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ORIGINAL ARTICLE

Histopathological findings in postoperative specimens in cervical cancer patients with stages IB2-IVA after neoadjuvant chemotherapy and preoperative plus postoperative radiotherapy

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Summary

Purpose: *To determine the incidence of the histopathological findings indicative for risk of recurrence in patients with locally advanced cervical cancer (LACC) who were treated with neoadjuvant chemotherapy (NCT) and radiation therapy (RT) before operation.*

Patients and methods: *Sixty-three patients were included: 45 patients (group 1) underwent external beam RT and then surgical treatment followed by postoperative RT, and 18 (group 2) patients were treated with NCT and surgery followed by postoperative RT. Surgery was class III-V radical hysterectomy with pelvic lymph node dissection (LND), and paraaortic LND at indication. NCT included 2-3 courses of cisplatin, ifosfamide and bleomycin administered at 3-week intervals. In group 1 FIGO stage IIB prevailed (n=29, 64.4%). Forty-four (97.8%) patients had squamous cell carcinoma and 1 (5.6%) adenosquamous carcinoma. In group 2 stage IIB also prevailed (n=13, 72.2%), whereas all 18 (100%) patients had squamous cell carcinoma. The average age in group 1 and 2 was 48.8 years (range 31-69) and 46.3 years (range 32-64), respectively.*

Results: *In group 1 lymph node metastases (LNM) were found in 35.56% of the cases, macroscopically detectable LNM in 15.6%, LNM above the common iliac artery level in 11.1%, multiple LNM (>3 LNM) in 17.8%, parametrial invasion in 4.4%, deep stromal invasion in 31.1%, lymphovascular space invasion (LVSI) in 13.3%, infiltration of canalis cervicalis in 15.6%, infiltration of isthmus uteri in 8.9% and ovarian metastases in 4.4%. In group 2 LNM were found in 38.89% of the patients, macroscopically detectable metastases in 22%, multiple (>3 LNM) LNM in 17%, LNM above the common iliac artery level in 22%, deep stromal invasion in 47%, parametrial infiltration in 24%, LVSI in 12%, tumor infiltration in canalis cervicalis in 12%, and ovarian metastases in 6%.*

Conclusion: *NCT followed by surgical treatment and RT leads to postoperative histological results that are not worse than the standard preoperative RT approach.*

Key words: cervical cancer, neoadjuvant chemotherapy, radiotherapy, stage IB2-IV

Introduction

In the past decade cervical cancer has become the most frequent gynecological malignancy in Bulgaria. The latest report of the National Cancer Registry in Bulgaria revealed an incidence rate of nearly 30/100,000 cases annually. Unfortunately 60% of these cases are in locally advanced stage.

The role of chemotherapy in the management of advanced cervical cancer has been long debated. Whereas some phase II trials have shown promising results with NCT followed by irradiation, most phase III trials failed to demonstrate any benefit with this sequential treatment in terms of locoregional control and survival, mainly because chemotherapy could cause accelerated tumor clonogenic resistant cell repopulation. Data of cisplatin-based NCT prior to sur-

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gery appear more promising. This treatment modality can increase the operability rate and reduce the incidence of positive nodes and other pathological risk factors [1]. The responsiveness of cervical cancer to NCT allows surgical treatment in a larger number of patients and results in longer overall and disease-free survival [2,3]. NCT did not reveal survival benefit in comparison to primary pelvic surgery for cervical cancer FIGO stages IB-IIA [4]. For LACC stages IB2-IIIB or IVA concomitant chemoradiation is another treatment option [5]. The main objective after NCT or chemoradiation is operability and the pathologic tumor response (lymph node involvement, parametrial invasion and tumor size) [6-8]. Some authors report that preoperative chemoradiation is associated with a lower rate of pelvic node disease in LACC patients compared to NCT [9], but others do not find significant difference between the above mentioned two modalities in terms of lymph node status and parametrial involvement [10].

Based on this background we aimed to determine the incidence rate of the histopathological findings indicative of a high risk of recurrence in patients with LACC who had undergone NCT and RT prior to operation. Such findings are LNM, LVSI, parametrial infiltration, metastases to the ovaries, and the cervical wall and cervical canal infiltration (deep stromal invasion). The registration and comparison of these data in radically operated patients after NCT or RT could answer the question over the place each of these approaches has in the combined treatment of LACC patients in FIGO stages IB2-IVA.

