

Clinicopathological Variables Predictive of Clinical Outcome in Patients with FIGO Stage Ib₂-IIB Cervical Cancer Treated with Cisplatin-based Neoadjuvant Chemotherapy Followed by Radical Hysterectomy

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Abstract. The aim of this retrospective investigation was to assess the prognostic relevance of some pre-treatment clinical variables and histological findings assessed on the surgical samples of 46 patients with stage Ib₂-IIB cervical cancer treated with cisplatin-based neoadjuvant chemotherapy followed by radical hysterectomy. Seven patients achieved a pathologically documented complete response, 6 had an optimal partial response, 29 had a suboptimal partial response, and 4 had stable disease. As for histological findings on surgical samples, 7 (15.2%) patients had positive lymph nodes, 10 (21.7%) had lymph-vascular space involvement, and 10 (21.7%) had positive parametria and/ or surgical margins. After surgery, 38 patients received further treatment with chemotherapy and/or irradiation. The median follow-up of survivors was 53 months (range, 4-167 months). Thirteen (28.3%) patients developed recurrent tumour, 11 (23.9%) patients died of tumour and one patient died of ictus with no clinical evidence of tumour. Recurrence-free and overall survival were significantly related to tumour stage (Ib₂-IIa versus IIB, $p=0.01$ and $p=0.02$, respectively), pathologically assessed lymph node status (negative versus positive, $p=0.0009$ and $p=0.007$), lymph-vascular space status (negative versus positive, $p=0.01$ and $p=0.009$), parametrial and/or surgical margin status (negative versus positive, $p=0.0001$ and $p=0.0005$), but not to haemoglobin

level before chemotherapy, patient age, tumour grade or chemotherapy regimen. A platelet count before chemotherapy above the median value of 272,000/ μ l was associated with a trend for a shorter recurrence-free survival ($p=0.06$) and with a significantly shorter overall survival ($p=0.04$) when compared with a lower platelet count. In conclusion, FIGO stage, lymph node status, lymph-vascular space status, parametrial and/or surgical margin status and pre-treatment platelet count are predictors of clinical outcome in patients with FIGO stage Ib₂-IIB cervical cancer undergoing cisplatin-based neoadjuvant chemotherapy followed by radical hysterectomy. A multivariate analysis on a larger series of homogeneously treated patients is warranted to better define the clinicopathological risk factors useful to adequately plan the therapeutic strategy.

Cervical cancer remains a major health problem worldwide, despite advances in screening, since a relatively high number of cases are in locally advanced stage of disease at presentation (1, 2). Of the 15,081 cervical cancer patients assessed by the International Federation of Gynecology and Obstetrics (FIGO) Annual Report n. 26, 1,275 patients were in stage Ib₂, 1,249 in stage IIa, 3,209 in stage IIB, 274 in stage IIIa, 2,946 in stage IIIB, and 472 in stage IVa (2). The standard treatment for locally advanced cervical cancer is represented by cisplatin-based concurrent chemotherapy and external pelvic irradiation followed by brachytherapy (1, 3). A recent meta-analysis of 13 randomised trials on concurrent chemo-radiation in cervical cancer has shown that this treatment modality significantly improved disease-free survival (hazard ratio [HR]=0.78; 95% confidence interval [95% CI]=0.70-0.87, $p=0.000005$), locoregional recurrence-free survival (HR=0.76; 95% CI=0.68-0.86, $p=0.000003$), metastasis-free survival (HR=0.81; 95% CI=0.72-0.91, $p=0.0004$) and overall survival (HR=0.81, 95% CI=0.71-

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0.91, $p=0.0006$) compared with irradiation alone, with an absolute gain in 5-year survival of 8%, 9%, 7% and 6%, respectively (4). There was a suggestion of a difference in the survival benefit with tumour stage, not across other patient subgroups. Acute haematological and gastrointestinal toxicity was increased with chemoradiation, whereas data were too sparse for an analysis of late toxicity.

In the last two decades several studies have shown that neoadjuvant chemotherapy followed by radical hysterectomy is able to obtain very satisfactory results in locally advanced cervical cancer (5-11). In particular, the meta-analysis of 5 randomised trials including a total of 872 patients showed that neoadjuvant chemotherapy followed by surgery is superior to irradiation alone in terms of overall survival, with an absolute gain in 5-year overall survival of 14% (from 50% to 64%, HR=0.65, $p=0.00004$) (7). In an Italian randomised trial, chemo-surgical treatment achieved better progression-free survival ($p=0.02$) and overall survival ($p=0.005$) compared with irradiation alone in patients with stage Ib₂-IIb disease, whereas there was no significant difference in the clinical outcome between these two treatment modalities in patients with stage III disease (9).

