Articles

Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer

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Summary

Background Stage Ib and IIa cervical carcinoma can be cured by radical surgery or radiotherapy. These two procedures are equally effective, but differ in associated morbidity and type of complications. In this prospective randomised trial of radiotherapy versus surgery, our aim was to assess the 5-year survival and the rate and pattern of complications and recurrences associated with each treatment.

Methods Between September, 1986, and December, 1991, 469 women with newly diagnosed stage Ib and IIa cervical carcinoma were referred to our institute. 343 eligible patients were randomised: 172 to surgery and 171 to radical radiotherapy. Adjuvant radiotherapy was delivered after surgery for women with surgical stage pT2b or greater, less than 3 mm of safe cervical stroma, cut-through, or positive nodes. The primary outcome measures were 5-year survival and the rate of complications. The analysis of survival and recurrence was by intention to treat and analysis of complications was by treatment delivered.

Findings 170 patients in the surgery group and 167 in the radiotherapy group were included in the intention-to-treat analysis; scheduled treatment was delivered to 169 and 158 women, respectively. 62 of 114 women with cervical diameters of 4 cm or smaller and 46 of 55 with diameters larger than 4 cm received adjuvant therapy. After a median follow-up of 87 (range 57–120) months, 5-year overall and disease-free survival were identical in the surgery and radiotherapy groups (83% and 74%, respectively, for both groups). 86 women developed recurrent disease: 42 (25%) in the surgery group and 44 (26%) in the radiotherapy group. Significant factors for survival in univariate and multivariate analyses were: cervical diameter, positive lymphangiography, and adeno-carcinomatous histotype. 48 (28%) surgery-group patients had severe morbidity compared with 19 (12%) radiotherapy-group patients (p=0·0004).

Interpretation There is no treatment of choice for early-stage cervical carcinoma in terms of overall or disease-free survival. The combination of surgery and radiotherapy has the worst morbidity, especially urological complications. The optimum therapy for each patient should take account of clinical factors such as menopausal status, age, medical illness, histological type, and cervical diameter to yield the best cure with minimum complications.

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Introduction

Stage Ib and IIa carcinoma of the cervix can be cured by radical surgery or radiotherapy with similar effectiveness, but the rate and types of complications differ. Radiotherapy is feasible and effective in almost all patients; 5-year survival after this therapy ranges from 78% to 91%.[1,2] By contrast, radical surgery affords the opportunity to study pathological findings, so that groups of at-risk patients who could benefit from adjuvant treatment can be identified. The 5-year cure rate after surgery for early-stage cervical tumours ranges from 54% to 90%; in most cases this rate is achieved with adjuvant therapy.[3,4] The treatment of choice will depend on the policy of the institution, the gynaecologist or radiation oncologist involved, and the age and the general health of the patient.

Apart from Newton's study[5] about stage-I diseases, there have been no randomised studies to compare radiotherapy with radical surgery in one institution over a short period of time. We conducted a prospective, randomised study to compare external and internal radiotherapy with radical hysterectomy and node dissection. Our main aim was to evaluate 5-year survival and the rate and pattern of complications and recurrences associated with each procedure.

Methods

Between September, 1986, and December, 1991, 578 patients with primary invasive cervical cancer were referred to the Departments of Obstetrics and Gynecology and Radiation Oncology, at the Istituto di Scienze Biomediche S Gerardo, University of Milan, Monza. All patients received standard pretreatment evaluation, which included complete blood analysis, intravenous pyelogram, lymphangiography, cystoscopy, chest radiography, and other tests when indicated. The cervical diameter was assessed by alginate mould.[6]

We used the International Federation of Gynaecology and Obstetrics (FIGO) clinical staging system to classify the stage of cancer.[7] If there was disagreement about the stage, the case was assigned to the earlier stage. 468 patients had FIGO stage Ib or

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IIa disease. 343 of these patients were enrolled after they had given their informed consent to take part. Eligibility criteria were: age 30–70 years; newly diagnosed stage Ib or IIa cervical cancer; no concurrent or previous malignant disease; WHO performance status of 1 or less; and feasibility of both radical surgery and radiotherapy.

The clinical evaluation of the patients was done by the gynaecological surgeon together with the radiation oncologist to avoid bias in the randomisation; in fact, patients with unfavourable clinical characteristics are usually treated by radiotherapy alone.