Patients and methods

Patients

The patient clinical characteristics are shown in Table 1. Included were 63 patients with histologically proven LACC, of whom 19 were studied retrospectively and 44 prospectively. The patients were registered in Varna and Pleven. The prospective study covered the period from March 2001 to November 2003. In group 1 included were 45 women with preoperative RT and surgical treatment followed by postoperative RT to reach a total dose up to 50-52Gy. Thirty-two women were registered and treated in the Clinic of Oncology and Gynecology at the Hospital of Active Treatment - Pleven, of whom 12 retrospectively and 20 prospectively; 13 were registered in the Oncological Clinic in Varna, of whom 7 retrospectively and 6 prospectively.

Eighteen patients underwent surgical treatment after NCT, followed by postoperative RT (registered at the Oncological Clinic in Varna) - group 2. All patients with NCT were studied prospectively. In this group 17 patients underwent radical surgical treatment, and one patient was submitted to intraoperative staging with biopsy of paraaortic lymph nodes.

Eligibility criteria

Eligibility criteria for patients submitted to NCT were: histologically proven LACC, FIGO stages IIB-IVA; no previous chemotherapy; ECOG performance status <1; adequate bone marrow reserve (white blood cell count >3,500/dl, platelets > 100,000/dl, Hb > 9 g/dl); normal liver and kidneys function; age up to 70 years; signed informed consent.

Eligibility criteria for patients submitted to radiotherapy were: histologically proven LACC, FIGO stages IB2-IIIB; ECOG performance status <1; adequate bone marrow reserve as above; signed informed consent.

Diagnostic and staging workup

At the time of patients' registration a biopsy (excisional or separated abrasion test) was performed for

Table 1. Patient characteristics

	Patients n (%)	*Age (years), mean (range)*	*Histological type n (%)*	*Stage n (%)*
Group 1	45 (100)	48.8 (31-69)	Squamous cell 44 (97.8) Adenosquamous 1 (2.2)	IB2-13 (28.9) IIB-29 (64.4) IIIB-2 (4.4) IVA-1 (2.2)
Group 2	18 (100)	46.3 (32-64)	Squamous cell 18 (100)	IIB-13 (72.2) IIIB-4 (22.2) IVA-1 (5.6)

Group 1: preoperative RT+surgical treatment+postoperative RT; Group 2: neoadjuvant chemotherapy+surgical treatment+postoperative RT

histological confirmation of the diagnosis. Clinical patients' staging was made after investigation with speculum and rectal examination performed by two experienced oncologists. Cases with parametrial infiltration in the distal third and suspicion about spread to the pelvic wall were staged IIIB. The estimation of the size of the cervical lesion (> or < 4 cm) was made visually in exophytic lesions.

The routine preoperative tests included venous urography, CT scan of the pelvis, x-rays of lungs, serum biochemistry and specific exams such as rectoscopy and cystoscopy.

Patients' follow-up

The follow-up covered the period from the patients' registration until the end of November 2003. Treatment started not later than 10 days after the registration. The disease-free period was defined as the time from the date of registration until the development of recurrence or metastasis (by colposcopy, palpation, biopsy, x-rays, CT scan and SCC tumor marker) when patients reported for examination every 3 months within the first 2 years after the end of treatment. Dead patients were identified from the death certificates of the Registry Office-Varna for the cases from Varna and Pleven.

Surgery

Patients were mainly operated at the Clinic of Oncology and Gynecology in Pleven. Surgery included removal of both uterus (class III-IV) and lymph nodes dissection (total pelvic LND, and in bulky lymph nodes at palpation paraaortic LND). The latter varied from biopsy to total paraaortic LND below the level of the superior mesenteric artery. From the NCT+surgical treatment group, 8 patients underwent class III radical hysterectomy, 8 class IV, 1 anterior exenteration and 1 exploratory laparotomy with intraoperative staging. From the RT+surgical treatment group, 44 patients underwent class III radical hysterectomy and 1 class V. All operated patients underwent total pelvic LND.

Radiation therapy

The main type of RT was percutaneous with ^{60}Co external beam, 200cGy daily, 4-field technique. The preoperative RT dose was 30 Gy, and the definitive 50-52 Gy. Postoperative RT was carried out in all patients (50-52 Gy in group 2 or addition up to this dose in preoperative RT in group 1 patients). In some cases intracavitary (combined) RT with ^{192}Ir sources, 70000cGy and 20000cGy to points A and B respectively, was employed.

