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Is there a role for postoperative treatment in patients with stage Ib_2–IIb cervical cancer treated with neo-adjuvant chemotherapy and radical surgery? An Italian multicenter retrospective study

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HIGHLIGHTS

- The achievement of an optimal pathological response on surgical specimen is a strong predictor of a better clinical outcome.
- Additional cycles of chemotherapy could be of benefit only for patients with suboptimal response and intra-cervical residual disease.
- Adjuvant chemotherapy or radiotherapy does not seem to improve clinical outcome with extra-cervical residual disease versus no further treatment.

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ABSTRACT

Purpose. Neoadjuvant chemotherapy [NACT] followed by radical hysterectomy is an alternative therapeutic option to concurrent chemotherapy–radiotherapy for locally advanced cervical cancer. However there are very few data about the effectiveness of any post-operative treatment in this clinical setting. The purpose of this study was to correlate the patterns of recurrence and the clinical outcomes of cervical cancer patients who received NACT, with postoperative adjuvant treatment.

Patients and methods. This retrospective multicenter study included 333 patients with FIGO stage Ib_2–IIb cervical cancer who underwent platinum-based NACT followed by radical surgery. Pathological responses were retrospectively assessed as complete; optimal partial; and suboptimal response. Overall optimal response rate was the sum of complete and optimal partial response rates.

Results. On the whole series, recurrence-free survival was significantly longer in patients who achieved an overall optimal response than in those who did not ($p < 0.0001$), and in patients who received adjuvant chemotherapy compared to those who did not ($p = 0.0001$). On multivariate analysis, consolidation therapy ($p = 0.0012$) was the only independent prognostic variable for recurrence-free survival; whereas FIGO stage ($p = 0.0169$) and consolidation therapy ($p = 0.0016$) were independent prognostic variables for overall survival.

Conclusion. Optimal responders after chemo-surgical treatment for FIGO stage Ib_2–IIb cervical cancer do not need any further treatment. Additional cycles of chemotherapy could be of benefit for patients with suboptimal response and intra-cervical residual disease. Both adjuvant chemotherapy and adjuvant radiation treatments do not seem to improve the clinical outcome of patients with extra-cervical residual disease compared to no further treatment.

Introduction

Concurrent chemotherapy and radiotherapy [CCRT] is the standard of care for locally advanced cervical cancer, able to achieve a 6% improvement in a 5-year survival compared to radiotherapy alone [1–3]. A larger survival advantage appears to occur when adjuvant chemotherapy is administered after CCRT [3–5]. Conversely, adjuvant hysterectomy in complete responders after CCRT gives no survival benefit [6].

Neoadjuvant chemotherapy [NACT] followed by radical hysterectomy is an alternative therapeutic option in this clinical setting, and the meta-analysis of five randomized trials has shown that chemo-surgical treatment significantly improves survival when compared to radiotherapy alone [7–14]. Benedetti-Panici et al. [9] reported that the survival benefit

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for NACT arm versus radiotherapy arm was significant for stage Ib_2–IIb but not for stage III disease. A multicenter randomized trial is currently comparing NACT plus radical surgery versus CCRT in patients with stage Ib_2–IIb cervical cancer (EORTC protocol 55994). Most authors found that the pathological response on surgical specimen is a strong predictive factor for the clinical outcome of patients treated with NACT and radical hysterectomy [7,11,15–17]. For instance, in the SNAP01—Italian Collaborative Study, women who achieved an optimal pathological response had a hazard ratio [HR] of death of 5.88 (95% CI = 2.50–13.84; $p < 0.0001$) compared to those who did not [11].

Conversely, there are very few data about the effectiveness of any post-operative treatment in this clinical setting.

The purpose of this retrospective multicenter study was to correlate the patterns of recurrence and the clinical outcomes of cervical cancer patients who underwent platinum-based NACT followed by radical hysterectomy with postoperative adjuvant treatment.

Materials and methods

This is a retrospective study approved by the participating centers of the Institutional Review Board. The study included 333 patients with FIGO stage Ib_2–IIb cervical squamous cell or adenocarcinoma who underwent platinum-based NACT followed by radical hysterectomy with pelvic lymphadenectomy at the Department of Gynecology and Obstetrics of the University of Pisa and Turin between 1992 and 2011 and at the Department of Gynecology and Obstetrics of the University of Brescia and at the Department of Gynecologic Oncology of the European Institute of Milan between 1999 and 2011. This was the treatment strategy chosen for patients with stage Ib_2–IIb disease 70-year as upper limit of age, and good performance status who signed an informed consent form. Patients with special histology (small cell carcinoma, glassy cell carcinoma and neuroendocrine tumors) as well as patients who did not complete the planned cycles of NACT or who did not undergo radical surgery after NACT because of progression of disease or poor general conditions were not included in the present study.

