy per fraction. This technique is widely accepted by many authors and we reported it previously\textsuperscript{13}. After the gap of 7-14 days, upon completion of external beam therapy, the patients continued treatment with brachytherapy. Boost dose was applied using interstitial brachytherapy (8 patients) and intraluminal brachytherapy (13 patients) on Microselectron HDR (High Dose Rate) machine (Nucletron, Holland) with radioactive source of Ir 192. The number of needles needed for interstitial brachytherapy and their disposition were chosen individually according to size and shape of the primary tumor and rest tumor, after applying external beam radiotherapy. Reference dose surface was adjusted on distance 5-7 mm from the other needles (dose was slightly higher than in the Paris dosage system). Clinical Target Volume (CTV) in brachytherapy of anal canal carcinoma, includes palpable and visible tumor mass or Gross Tumor Volume (GTV) with adjacent margin of 5 mm at least, and if there are small palpable lymph nodes, they can also be included into CTV\textsuperscript{14,15}. Application of needles, was carried out by palpation and through template of semicircular shape, leaned to perineum, at approximately 5 mm inside anorectal mucosis. In majority of patients implant consists of 5-7 cm long 5 needles forming arch shape, at 1 cm distance. The dose ranged between 6-18 Gy in 1-3 fractions. In smaller tumors, especially after completed external beam radiotherapy with widened fields, and significant regression of primary tumor, individualization of interstitial brachytherapy was performed by individualization of dose (3-6 Gy/fraction) and fractions (3-2 fractions). In some selected patients (Figure 1 and 2) only 3 needles were used. The needles are applied during spinal or local anesthesia. In 13 patients when thickness of the rest tumor, after external beam radiotherapy, was less than 5 mm, intraluminal brachytherapy was applied using vaginal cylinder of 2 cm diameter, with individual protection of the tissue opposite to lesion, whenever possible. Dos-
Acute complications occurred during and immediately after radiotherapy (dermatitis, cystitis, diarrhea, nausea, vomiting, acute proctitis) are scored according to WHO criteria. Treatment response was evaluated 2 and 4 months after the end of radiotherapy. The patients were strictly monitored on a 2-3 month basis for two years from treatment and at 6-month intervals thereafter.

Late post irradiation complications, diagnosed 6 months and later after radiotherapy (skin atrophy, hyper pigmentation, telangiectases, proctitis, hemorrhagic cystitis, stenosis, fistules, stricture) are graded to RTOG/EORTC recommendations.

A probability of Disease Free Survival (DFS) and Overall Survival (OS) was analyzed by the Kaplan-Meier statistic method. Overall survival was calculated from the start of radiotherapy treatment until patient’s death and disease free survival from the start of radiotherapy until the moment when progression of disease was firstly noted.

This study was approved by the Local Ethical Committee.

RESULTS

From March 1997 to May 2004, a total of 21 patients with anal canal carcinoma were treated with definitive radiotherapy treatment. The mean age was 57.8 years (range 38-81 years) with significant domination of females in relation to males, i.e. 17 to 4 patients (4:1). T3 disease stage was diagnosed in 11 patients (52.4%), T2 in 6 patients (28.6%), and T4 in 4 patients (19%). None of the patients had T1 disease stage. Positive lymph nodes were diagnosed in 5 patients.

Biopsy was performed in 15 patients (71.4%), and in 6 patients (28.6%) pathohistological diagnosis was determined on the basis of local tumor excision or hemorrhoidectomy. Regarding tumor grade, 9 patients (42.9%) had undifferentiated grade, 7 (33.3%) had grade I, 3 patients (14.3%) had grade II and 2 patients (9.5%) had grade III squamocellular carcinoma (Table 1).