Chemotherapy

NCT included the following drugs: cisplatin 50 mg/m^2 in 500 ml N/S, 60 min infusion, and hydration with 500 ml Ringer's for 30 min and 250 ml manitol for 30 min, on day 1; ifosfamide 1 g/m^2/day i.v. on days 1-5, in 500 ml N/S, 2h infusion and mesna 200 mg/m^2 in 500 ml N/S, 30 min infusion given before ifosfamide and 4h and 8h after ifosfamide administration; and bleomycin 30 mg in 500 ml N/S in 30 min on days 1 and 8.

Courses were repeated every 3 weeks. All patients with no early progression received 2-3 courses of chemotherapy. The local treatment (surgery or RT) started 3-6 weeks after the last course of chemotherapy.

Criteria of chemotherapy response

The standard WHO criteria were used: complete response (CR) - disappearance of all signs of disease; complete pathological response (pCR) - absence of tumor cells in the histological specimens tested postoperatively; partial response (PR) - tumor reduction ≥50% of its initial size; stable disease (SD) - tumor reduction <50% or increase <25%; progressive disease (PD) - tumor increase >25% or appearance of new tumor lesion(s).

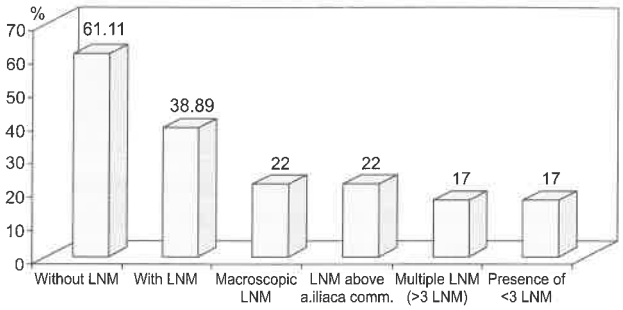
Patients receiving one course of chemotherapy only (due to patient's refusal or because of the opinion of the attending doctor) were not evaluable.

Statistics

The results taken were processed by applying computer programs EXCEL, SPSS and STATGRAPHICS PLUS and were given in tables, figures and quantities (percentage, average values, standard deviation, median, correlation, etc). The following parametric statistical methods were used: Student's t-test, Fisher's exact test, ANOVA, correlation coefficient (Pearson) and the non-parametric methods (Pearson x^2, Kruskal - Wallis test, Spearman's and Prison's correlation coefficients, and the contingency coefficient).

Results

In group 2 LNM were found in 38.89% of the patients. Macroscopic metastases (bulky lymph nodes) were detected in 22% of the operated patients. LNM



LNM: lymph node metastases

Figure 1. Incidence rate and main characteristics of LNM in group 2.

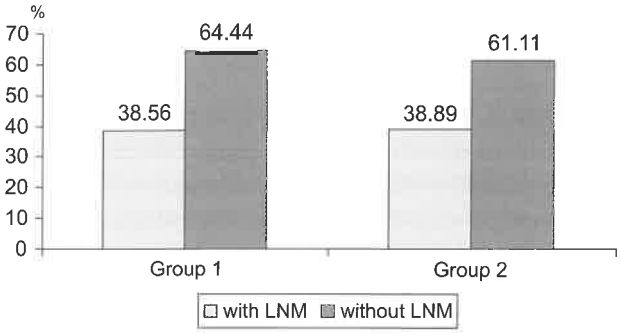


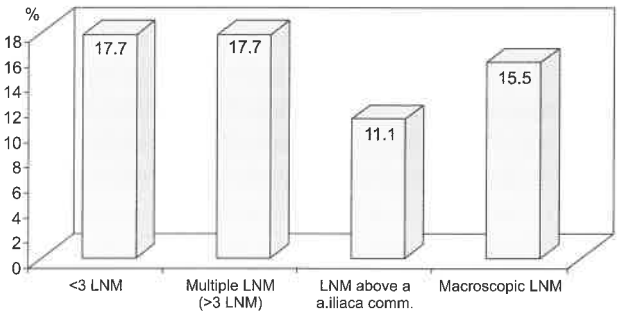
Figure 3. Incidence rate of LNM in group 1 (CRT+surgery) and group 2 (NCT+surgery).

above the common iliac artery were found in 22% of the cases. Multiple LNM (>3 LNM) and presence of less than 3 LNM were seen in 17% in each of these two categories (Figure 1).