Patients' information from the hospital records, including surgical notes and pathological reports, was collected using a common form with standardized items and was stored in a database shared by all the participants in the study.

Patient characteristics at initial diagnosis (such as date, age, FIGO stage, histological type, and tumor size), NACT regimen, type of radical hysterectomy, and pathological responses on surgical specimens were reported for each case.

Pre-treatment evaluation included history, physical examination, vaginal–pelvic examination, colposcopy, biopsy, complete blood analysis, chest X-ray, and abdominal–pelvic computed tomography [CT] scan and Magnetic Resonance Imaging [MRI]. Cystoscopy and/or proctoscopy were performed if there was a clinical or on CT and/or on MRI suspicions of bladder or rectal involvement. Further investigation was performed when indicated.

Physical and vaginal–pelvic examination and abdominal–pelvic CT scan and MRI were repeated 3–4 weeks after the completion of chemotherapy. All patients underwent type II–III radical hysterectomy according to the Piver–Rutledge classification with pelvic lymphadenectomy within 3–6 weeks from the last cycle of chemotherapy.

Pathological responses were retrospectively assessed as follows: complete response was defined as the complete disappearance of the tumor in the cervix with negative nodes; optimal partial response was defined as a persistent residual disease with <3 mm stromal invasion including in situ carcinoma on the surgical specimen and negative nodes; and suboptimal response consisted of persistent residual disease with >3 mm stromal invasion on the surgical specimen and negative nodes (intra-cervical residual disease), or positive nodes with positive or negative parametria and/or surgical margins (extra-cervical residual disease with positive nodes), or positive parametria and/or surgical margins with negative nodes (extra-cervical residual disease with negative nodes). Overall optimal response rate was the sum of complete and optimal partial response rates.

Those patients who did not achieve complete, optimal partial or suboptimal response were defined as non-responders.

Postoperative management was individually established on the basis of histological findings on surgical specimen, patient age and general conditions, and standard therapeutic strategy of each center, after an exhaustive discussion with the patient herself by a multidisciplinary team.

The patients were periodically followed-up with clinical and radiological examinations until they died or until June 2012. The median follow-up of survivors was 66.5 months (range, 8–212 months).

Statistical methods

The statistical package SAS, release 6.7, was used for computations.

The time from the first cycle of NACT to the detection of recurrence was defined as recurrence-free survival. The time from the first cycle of NACT to death or last observation was defined as overall survival.

The cumulative probability of recurrence-free survival and overall survival was estimated by the product-limit method. The log-rank test was used to compare the homogeneity of recurrence-free survival and survival functions across strata defined by categories of prognostic variables.

A multiple regression analysis based on the Cox proportional hazard model was used to jointly test the relative importance of variables as predictors of recurrence-free survival and overall survival.

Results

FIGO stage was Ib_2 in 179 patients, IIa in 44, and IIb in 110 subjects. Histological types were squamous cell carcinoma in 268 patients and

Table 1
Recurrence rates and sites according to postoperative treatment.

Postoperative treatment	Patients	Recurrences			Overall
		P	EX	P + EX	
Optimal responders (n. 63)[a]					
No further treatment	36	4 (11.1%)			4 (11.1%)
Chemotherapy	21		1 (4.7%)		1 (4.7%)
EBRT ± BRT	6	2 (33.3%)			2 (33.3%)
Suboptimal responders, intra-cervical residual disease (n. 124)[a]					
No further treatment	47	3 (6.3%)	1 (2.1%)		4 (8.5%)
Chemotherapy	34	4 (11.8%)			4 (11.8%)
CCRT ± BCT	20	4 (20.0%)	2 (10.0%)	1 (5.0%)	7 (35.0%)
EBRT ± BCT	23	2 (8.7%)	1 (4.3%)		3 (13.0%)
Sub-optimal responders, extra-cervical residual disease with positive nodes (n = 75)					
No further treatment	10			1 (10.0%)	1 (10.0%)
Chemotherapy	4	1 (25.0%)			1 (25.0%)
CCRT ± BCT	34	5 (14.7%)	6 (17.6%)	1 (2.9%)	12 (35.4%)
EBRT ± BCT	27	9 (33.3%)	3 (11.1%)		12 (44.4%)
Sub-optimal responders, extra-cervical residual disease with negative nodes (n = 18)					
No further treatment	1				
Chemotherapy	4	1 (25.0%)			1 (25.0%)
CCRT ± BCT	7	1 (14.2%)	1 (14.2%)	2 (28.5%)	4 (57.1%)
EBRT ± BCT	6				
No responders (n. 49)					
No further treatment	7	2 (28.6%)	2 (28.6%)		4 (57.1%)
Chemotherapy	3				
CCRT ± BCT	25	7 (28.0%)	3 (12.0%)	2 (8.0%)	12 (48.1%)
EBRT ± BCT	14	5 (35.7%)	1 (7.1%)		6 (42.8%)

P, pelvic; EX, extrapelvic; EBRT, external beam irradiation; BCT, brachytherapy; CCRT, concurrent chemoradiation.