The aim of this retrospective investigation was to assess the prognostic relevance of some pre-treatment clinical variables and histological findings assessed on the surgical samples from patients with stage Ib₂-IIb cervical cancer treated with neoadjuvant chemotherapy followed by radical hysterectomy.

Patients and Methods

This retrospective study was conducted on 46 patients with FIGO stage Ib₂-IIb cervical cancer who underwent cisplatin-based neoadjuvant chemotherapy followed by radical hysterectomy with pelvic lymphadenectomy at the Department of Gynecology and Obstetrics of the University of Pisa between 1995 and 2009.

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. Cystoscopy and/or proctoscopy were performed if there was clinical or CT suspicion of bladder or rectal involvement. Further investigation (*i.e.* magnetic resonance imaging [MRI], intravenous pyelography, transvaginal and/or transrectal ultrasound) were performed when appropriate.

Physical and vaginal pelvic examination and abdominal-pelvic CT scan were repeated 3-4 weeks after the completion of chemotherapy. All 46 patients underwent radical hysterectomy and pelvic lymphadenectomy within 5-6 weeks after the last cycle of chemotherapy. Clinical responses were determined according to the World Health Organization criteria (12). Pathological responses were retrospectively assessed according to the criteria suggested by Buda *et al.* (10). Complete response was defined as the complete disappearance of tumour in the cervix with negative lymph nodes; optimal partial response was defined as a persistent residual disease with less than 3 mm stromal invasion including *in situ* carcinoma on the surgical specimen; and suboptimal response consisted of persistent residual disease with more than 3 mm stromal invasion on the surgical specimen.

Postoperative management was individually established on the basis of histological findings on surgical samples, patient age and general conditions, after an exhaustive discussion with the patient herself. All patients were periodically followed-up with clinical, cytological and radiological examinations until they died or until April 2009. The median follow-up of survivors was 53 months (range, 4-167 months).

Statistical methods. The time from the first cycle of neoadjuvant chemotherapy to the detection of recurrence was defined as recurrence-free survival. The time from the first cycle of neoadjuvant chemotherapy to death or last observation was defined as overall survival. The analysed prognostic variables included patient age, FIGO stage, tumour grade, haemoglobin level and platelet count before chemotherapy, chemotherapy regimen, and pathologically assessed lymph node status, lymph-vascular space status and parametrial and/or surgical margin status.

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

Results

Patient characteristics at diagnosis and the chemotherapy regimens used are shown in Table I and Table II, respectively.

Patients treated before 1997 received cisplatin in combination with vincristine and bleomycin or with 5-fluorouracil, whereas those treated afterwards usually underwent cisplatin- and paclitaxel-based chemotherapy. The combination of ifosfamide+cisplatin was given to two patients who had a hypersensitivity reaction to paclitaxel. The regimen consisting of epidoxorubicin+paclitaxel+cisplatin was administered to two patients with cervical adenocarcinoma.

All patients completed the planned cycles of chemotherapy and were evaluable for response. Nine (19.5%) patients achieved a clinical complete response, 31 (67.4%) patients had a partial response, 5 (10.9%) patients had stable disease and one (2.2%) patient had progression of disease, for an overall response rate of 86.9%.

All the patients underwent type II-III radical hysterectomy with pelvic lymphadenectomy. Seven patients achieved a pathologically documented complete response, 6 patients had an optimal partial response, 29 patients had a suboptimal partial response, and 4 patients had a stable disease. An optimal pathological response (complete+partial optimal) was obtained in 13 (28.3%) patients.

As for histological findings on surgical samples, 7 (15.2%) patients had positive lymph nodes, 10 (21.7%) patients had lymph-vascular space involvement, and 10 (21.7%) patients had positive parametria and/or surgical margins.