The patients were randomly assigned radical surgery (n=172) or radical radiotherapy (n=171). Patients were also stratified by cervical diameter (≤4 cm or >4 cm). Treatment was assigned by block randomisation (clusters of ten cases of each stratum of cervical diameter) from a computer-generated table that had been created before the start of the study. The treatments in the table were coded so that no-one could discover treatment allocation before randomisation. The codes were revealed after we had obtained the patient's informed consent.

Radiotherapy included: external pelvic irradiation with 18 MV photon beam by the multiportal technique; one dose of 1·8–2·0 Gy at the isocentre; and two or more portals treated daily. The median total dose of radiation was 47 (range 40–53) Gy during 3–5 weeks, depending on the tumour volume and nodal status. After 2 weeks, one caesium-137 LDR insertion was carried out. A complete computerised plane was made, according to the International Commission on Radiation Units and Measurements report no 38.[8] The total dose at point A (external beam plus brachyradiotherapy) ranged from 70 Gy to 90 Gy (median 76 Gy). The total dose to the pelvic wall exceeded 50 Gy; an additional dose was administered to the parametria by external beam if necessary. When lymphangiography showed common iliac or paraortic metastases, paraortic lymph nodes were treated with a dose of 45 Gy over 5 weeks and two shaped opposed fields (AP-PA). A boost of 5–10 Gy was given to the positive nodes.

Radical surgery consisted of a class III radical abdominal hysterectomy, as described by Piver and co-workers.[9] In all cases, a lower midline incision was made, which skirted the umbilicus and extended to the cephalad when indicated. Dissection of the pelvic lymph node consisted of removal of all fatty lymph-node bearing tissue anterior, lateral, and posterior to the common, external, and internal iliac vessels, and anterior to the obturator nerve. In cases of enlarged paraortic nodes, only sampling or selective procedures were done. In patients aged 40 years or younger with squamous histology, one ovary was preserved and suspended to the ipsilateral paracolic space outside the pelvis. The pathologist provided us with histological subtypes, grade, depth of invasion, tumour size, presence of capillary-like-space involvement, paracervical-tissue involvement, and number, site, and type of lymph-node metastases.

Patients who had at least one of the following pathological risk factors received adjuvant radiotherapy: surgical stage greater than pT2a; less than 3 mm of uninvolved cervical stroma; cut-through; and lymph-node metastases. Adjuvant radiotherapy consisted of external pelvic irradiation (18 MV X-rays) with the multiportal technique, one fraction of 1·8–2·0 Gy daily, with a total dose of 50·4 Gy over 5–6 weeks. The paraortic region was irradiated in case of metastases in the surgical specimen in common iliac or paraortic nodes with a dose of 45 Gy over 5 weeks.

The primary outcome measures were 5-year overall survival and the rate of complications. The secondary outcome measure was recurrence of the disease.

We classified complications as: grade 1, mild symptoms not affecting the patient's health and easily cured; grade 2, symptoms that can be resolved by long-term medical therapies; grade 3, major symptoms that require surgery or invasive procedures and affect the performance status of the patient, or fatal complications.