[a] The present analysis did not include the patient who had adjuvant chemotherapy followed by EBRT (sub-optimal responder with intra-cervical disease) and 3 patients who had BCT alone (one optimal responder and two sub-optimal responders with intra-cervical disease).

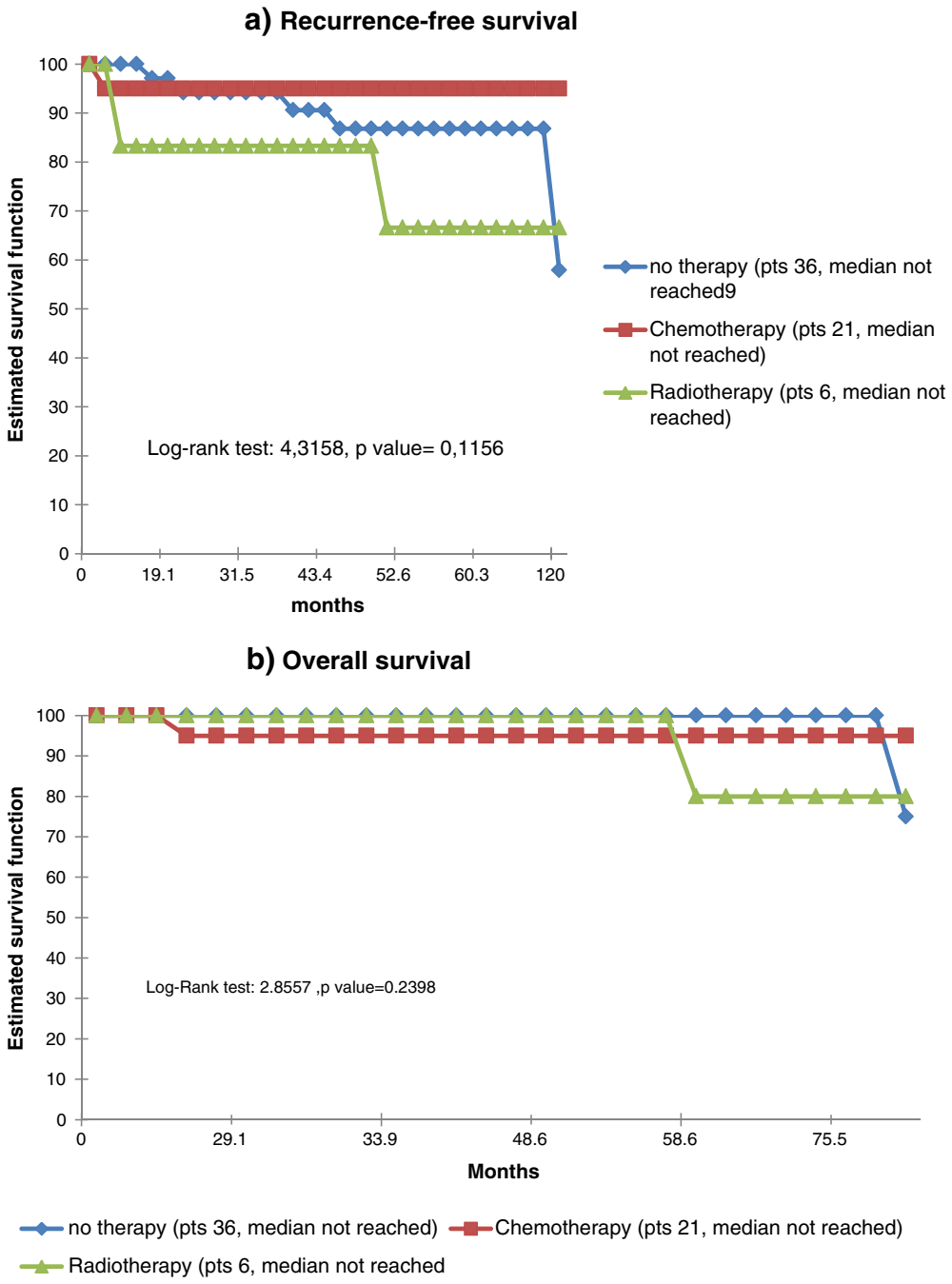

Fig. 1. Recurrence-free survival (a) and overall survival (b) in overall optimal responders by post-operative treatment.

adenocarcinoma or adenosquamous carcinoma in 65. NACT regimen was platinum- and paclitaxel-based in 284 patients and platinum-based in 49. Type of radical hysterectomy according to the Piver–Rutledge classification was type II in 88 patients and type III in the remaining 225. All patients underwent systematic pelvic lymphadenectomy. Aortic node dissection was performed in selected cases of patients with positive pelvic nodes at frozen sections.