After surgery, 18 patients received additional cycles of consolidation chemotherapy with the induction regimen, 12 underwent concurrent cisplatin-based chemotherapy and

Table I. Patient characteristics at diagnosis.

| | n |
|--------------------------------|---|
| Age | median=47 years (range, 27 to 70 years) |
| FIGO stage | |
| Ib ₂ | 9 |
| IIa | 9 |
| IIb | 28 |
| Histological type | |
| Squamous cell carcinoma | 42 |
| Adenocarcinoma | 4 |
| Tumour Grade | |
| Well/moderately differentiated | 22 |
| Poorly differentiated | 24 |
| Platelet count | |
| before chemotherapy | |
| median (range) | 272,000 μ l (142,000-620,000 μ l) |
| Haemoglobin level | |
| before chemotherapy | |
| median (range) | 11.8 g/dl (8.5-14.5 g/dl) |

Table II. Chemotherapy regimens.

| Chemotherapy regimen | No patients |
|----------------------|-------------|
| TIP | 22 |
| TP | 11 |
| PVB | 6 |
| TEP | 3 |
| IP | 2 |
| P + 5-FU | 2 |

TIP: Ifosfamide 5 g/m² (+mesna 5 g/m² 24-h continuous infusion) day 1+ paclitaxel 175 mg/m² (3-h infusion) day 2 + cisplatin 75 mg/m² day 2 every 3 weeks for 3 cycles ; TP: paclitaxel 175 mg/m² (3-h infusion) day 1 +cisplatin 75 mg/m² day 1 every 3 weeks for 3 cycles; PVB: vincristine 1 mg/m² day 1+cisplatin 50 mg/m² day 1+bleomycin 30 mg (24-h infusion) day 1 weekly for 6 cycles; TEP: epidoxorubicin 80 mg/m² day 1+ paclitaxel 175 mg/m² (3-h infusion) day 1+ cisplatin 75 mg/m² day 2 every 3 weeks for 3 cycles; IP: ifosfamide 5 g/m² (+ mesna 5 g/m² 24-h continuous infusion) day 1+ cisplatin 75 mg/m² day 2 every 3 weeks for 3 cycles. P+5-FU: cisplatin 100 mg/m² day 1+ 5-fluorouracil 1000 mg/m² /die (continuous infusion) day 1-4 every 3 weeks for 3 cycles.

external pelvic irradiation with or without brachytherapy, 7 received external pelvic irradiation with or without brachytherapy, one patient underwent 2 cycles of consolidation chemotherapy with the induction regimen followed by external pelvic and para-aortic irradiation, and 8 patients had no further treatment.

At the time of the present analysis, 13 (28.3%) patients had developed recurrent tumour, 11 (23.9%) patients had died of tumour, and one patient had died of ictus with no clinical evidence of tumour. The site of recurrent disease was the pelvis in 5 patients, para-aortic nodes in 3, the liver in 4, and the pelvis plus liver in one patient.

Recurrence-free survival was significantly related to FIGO stage (Ib₂-IIa *versus* IIb, $p=0.01$) (Figure 1a), pathologically assessed lymph node status (negative *versus* positive, $p=0.0009$) (Figure 2a), lymph-vascular space status (negative *versus* positive, $p=0.01$), (Figure 3a), parametrial and/or surgical margin status (negative *versus* positive, $p=0.0001$) (Figure 4a), but not to haemoglobin level before chemotherapy (>11.8 g/dl *versus* ≤ 11.8 g/dl), patient age (≤ 47 years *versus* >47 years), tumour grade (well/moderately differentiated *versus* poorly differentiated) or chemotherapy regimen (paclitaxel-based *versus* no-paclitaxel based regimen). There was a trend for a better recurrence-free survival in patients with a pre-chemotherapy platelet count $\leq 272,000/\mu$ l compared with those with a higher platelet count but the difference failed to reach statistical significance (Figure 5a).

At the time of writing, all 9 (100%) patients who achieved a complete clinical response were alive and recurrence free compared with 23 (62.2%) out of 37 who did not ($p=0.071$).

As for pathological response, 12 (92.3%) out of 13 patients who achieved an optimal pathological response were alive and recurrence-free compared with 20 (60.6%) out of 33 who did not ($p=0.08$).

Overall survival was significantly related to FIGO stage (Ib₂-IIa *versus* IIb, $p=0.02$), (Figure 1b), pathologically assessed lymph node status (negative *versus* positive, $p=0.007$) (Figure 2b), lymph-vascular space status (negative *versus* positive, $p=0.009$) (Figure 3b), parametrial and/or surgical margin status (negative *versus* positive, $p=0.0005$) (Figure 4b), platelet count before chemotherapy ($\leq 272,000/\mu$ l *versus* $>272,000/\mu$ l, $p=0.04$) (Figure 5b), but not to haemoglobin level before chemotherapy, patient age, tumour grade or chemotherapy regimen.