Acute complications were diagnosed in 15 patients (71.4%). The most frequent acute complication was dermatitis (grade II and III) in 14 patients (66.7%), then proctitis in 3 patients (14.3%), nausea in 2 patients (9.5%) and diarrhea in one patient (4.8%). Five patients had more than one complication. External beam radiotherapy was not interrupted due to acute complications, and with adequate symptomatic therapy, was completed in all patients.

Fourteen patients (66.7%) had complete regression on the first follow-up, and 7 ones (33.3%) had partial response. On the second follow-up, complete response to conducted radiotherapy was achieved in 3 patients diagnosed with partial regression, while remaining 4 patients had to undergo surgery. Total number of patients with complete regression was 17 (81%).

Median follow-up was 42 months (min. 12, max. 90 months). There was no evidence of disease in sixteen patients (76%) out of 21 on the last follow-up. Two patients had distant metastases and three patients had local recurrence, local recurrence with liver metastases and residual disease, respectively.

Five-year overall survival in this study was 71% (5 patients succumbed to disease) and disease free survival was 61 %.

Late post-irradiation complications were observed in 14 patients (66.7%). Complications were mostly diagnosed on skin and they were lower grade. Skin fibrosis of irradiated region with atrophy was registered in 9 patients, and telangiectases in one patient. Four patients had post irradiation complications of anal canal in the form of strictures with moderate reduction of sphincter tonus, requiring no dilatation (grade II complication). Five patients had mild sphincter tonus reduction without incontinence (grade I toxicity). One patient had sexual dysfunction, while hemorrhagic proctitis was diagnosed in 5 patients. Five patients had late post irradiation sequelae. High grade complications were not registered.

DISCUSSION

Treatment results of 21 patients with anal canal carcinoma, who underwent external beam radiotherapy and brachytherapy boost are shown in this study. Mean age was 57.8 years with greater incidence of females in relation to males (4:1). In the study of Gerard et al., 19 patients were with a mean age of 64.8 years (range 39-88 years) and 14:5 relation of females to males. The study of a group of authors from Paris shows mean age of patients of 62 years (range 47-84, 5 years), treated with
combined radiotherapy, out of which 15 patients were females, and only two males.

According to our results, the most common were patients with T2 and T3 stage disease. Other authors also had similar distribution. Gerard et al.\textsuperscript{15} used radiotherapy to treat 11 patients with T2 stage, and 6 patients with T3 stage, and one patient with T1 and T4 stage disease, respectively. In the paper of Wagner et al.\textsuperscript{21} out of 49 patients treated only with radiotherapy, 13 patients had stage T1 and T3 each, 22 patients T2, and only one was with T4 stage disease. The French authors\textsuperscript{19} had 128 patients, out of 248, with stage T2 and 100 patients with stage T3.

Positive lymph nodes in our paper were diagnosed in 5 patients or 23.8%. In Gerard et al.\textsuperscript{19} study 8 patients were in node positive disease stage and 11/49 patients in Wagner’s study\textsuperscript{15}. The following grade distribution was noted in the study with 95 patients\textsuperscript{21}, out of which 88 had squamocellular cancer type; 33 patients had tumor of unknown grade, one patient had well differentiated tumor, 20 patients had grade II and 19 ones grade III. Out of 17 patients, treated with combined radiotherapy, in the study of French authors\textsuperscript{19}, 3 patients had disease grade I, 9 patients were with grade II, one with grade III, and in two patients tumor grade was not available.

We noted acute complications in 15 patients. They were lower grade and radiotherapy, with good treatment tolerance, was completed without breaks in all patients. Wagner et al.\textsuperscript{21} diagnosed acute complications at the end of radiotherapy in 11 patients, in the form of anal pain, and skin reactions of perineum and vulva. These discomforts were cured in all patients during 3-4 weeks after radiotherapy. Similar results of acute complications can also be found in Gerard’s study\textsuperscript{19,22}.