Pathological response was complete in 30 patients, optimal partial in 34, and suboptimal in 220, whereas no response was found in 49. As far as sub-optimal responders are concerned, 127 patients had intra-cervical residual disease, 75 had extra-cervical residual disease with positive nodes, and 18 had extra-cervical residual disease with negative nodes.

After surgery, 66 patients (19.8%) received two cycles of adjuvant chemotherapy with the induction regimen, 74 (22.2%) underwent external pelvic irradiation [EBRT] with or without brachytherapy (BCT), 88 (26.4%) received cisplatin-based CCRT on the pelvis with or without BCT (three of them with additional irradiation on the aortic area), three (0.9%) had BCT alone, 1 patient (0.3%) underwent two cycles of adjuvant chemotherapy with the induction regimen followed by EBRT, and 101 patients (30.3%) had no further treatment.

At the time of the present analysis, 79 (23.7%) out of the 333 patients relapsed after a median time of 14.9 months (range, 4.5–123 months). Recurrent disease was pelvic in 50 (63.3%) cases, extra-pelvic (aortic or distant) in 22 (27.8%), and both pelvic and extra-pelvic in 7 (8.9%).

According to pathological response, tumor relapsed in 7 (10.9%) out of the 64 overall optimal responders (6 pelvic recurrences and 1 extra-pelvic recurrence) and 50 (22.7%) out of the 220 sub-optimal responders (30 pelvic recurrences, 15 extra-pelvic recurrences, and 5 pelvic plus extra-pelvic recurrences). Among the sub-optimal responders, tumor