All 9 (100%) patients who achieved a complete clinical response were alive *versus* 25 (67.6%) out of 37 who did not ($p=0.118$). Twelve (92.3%) out of 13 patients who achieved an optimal pathological response were alive *versus* 22 (66.7%) of the 33 who did not ($p=0.158$).

Discussion

The role of neoadjuvant chemotherapy in cervical cancer has been much debated in the last two decades. Several pre-treatment clinical variables have been found to negatively correlate with the clinical outcome of patients, such as advanced FIGO stage (III *versus* Ib₂-IIb) (6,9,10), bulky tumour size (>5 cm *versus* <5 cm) (5, 6, 9), high tumour grade (6), parametrial involvement (6) and lymph node involvement assessed by diagnostic imaging techniques (9).

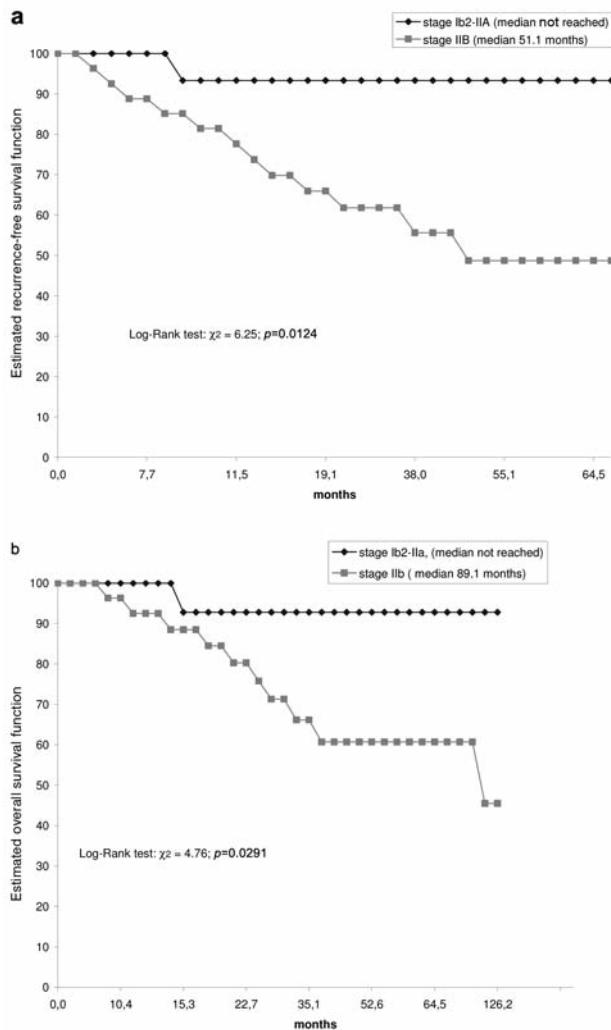


Figure 1. a) Recurrence-free survival by FIGO stage. b) Overall survival by FIGO stage.

Similarly, suboptimal pathological response (10,13-15), lymph-vascular space involvement (5), persistent tumour in the parametria (5,6, 14), and metastatic lymph nodes (5, 6, 13,14) at histological examination of surgical samples have been associated with an unfavourable prognosis.

In the present series, including patients with stage Ib₂-IIb cervical cancer undergoing chemotherapy followed by radical surgery, FIGO stage, pathologically assessed lymph node status, lymph-vascular space status, parametrial and/or surgical margin status were significantly related to both recurrence-free survival and overall survival.

The prognostic relevance of pre-treatment platelet count and haemoglobin level in cervical cancer patients undergoing chemo-surgical treatment is still uncertain. Thrombocytosis at diagnosis is a poor prognostic factor for different malignancies,