In our tested group, complete response was diagnosed in 17 patients (81%), and partial in 4 patients (19%), while local control was in 19 patients (90.4%). Out of four patients with partial regression, who underwent surgery, abdominoperineal resection (radical surgery) was performed on two patients. Berger et al.\textsuperscript{15} published similar results obtained on 69 patients, where complete response to conducted radiotherapy was also 81%, and local control after two years was 61% and after five years 47%. The study of Gerard et al.\textsuperscript{19} shows complete regression in 15/17 patients. One patient had local recurrence, and another one had lumbar vertebra metastasis. The French authors\textsuperscript{19} diagnosed complete regression in 80% of patients, while local control of the disease, including the patients with performed abdominoperineal resection was 84%.

Our results show that the five-year overall survival of the patients with anal canal carcinoma was 70.1%, and disease free survival was 61%. Similar results were presented in two studies: five-year overall survival was 66%, and 66.5%, respectively\textsuperscript{15}. The French authors\textsuperscript{19} show five-year survival of 66.7%, while disease free survival was 71.9%. The study we performed noted late complications in 14 patients (66.7%), the most frequently on skin. Mild reduction of sphincter tonus, without incontinence (grade I) was registered in 4 patients, and medium sphincter tonus reduction with stenosis (grade II) in two patients. Complications of grade III and IV (requiring sphincter dilatation or surgical treatment) were not diagnosed in any patient. Late complications were diagnosed in 40 patients, out of 79, in study of Sandhu\textsuperscript{23} or 50.63% in the form of skin fibrosis in 21 patients, incontinences in 4 patients (colostomy was performed in one patient, 2 patients had sphincter stricture and one had sphincter dilatation), 4 patients had proctitis, and even 9 patients had ulceration and necrosis of anal canal (three patients were treated with APR by Milles, and colostomy was performed on 2 patients). Preservation of anal sphincter with local control of the disease was achieved in 56 patients (71%). In the study of Wagner et al.\textsuperscript{21} 12/49 patients had late complications grade II and III in the form of proctitis, necrosis and ulcerations, and ARP was performed on 5 patients (10.2%).

Despite the results of many studies of anal canal carcinoma treatment, there are still numerous questions that remain to be answered with current radiotherapeutic approaches.

The design of pelvic radiotherapy fields recommended is based upon knowledge of the natural history of the disease and the primary nodal drainage, including internal iliac and presacral nodes. Clinical target volume (CTV) in well differentiated and limited squamocellular anal canal carcinoma includes palpable and visible tumor mass or gross tumor volume (GTV) and lymph nodes in pelvic and inguinal region. Total radiotherapy dose needed for eradication of squamocellular anal canal carcinoma is between 50 and 70 Gy depending on the size of primary. Majority of institutions in the world start the treatment with initial external beam radiotherapy (40-50 Gy) with inclusion of pelvic structures of interest into irradiation field, and then, after certain pause, treatment is continued with local boost dose on tumor and its adjacent tissues. The inclusion of ingvinal nodes, although recommended by the majority of authors, still remains controversial. Very large volumes appear non-optimal and poorly tolerated. Several techniques are employed, such as two opposed parallel fields, three or four field techniques in prone position to minimize the volume of irradiated small bowel or a direct perineal field. Papillon’s technique using a direct perineal and sacral field, although effective, is difficult to widely reproduce. There is no consensus about the field arrangements and doses, and they are different in various studies.

The minimum requested dose of external beam radiotherapy is 45-50 Gy. Many retrospective studies have shown dose-response relationship in anal canal treatment. A higher local control can be obtained with total tumor dose more than 55 Gy of external beam radiotherapy or more than 60 Gy for the gross tumor volume. But the total dose should not exceed 60-65 Gy for two reasons: the likelihood of cure at this dose level is relatively high and doses in excess of 65 Gy are likely to result in an unacceptable high incidence of necrosis. The daily fraction should be ranged between 1.8 to 2.0 Gy. Fractionation doses greater than 2.0 Gy are associated with an increased...
External beam radiotherapy plus brachytherapy boost in treatment of anal canal carcinoma