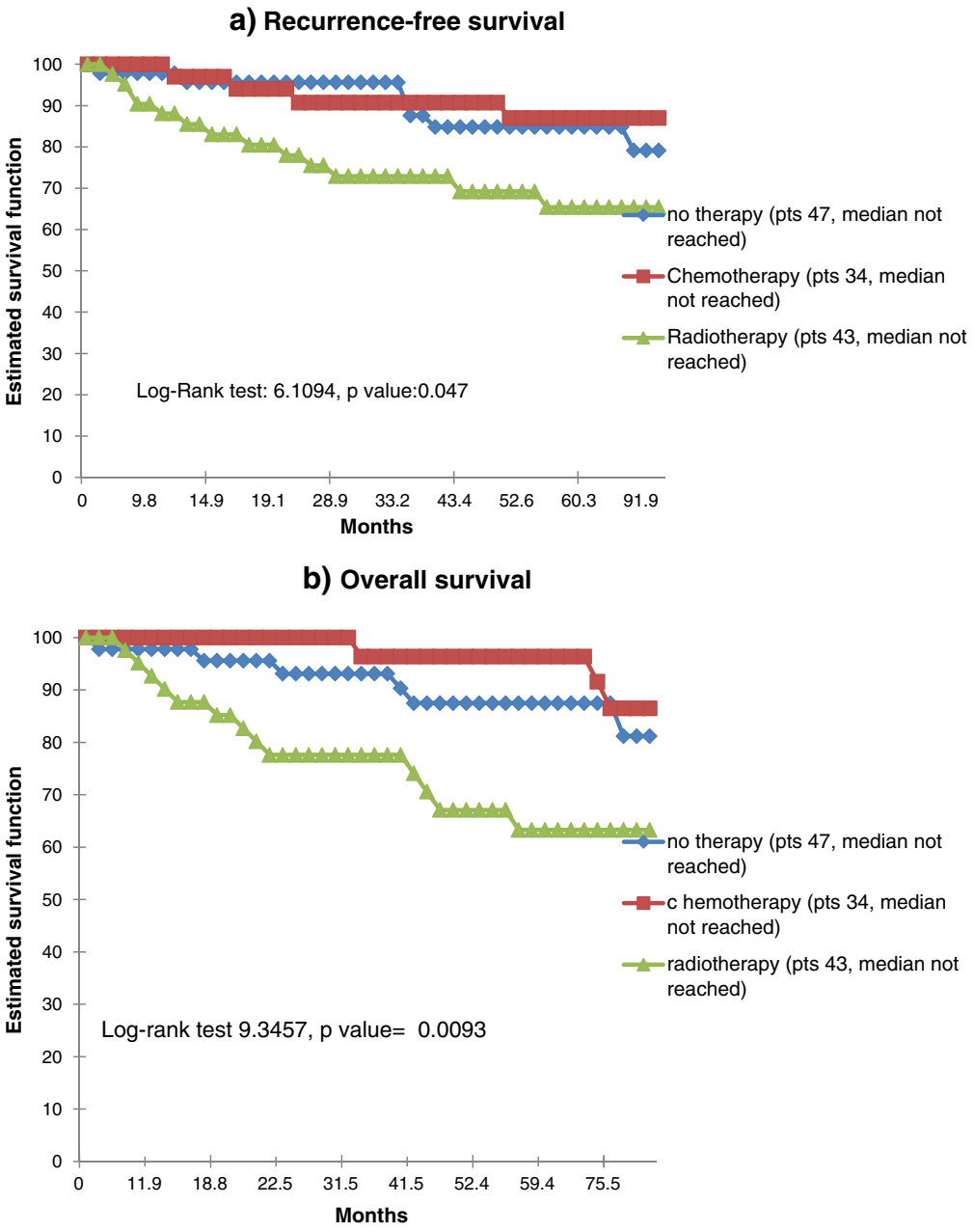

Fig. 2. Recurrence-free survival (a) and overall survival (b) in sub-optimal responders with intra-cervical residual disease by postoperative treatment.

relapsed in 19 (15.0%) out the 127 patients with intra-cervical residual disease (13 pelvic recurrences, 5 extra-pelvic recurrences, and 1 pelvic plus extra-pelvic recurrence), 26 (34.7%) out of the 75 patients who had extra-cervical residual disease with positive nodes (15 pelvic recurrences, 9 extra-pelvic recurrences, and 2 pelvic plus extra-pelvic recurrences), and 5 (27.8%) out of the 18 patients who had extra-cervical residual disease with negative nodes (2 pelvic recurrences, 1 extra-pelvic recurrence, and 2 pelvic plus extra-pelvic recurrences). Twenty-two (44.9%) out of the 49 non-responders recurred (14 pelvic recurrences, 6 extra-pelvic recurrences, and 2 pelvic plus extra-pelvic recurrences).

Table 1 showed the patterns of recurrences according to postoperative treatment.

The present analysis did not include the patient who had adjuvant chemotherapy followed by EBRT (sub-optimal responder with intra-cervical disease) and the 3 patients who had BCT alone (one overall optimal responder and two sub-optimal responders with intra-cervical disease). The former patient developed a distant failure, whereas none of the latter ones relapsed.

The risk of recurrence in overall optimal responders was the same in patients who received any adjuvant treatment (3 out of the 27, 11.1%) and in those who did not (4 out of the 36, 11.1%).

Recurrence-free survival and overall survival of overall optimal responders were similar in patients who had adjuvant chemotherapy, adjuvant CCRT or EBRT ± BCT, or no adjuvant treatment (Fig. 1a and b).

Among the sub-optimal responders with intra-cervical residual disease, a distant recurrence (with or without pelvic failure) occurred in none of the 34 patients who had adjuvant chemotherapy versus 4 out of the 43 (9.3%) patients who underwent adjuvant CCRT or EBRT ± BCT. Recurrence-free survival and overall survival of sub-optimal responders with intra-cervical residual disease were significantly better in patients who received adjuvant chemotherapy ($p = 0.047$ and $p = 0.0093$, respectively) (Fig. 2a and b) Among the sub-optimal responders who had extra-cervical residual disease with either positive