Other histological findings revealing high post-operative risk in group 2 were: deep stromal invasion (47%), infiltration of parametria (24%), infiltration of isthmus uteri (24%), LVSI (12%), infiltration of canalis cervicalis (12%) and metastases to the ovary (6%) (Figure 2).

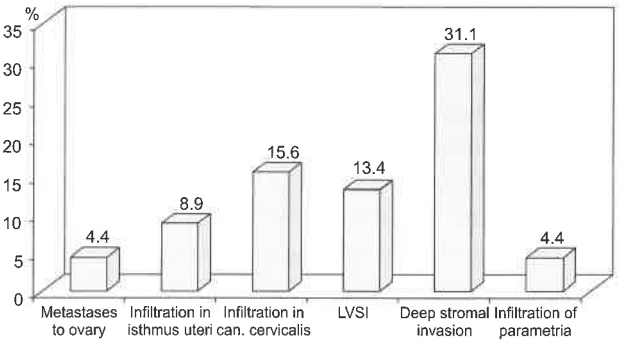
In group 1 LNM were found in 38.56% of the patients (Figure 3). Macroscopic LNM were detected in 15.6% of the patients and LNM above the common iliac artery in 11.1%. Multiple LNM (>3 LNM) and presence of less than 3 LNM were seen in 17.8% in each of these two categories (Figure 4).

Other (except LNM) histopathological findings showing high risk for recurrence are illustrated in Figure 5. Deep stromal invasion was observed in 31.1%, LVSI in 13.3% and infiltration of parametria in 4.4% of the cases. Infiltration in canalis cervicalis and isthmus uteri were observed in 15.6% and 8.9%, respectively. Metastases to the ovary were detected in 4.4% of the patients (Figure 5).



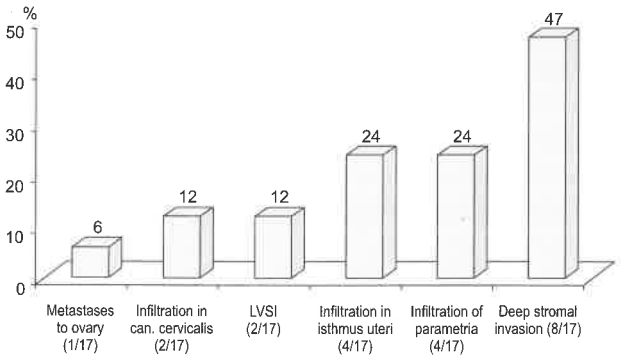
LNM: lymph node metastases

Figure 4. Incidence rate and main characteristics of LNM in group 1.



LVSI: lymphovascular space infiltration

Figure 5. Incidence rate of other histopathological high risk factors for relapse in group 1.



LVSI: lymphovascular space infiltration

Figure 2. Incidence rate of other histopathological high risk factors for relapse in group 2.

The comparison between two groups in terms of LNM, level, number of LNM and macrometastases, as well as of depth of infiltration, LVSI, infiltration in canalis cervicalis, isthmus uteri and ovary showed no statistical significance ($p > 0.05$) (Figure 3, Table 2).

The only statistically significance difference was observed in parametrial infiltration (group 1 4.4% vs. group 2 24%, $p < 0.05$; Table 3).

Table 2. Level, number of LNM and macrometastases (groups 1 and 2)

	LNM <3	*LNM >3*	*LNM above the common iliac artery*	*Macrometastases*
	n (%)	*n (%)*	*n (%)*	*n (%)*
Group 1	8/45 (17.7)	8/45 (17.7)	5/45 (11.1)	7/45 (15.5)
Group 2	3/18 (16.6)	3/18 (16.6)	4/18 (22.2)	4/18 (22.2)
p-value	NS	NS	NS	NS

LNM: lymph node metastases, NS: non significant

Table 3. Factors of high risk for recurrence in groups 1 and 2

	Parametrial invasion	*Depth of infiltration*	*LVSI*	*Infiltration of canalis cervicalis*	*Infiltration of isthmus uteri*	*Metastases to ovary*
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Group 1	2/45 (4.4)	14/45 (31.1)	6/45 (13.4)	7/45 (15.6)	4/45 (8.9)	2/45 (4.4)
Group 2	4/17 (24)	8/17 (47)	2/17 (12)	2/17 (12)	4/17 (24)	1/17 (6)
p-value	<0.05	NS	NS	NS	NS	NS

LVSI: lymphovascular space infiltration, NS: non significant

Discussion

The histological proof of LNM, parametrial tumor invasion, LVSI, deep stromal invasion, and tumor extension to canalis cervicalis and isthmus uteri aggravate the prognosis of patients who have undergone surgical treatment. On one hand these unfavorable histopathological findings are significant for disease progression and tendency to dissemination outside the locoregional limits of the true pelvis, and on the other hand they are indicative of the insufficient effect of the preoperative therapeutic manipulations. All these findings are integrated within one general category - residual tumor.