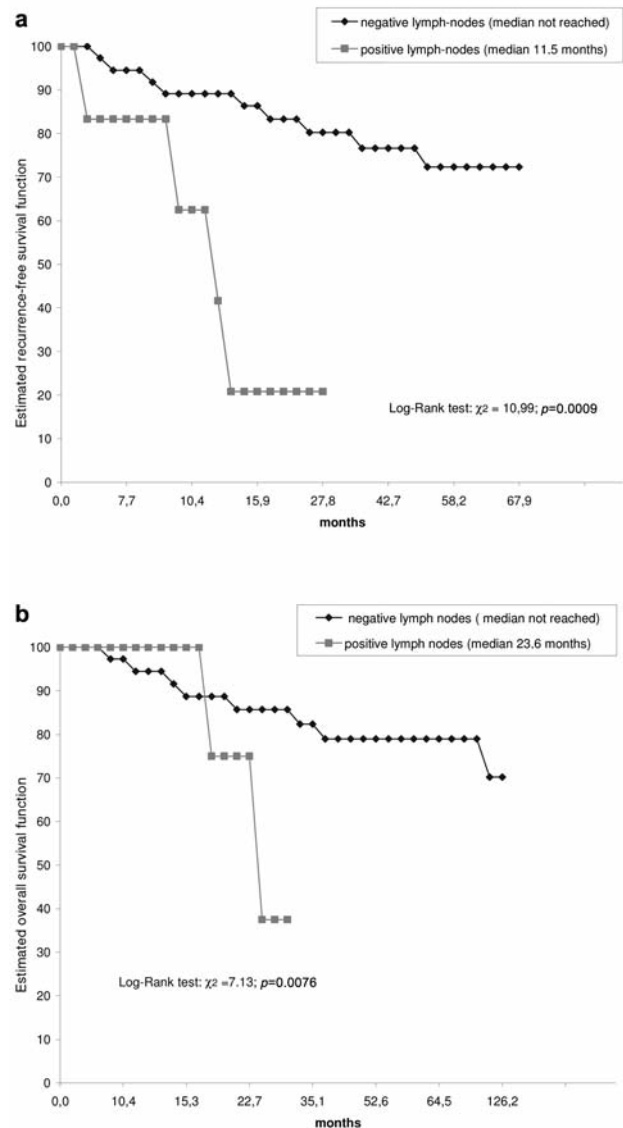


Figure 2. a) Recurrence-free survival by lymph-node status. b) Overall survival by lymph-node status.

including cervical cancer, probably because it reflects a cascade of biological events correlated with tumour aggressiveness (16-25). Malignant cells often produce cytokines such as interleukin-6 and growth factors able to induce megacaryopoiesis (16, 26-29), and platelets in turn can secrete growth factors able to stimulate cancer cell proliferation, to enhance angiogenesis and to promote metastasis (30-32).

In a study including 113 women with cervical carcinoma treated with radiotherapy, Hernandez *et al.* (20) found that 5-year survival was 65% for patients with a pre-treatment platelet count $<400,000/\mu\text{l}$ compared with 25% for those with higher platelet count ($p<0.0001$) and that thrombocytosis retained

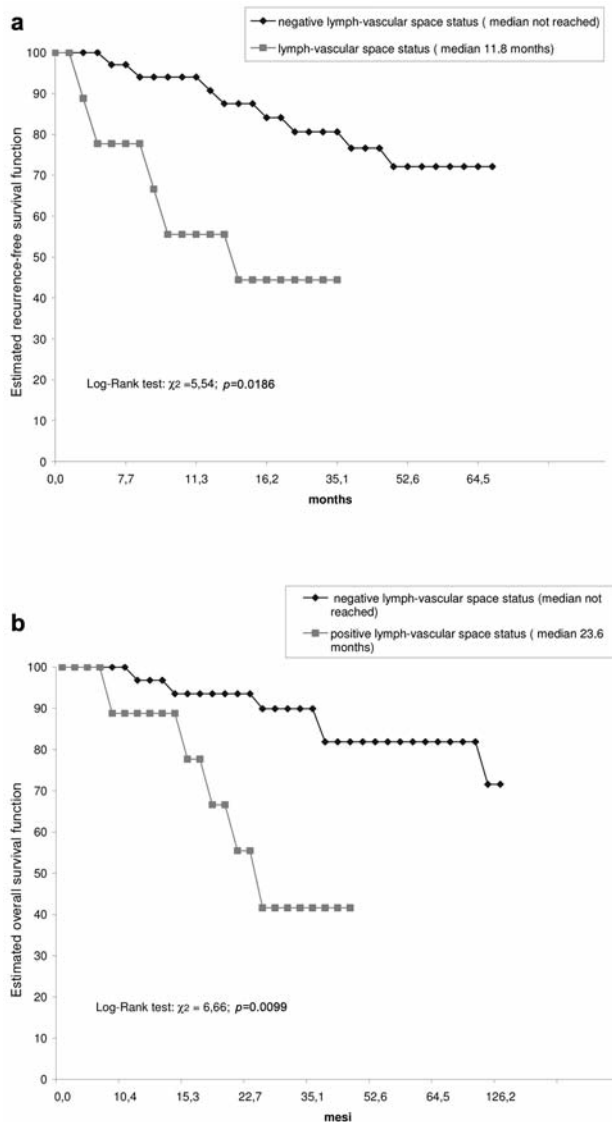


Figure 3. a) Recurrence-free survival by lymph-vascular space status. b) Overall survival by lymph-vascular space status.