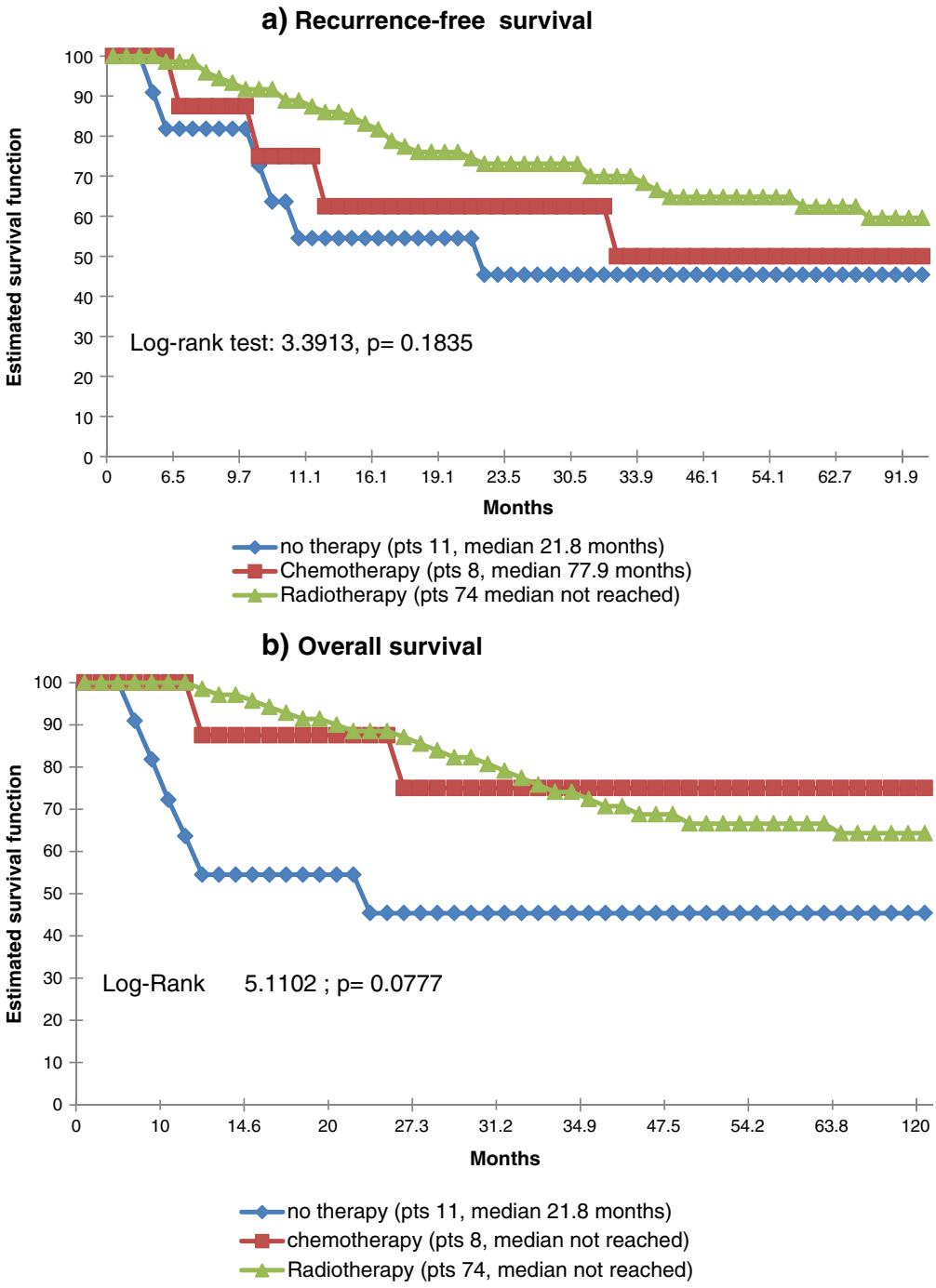

Fig. 3. Recurrence-free survival (a) and overall survival (b) in sub-optimal responders with extra-cervical residual disease (with either positive or negative nodes) by post-operative treatment.

or negative nodes, a distant recurrence (with or without pelvic failure) occurred in none of the 8 patients who had adjuvant chemotherapy versus 13 out of the 74 (17.5%) patients who underwent postoperative CCRT or EBRT ± BCT. Recurrence-free survival and overall survival of sub-optimal responders who had extra-cervical residual disease with either positive or negative nodes were not significantly different according to post-operative management (Fig. 3a and b).

On the whole series, recurrence-free survival was significantly longer in patients who achieved an overall optimal response than in those who did not ($p < 0.0001$), and in patients who received adjuvant chemotherapy compared to those who did not ($p = 0.0001$) (Table 2). Overall survival was significantly longer in patients with FIGO stage Ib_2–IIa than in those with stage IIb disease ($p = 0.0072$), in patients who received platinum/paclitaxel-based NACT than in those who received platinum-based NACT ($p = 0.0464$), in patients who achieved an overall optimal response than in those who did not ($p < 0.0001$), and in patients who received adjuvant chemotherapy compared to those who did not ($p < 0.0001$) (Table 3).

On multivariate analysis, consolidation therapy ($p = 0.0012$) was the only independent prognostic variable for recurrence-free survival;

Table 2
Variables predictive of recurrence-free survival and overall survival by univariate analysis.