In the NCT group we found 38.89% incidence rate of LNM: for stage IIB this rate was 46%, and for stage IIIB it was 25%. In the preoperative RT group LNM were found in 35.56%: for stage IB2 the rate was 38.46%, for stage IIB it was 31% and for IIIB 50%. Having compared the LNM characteristics, i.e. number, level, and macroscopic appearance, we did not find any statistical difference ($p > 0.05$) between the two groups of patients. According to literature data, patients with stage IIIB show a high rate of LNM - 40-50% regional [11-14] and 30% paraaortic [15]; however, stage IIIB patients were 22% (4 of 18) in the NCT group, while in the RT group they were 4% (2 of 45) of the total number of patients ($p < 0.05$). As a whole this means that when comparing group 1 and 2, chemotherapy is not less effective than RT with respect to the histopathological response, and tumors in a more advanced stage are not an obstacle to the effectiveness of chemotherapy concerning LNM. Our results in the NCT group (38.8% with LNM and 24% with parametrial invasion) compare favorably with those of other authors who used other chemotherapeutic regimens. In 1996 Benedetti-Panici et al. reported 36% incidence rate of LNM in patients with stage IIIB operated radically (class III-V) after NCT [16]. The same authors, in a large-scale randomized multicentric study of NCT followed by surgical treatment in patients with stage IB2-IIIB reported in 2002 29% LNM, 13% pCR and 23% histologically confirmed parametrial invasion. The authors found that the tumor persistence (presence of LNM, invasion of the parametria) occurred more frequently in stage IIIB as compared to stage IB2-IIB (50% and 37%, respectively) [17]. In 1996 Sardi reported 37.5% pelvic LNM (18 of 48) and 14.5% paraaortic LNM in stage IIIB patients who had undergone radical surgery after NCT [18]. In 2001 Lopez-Graniel et al. attained much better results in stage IB2-IIIB patients operated after NCT: 17% LNM without multiple metastases (< 3), 4.3% parametrial invasion and 13% pCR. The beneficial effect, despite the great percentage of stage IIB and IIIB patients, was probably due to the administered combination: cisplatin - 100 mg/m^2, day 1, and gemcitabine 1000 mg/m^2, days 1 and 8 [19]. In 2001 Hwang et al. also reported their results in 80 women staged IB2-IIB with 25% pCR and 21.8% LNM, which were better than those taken in the present study [3].

In order to illustrate the effect of chemotherapy on the histopathological factors and reduction of the residual tumor many authors have compared the effect

of the cytotoxic agents before surgery with control groups of patients operated without prior chemotherapy at different LACC stages. In 1997 Serur et al. after having administered NCT in stage IB2 patients reported incidence of LNM, LVSI, deep stromal invasion over 2/3 of the cervical wall, and infiltration in the parametria of 10%, 20%, 30% and 0%, respectively, while in the group without NCT these histopathological parameters were more frequently found (37.5%, 46.5%, 68.8% and 15.5%, respectively) [20]. Sananes et al. in 1998 made a similar comparative study of stage IIB patients and found an incidence rate of LNM, parametrial invasion and LVSI in NCT treated patients of 25%, 34% and 28% respectively, while the corresponding rates in patients without NCT were 41%, 76% and 59%, respectively [21].

In our comparative analysis of the histopathologic findings in the surgical specimen of the patients operated after NCT and RT no statistically significant difference in any of the following indicators was found: LVSI, deep stromal invasion, tumor infiltration in canalis cervicalis and isthmus uteri and metastases to the ovaries, except parametrial invasion ($p < 0.05$) - 4.44% in group 1 (RT+surgery) and 24% in group 2 (NCT+surgery). This could be explained by the fact that in group 1 approximately 1/3 (13 of 45) of the patients had stage IB2 disease (tumor limited to the cervix), while group 2 patients had stage IIB and IIIB with clinically detectable parametrial infiltration. This makes it difficult to assess the efficacy of chemotherapy in reducing the parametrial invasion.

In conclusion it could be said that NCT followed by surgical treatment leads to postoperative histological results that are not worse than those taken with the standard preoperative RT.

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