prognostic relevance on multivariate analysis ($p < 0.001$). In a Gynecologic Oncology Group [GOG] study on 219 women with stage Ib cervical cancer who underwent radical hysterectomy, 5-year survival was 65% for the patients with a preoperative platelet count $>300,000/\mu\text{l}$ compared with 84% for those with platelet count $\leq 300,000/\mu\text{l}$ ($p = 0.004$), and thrombocytosis continued to correlate with poor survival even after adjusting for tumour size, lymph node status, patient age and race ($p = 0.04$) (23). Conversely, in other series, an elevated pre-treatment platelet count was related to poorer recurrence-free survival and overall survival on univariate but not on multivariate analysis (21, 24). In another GOG study including 294 women with stage IIB-

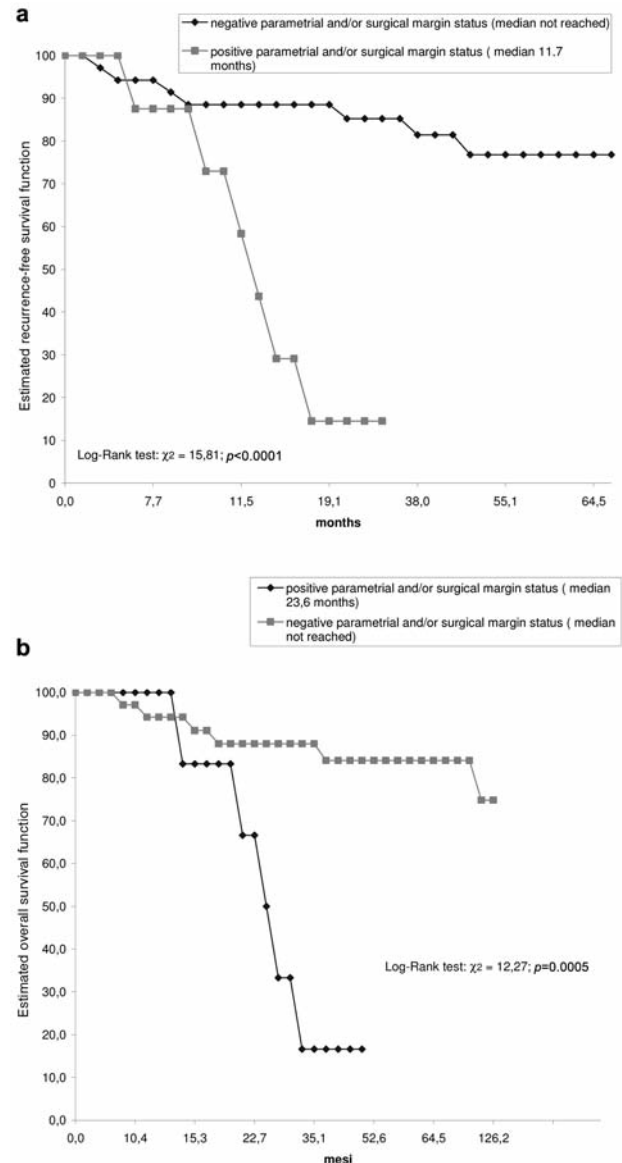


Figure 4. a) Recurrence-free survival by parametrial and/or surgical margin status. b) Overall survival by parametrial and/or surgical margin status.