Variables	Pts	5-year RFS	p value	5-year OS	p value
Age					
≤46 years	177	73.9%	0.2045	77.5%	0.2471
>46 years	156	66.4%		73.4%	
Histology					
Squamous cell	268	70.1%	0.9070	76.3%	0.4689
Adenocarcinoma	65	71.5%		71.1%	
FIGO stage					
Ib–IIa	223	72.7%	0.0755	78.6%	0.0072
IIb	110	65.7%		68.9%	
CT regimen					
Platinum/TAX	284	71.6%	0.1492	77.0%	0.0464
Platinum-based	49	63.3%		67.3%	
Pathological response					
Optimal	64	87.4%	<0.0001	96.0%	<0.0001
Intracervical residual disease	127	78.5%		81.6%	
Extracervical residual disease[a]	93	59.4%		63.8%	
No response	49	47.5%		53.7%	
Consolidation therapy[b]					
No therapy	101	77.9%	0.0001	84.2%	<0.0001
CCRT or EBRT ± BCT	162	59.2%		62.7%	
Chemotherapy	66	85.5%		91.6%	

Pts, patients; RFS, recurrence-free survival; OS, overall survival; TAX, paclitaxel; CCRT, concurrent chemoradiation; EBRT, external beam irradiation; BCT, brachytherapy.
[a] With either positive or negative nodes.
[b] The patient who had chemotherapy followed by EBRT and the 3 patients who had BCT alone were not included in this analysis.

whereas FIGO stage ($p = 0.0169$) and consolidation therapy ($p = 0.0016$) were independent prognostic variables for overall survival (Table 4).

Discussion

NACT followed by radical hysterectomy is an interesting alternative therapeutic option to CCRT for patients with stage Ib_2–IIb cervical cancer [7–17]. The achievement of an optimal pathological response on surgical specimen is a strong predictor of a better clinical outcome [7,11,15–17]. In the present investigation, patients who did not obtain an overall optimal response had a 2.259-fold higher risk of recurrence and a 5.392-fold higher risk of death than those who obtained an overall optimal response.

A few papers appear to suggest a survival advantage for cervical carcinoma patients who received adjuvant chemotherapy after definitive CCRT [3–5]. Conversely, very few data are currently available as for adjuvant post-operative therapy in patients treated with NACT and radical hysterectomy (7, 9, 11, 13, 16). In the early experience of Benedetti Panici et al. [7], including 75 women with stage Ib_2–III disease who received 3 cycles of cisplatin (100 mg/m^2 day 1) + bleomycin (15 mg days 1 and 8) + methotrexate (300 mg/m^2 day 8 with leucovorin rescue) every 3 weeks prior to radical hysterectomy, postoperative treatment consisted of two additional cycles of the same chemotherapy in patients with histologically proven positive nodes regardless of surgical resection margin status, EBRT in those with positive surgical margins and negative nodes, and no further treatment in those with a pathological complete response or in those with negative surgical margins and negative nodes.

Giaroli et al. [16], who employed cisplatin (50 mg/m^2 day 1) + vincristine (1 mg/m^2 day 1) + bleomycin (25 mg/m^2 day 1–3) every 10 days for 3 cycles as NACT regimen, reported that most of their 169 patients underwent postoperative pelvic EBRT, whereas 7 women only with para-aortic metastases received adjuvant chemotherapy with cisplatin + methotrexate + vinblastine + cyclophosphamide.

In an Italian multicenter study comparing cisplatin-based NACT followed by radical hysterectomy versus radiotherapy in 441 women with stage Ib_2–III cervical carcinoma, patients enrolled in the chemo-surgical arm received EBRT if surgical margins were positive and no additional treatment if both surgical margins and lymph nodes were negative or no residual tumor was detected on surgical sample [9]. In the case of nodal involvement, the choice of adjuvant treatment was based on the institution's policy (i.e., chemotherapy, EBRT, or no further therapy). About one third of the failures showed a distant component with no significant difference between chemo-surgery arm and radiotherapy arm with regard to the pattern of recurrence [9]. These results, as well as the similar data reported by Sardi et al. [8] appeared to suggest that the relatively short duration of NACT might be not enough to control distant micro-metastases.

In the SNAP01 trial, comparing NACT with ifosfamide (5 g/m^2 24-hour infusion) + cisplatin (75 mg/m^2) (IP regimen) versus ifosfamide (5 g/m^2 24-hour infusion) day 1 + paclitaxel (175 mg/m^2 day 2) + cisplatin (75 mg/m^2 day 2) (TIP regimen) every 3 weeks for three cycles, women who achieved an optimal pathological response were scheduled to receive two additional cycles of chemotherapy after surgery with the same NACT regimen, whereas those women with positive nodes, parametrial involvement, cut-through or suboptimal response were candidates for EBRT or CCRT. Tumor relapsed in 30 out of the 108 patients (27.8%) of IP arm and 25 out of the 96 (26.0%) of TIP arm, and recurrent disease was local and distant ± local in 17 (56.7%) and 12 (40.0%), respectively, of the former (missing in 1), and in 14 (56.0%) and 11 (44.0%), respectively, of the latter. In the SNAP02 trial, comparing NACT with TIP versus paclitaxel (175 mg/m^2) + cisplatin (75 mg/m^2) (TP) every 3 weeks for three cycles, the criteria for postoperative treatment were the same as SNAP1 trial [13]. Disease recurred in 27 out of the 80 patients (33.8%) of TP arm and 20 out of the 74 (27.0%) of TIP arm, and failure site was local and distant ± local in 10 (37.0%) and 9 (33.3%), respectively, of the former (missing in 8), and in 5 (25.0%) and 9 (45.0%), respectively, of the latter (missing in 6). However in both SNAP trials there were relevant discrepancies between the scheduled postoperative regimen and the effectively used postoperative treatment, and neither studies investigated the relationship between postoperative treatment and the pattern of failures.