risk of late complications especially in combined modality treatment with chemotherapy. When making comparisons of toxicity between different studies, it must be remembered that the target volume varies with different techniques, as well as total dose, dose per fractions and overall time. The boost dose ranged between 15–25 Gy is applied in very different ways by external beam radiotherapy (direct perineal fields with photons or electrons, four field box techniques with photons) or brachytherapy (interstitial or intraluminal). Most of authors use a gap between the first part of EBRT and the boost. This refers to data of slow regressing velocity of anal canal carcinoma and perineal skin reactions after 4 weeks of irradiation. The exact duration of this gap is unknown. If a perineal field is used as a boost, use of the electrons should be avoided unless all of the perineal skin in field is involved by the tumor. Otherwise, a high radiotherapy dose will be resulting in a high risk of subcutaneous fibrosis. When complete response is reached before brachytherapy, 15 Gy may be enough and could reduce the risk of necrosis. If residual disease is present at the time of brachytherapy the dose can be 20-25 Gy into the initial volume or 15 Gy plus booster dose of 10-15 Gy on 2 or 3 lines centering the residual disease. An interstitial 192 Iridium could be of benefit for a good therapeutic index.

Chemotherapy in anal canal treatment has been postulated to decrease the incidence of micrometastases and to act as a radiopotentiator. Some studies have shown an advantage of chemotherapy combined with radiotherapy in terms of local control with higher acute toxicity and a low rate of late toxicity, but no survival benefit has been demonstrated. The optimal radiation dose, when combined with chemotherapy is about 55 Gy. The best chemotherapy regimen and the number of cycles have not been defined yet.

Some authors recommended a treatment protocol for anal canal carcinoma according to tumor stage and tumor size. Radiotherapy alone seems to obtain good results for patient with a tumor size of less than or equal to 4 cm in length. Combined modality treatment radiotherapy plus chemotherapy may improve local control for patients with tumor size greater or equal to 4 cm in length and/or fixed size with or without palpable nodes.

**CONCLUSIONS**

Radiotherapy is a treatment of choice in patients with anal canal carcinoma. In the future, randomized trials with great number of patients and long follow-up should be performed in order to optimize different irradiation techniques and boost dose, as well as to evaluate the impact of higher radiation dose on local control, complications, disease free survival and overall survival and to define best chemotherapy protocol.

**SUMMARY**

Uvod: Radioterapija predstavlja standardni terapijski pristup u lečenju karcinoma analnog kanala u poslednjih 30 godina. Ipak, danas još uvek postoje mnoga otvorena pitanja kao što su optimalne radioterapijske tehnike, adekvatna boost doza ili primeni najboljih konkomitantnih hemioterapijskih režima. Osim postizanja izlečenja i lokalne kontrole, drugi važni ciljevi su očuvanje funkcije sfinktera i izbegavanje trajne kolostome odnosno minimiziranje toksičnosti lečenja.


Rezultati: Od ukupno 21 pacijenta, akutne komplikacije su bila u 15 pacijenata (71,4%). Najčešće komplikacija bila je dermatitis. U 17 pacijenata (81%) registrisana je kompletna regresija nakon radioterapije. U srednjem vremenu praćenja od 42 meseca 5-godišnje sveukupno preživljanje iznosilo je 71,4%, a preživljanje bez znakova bolesti 61%. Kasne komplikacije su bila u 20 pacijenata (66,7%) i one su bile nižeg gradusa.

Zaključak: U našem radu prikazani su rezultati lečenja primenom transkutane zračne terapije i brahiterapije kao jedinog modaliteta lečenja. Potrebne su velike randomizovane studije sa ciljem poboljšanja rezultata lokalne kontrolе i smanjivanje toksičnosti lečenja.

Ključne reči: analni kanal, radioterapija, brahiterapija

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