IVA disease without para-aortic metastases treated with irradiation and concurrent hydroxyurea or misonidazole, the pre-treatment platelet count was not a significant predictor of survival when it was included in the Cox proportional hazard model as a continuous variable (25). However, when the data were stratified dichotomously as platelet count $>400,000/\mu\text{l}$ versus $\leq 400,000/\mu\text{l}$, there was a statistically significant relation to patient survival (risk ratio [RR]=1.55, 95% CI=1.08-2.21). The uncertainties in the literature about the prognostic relevance of the pre-treatment platelet count in cervical cancer may be partly dependent on both the heterogeneity of patient populations

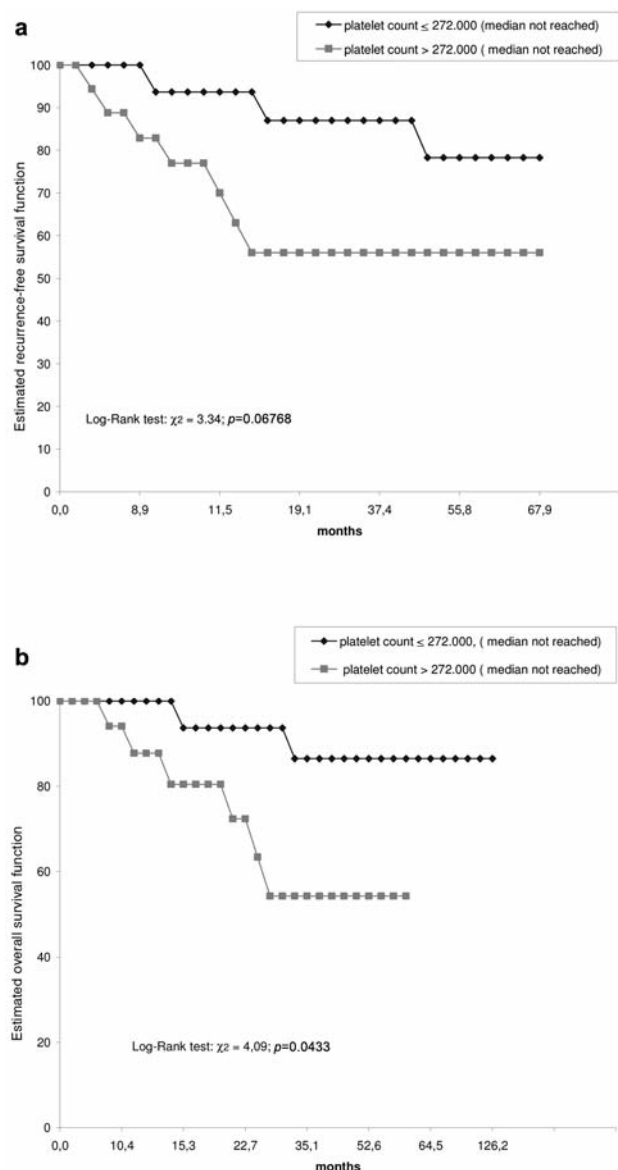


Figure 5. a) Recurrence-free survival by platelet count before chemotherapy. b) Overall survival by platelet count before chemotherapy.

regarding tumour stage and treatment modalities, and the differences in the cut-off value for the platelet count chosen for the definition of thrombocytosis.

Anaemia has been reported to be a poor prognostic factor in different malignancies including cervical cancer (33-42). Several investigators have suggested that anaemia at presentation and/or during treatment might heavily impair the clinical outcome of cervical cancer patients undergoing radiotherapy (34, 35, 40) or chemoradiation (36, 38). Few data are currently available as for the prognostic relevance of pre-treatment haemoglobin levels in patients undergoing

neoadjuvant chemotherapy (41-43). In a retrospective Italian study on 73 patients with locally advanced cervical cancer treated with platinum-based neoadjuvant chemotherapy, the patients with a pre-treatment haemoglobin level ≥ 12 mg/dl showed a 5-year survival of 87% compared with 63% for those with a lower haemoglobin level ($p=0.008$) (42).

In the present series a pre-chemotherapy platelet count above the median value of 272,000/ μ l was associated with a trend for a shorter recurrence-free survival ($p=0.06$) and with a significantly shorter overall survival ($p=0.04$) when compared with a lower platelet count, whereas pre-chemotherapy haemoglobin levels appeared to have no prognostic relevance.

In conclusion, FIGO stage, lymph node status, lymphovascular space status, parametrial and/or surgical margin status and pre-treatment platelet count are predictors of clinical outcome in patients with FIGO stage Ib₂-IIb cervical cancer undergoing cisplatin-based neoadjuvant chemotherapy followed by radical hysterectomy. A multivariate analysis on a larger series of homogeneously treated patients is warranted to better define the clinicopathological risk factors useful to adequately plan the therapeutic strategy.

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