In the present study, tumor relapsed in 10.9% of overall optimal responders, 22.7% of sub-optimal responders and 44.9% of non-responders. Among the overall optimal responders, the risk of recurrence, recurrence-free survival and overall survival was the same in patients who had any adjuvant treatment and in those who had not, and recurrent disease was almost exclusively pelvic. Among the sub-optimal responders, a distant recurrence (with or without pelvic failure) occurred in none of the 42 patients who had adjuvant chemotherapy versus 17 (14.5%) out of the 117 who received postoperative CCRT or EBRT ± BCT, whereas pelvic failure developed in 6 (14.2%) of the former and 25 (21.3%) of the latter. It is noteworthy that recurrence-free survival and overall survival of sub-optimal responders with

Table 3
Variables predictive of recurrence-free survival and overall survival by Cox proportional hazard model.

Variable	Parameter estimated	Standard error	Wald χ^2	HR	95% CI	p value
Recurrence-free survival						
Consolidation therapy	0.42579	0.13173	10.4474	1.531	1.182–1.982	0.0012
Overall survival						
Stage	0.55188	0.2308	5.7040	1.737	1.104–2.731	0.0169
Consolidation therapy	0.47512	0.15089	9.9152	1.608	1.196–2.162	0.0016

intra-cervical residual disease were significantly better in patients who had adjuvant chemotherapy ($p = 0.047$ and $p = 0.0093$, respectively). Conversely, the clinical outcome of sub-optimal responders who had extra-cervical residual disease with either positive or negative nodes was not significantly different according to post-operative management. The small number of women who had no adjuvant treatment (n. 11) or who had adjuvant chemotherapy (n. 8) versus those who had adjuvant CCRT or EBRT ($n = 74$) does not allow to drawn any definitive conclusion. It is possible to speculate that patients with unsatisfactory response to NACT have limited benefit from both further cycles of the same induction regimen or the administration of CCRT or EBRT since chemo-resistant tumors are often radio-resistant too. A phase III randomized trial of the Gynecologic Oncology Group (GOG) has recently demonstrated that the addition of bevacizumab to chemotherapy (cisplatin 50 mg/m^2 + paclitaxel 135–175 mg/m^2 or topotecan 0.75 mg/m^2 day 1–3 + paclitaxel 175 mg/m^2 day 1 every 3 weeks) is associated with a 3.7-month increase in median overall survival (HR = 0.71, 97.6% CI = 0.54–0.95, $p = 0.0035$) when compared to chemotherapy alone in patients with recurrent cervical cancer [18]. New adjuvant treatments, i.e. the combined use of bevacizumab plus chemotherapy, could be tested in sub-optimal responders to NACT who have extra-cervical residual disease.

The weaknesses of the investigation are represented by its retrospective nature, by the lack of a centralized pathological review by a single pathologist with expertise in gynecologic pathology, and by the lack of standardization in the postoperative treatment. Moreover it is difficult to draw meaningful conclusions about the relative roles of adjuvant chemotherapy and radiotherapy when the criteria for choice of one versus the other are not a priori defined for the different types of responders. However, the strengths of the study are represented by the large number of patients and by the description of rate and pattern of recurrence according to pathological response and postoperative treatment.

The results of the present retrospective analysis appear to suggest that chemo-surgical approach is an effective therapeutic option for FIGO stage Ib_2–IIb cervical cancer, even though data from randomized clinical trials are not available yet to compare such a treatment modality to CCRT as standard of care for locally advanced cervical cancer [1–3]. Optimal responders do not need any further treatment. Additional cycles of chemotherapy, as opposed to adjuvant CCRT or EBRT, could be of benefit for patients with suboptimal response and intra-cervical residual disease. Both adjuvant chemotherapy and adjuvant CCRT or EBRT do not seem to improve the clinical outcome of patients with extra-cervical residual disease compared to no further treatment.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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