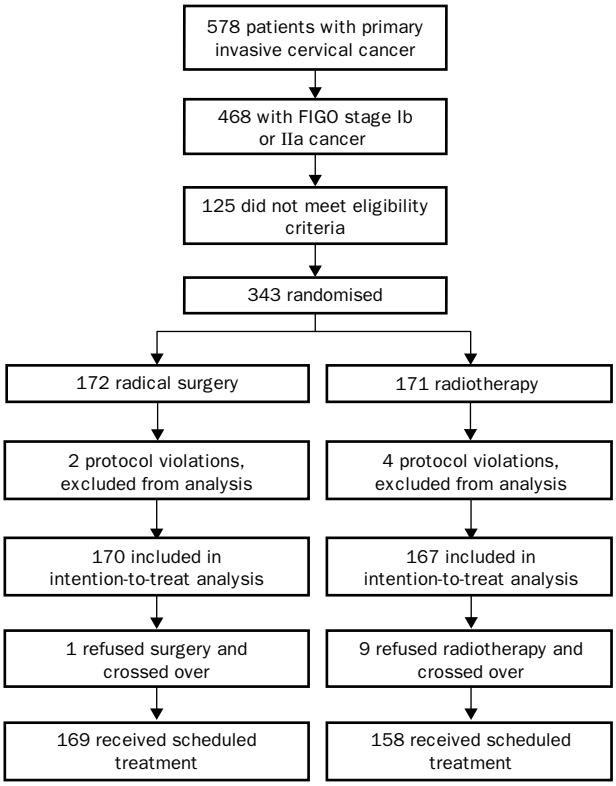

Figure 1: **Trial profile**

Statistical analysis

The minimum detectable difference in survival and morbidity was defined as 15% for α=0·05 and 1-β=80%. No interim analysis was done. We used χ^2 test with Yates' continuity correction to test the association between discrete variables. We compared quantitative data by one-way analysis of variance. Survival curves were calculated by the life-table method and compared by the log-rank test. A significance level of 95% was chosen. Survival and relapses were analysed by intention to treat. We analysed the rate of complications by the actual treatment delivered to each patient so that we could assess accurately the type and cause of morbidity associated with each treatment. We used multivariate Cox regression analysis to assess the effect of cervical size, age, FIGO state, histological type, grade of differentiation, radiological lymph-node status, and treatment group on overall survival.

Results

The trial profile shows the flow of patients in the study (figure 1). Of the 468 patients with FIGO stage Ib or IIa cervical cancer, 125 were excluded because of age (<30 years, >70 years; n=43), medical illness (n=54), previous or concurrent malignant disease (n=21), or the referring physician's or patient's preference for surgery, radiotherapy, or chemoradiotherapy (n=7).

Thus, 343 patients were randomised: 172 to radical surgery and 171 to radiotherapy. After randomisation, there were six protocol violations: two in the surgery group (one progression before operation and one refusal of any therapy after randomisation) and four in the radiotherapy group (two patients whose cancer was incorrectly staged and two with synchronous neoplasia). We excluded these cases from the analysis. Therefore 170 patients in the surgery group and 167 in the radiotherapy group were included in the intention-to-treat analysis. Ten patients crossed over treatment: one refused surgery and was irradiated, and nine refused radiotherapy and

	Surgery (n=170)		Radiotherapy (n=167)	
	≤4 cm	>4 cm	≤4 cm	>4 cm
Number of patients	115	55	113	54
Mean (SD) age in years	51·8 (11·3)	46·1 (10·1)	55·2 (10·9)	50·0 (9·8)
FIGO stage				
Ib	107 (93%)	47 (85%)	99 (88%)	45 (83%)
IIa	8 (7%)	8 (15%)	14 (12%)	9 (17%)
Positive lymphangiography	12 (10%)	12 (22%)	9 (8%)	13 (24%)
Histological type				
Squamous	94 (82%)	44 (80%)	97 (86%)	45 (83%)
Adenocarcinoma	18 (16%)	8 (15%)	13 (11%)	7 (13%)
Small cells	3 (2%)	3 (5%)	3 (3%)	2 (4%)

Table 1: **Distribution of factors affecting prognosis by cervical diameter in patients in surgery and radiotherapy groups**

underwent surgery. These cases were analysed according to the original group they were allocated to (intention to treat). Five patients in the radiotherapy group did not receive brachyradiotherapy after external irradiation because of unfavourable anatomy and subsequently underwent radical surgery. Thus, 169 in the surgery group and 158 in the radiotherapy group underwent the scheduled treatment (compliance of 98% for surgery and 92% for radiotherapy).

There were no significant between-group differences in the distribution of factors affecting prognosis (table 1). The mean age of patients in the radiotherapy group was slightly greater than that of patients in the surgery group. Lymphangiography revealed positive nodes in 24 (14%) surgery-group patients and in 22 (13%) radiotherapy-group patients. Six of the 24 surgery-group patients showed no lymph-node metastasis in the surgical specimen. Of the 145 surgery-group patients with negative lymphangiography, 27 had nodal metastases, which accounted for a specificity of 95% and a sensitivity of 40%.

The distribution of pathological risk factors differed significantly according to cervical diameter, especially for surgical stage, cut-through, and lymph-vascular-space involvement (table 2). Adjuvant radiotherapy was done in 62 (54%) of the 114 surgery-group patients who had a cervical diameter of 4 cm or smaller and in 46 (84%) of 55 surgery-group patients who had a cervical diameter larger than 4 cm. 19 patients whose cervical diameter was 4 cm or less and three patients whose cervical diameter was greater than 4 cm had lymph-vascular-space involvement as the only pathological risk factor; these patients did not receive postoperative irradiation.

Survival and recurrence

Median follow-up was 87 (range 57–120) months. No patient was lost to follow-up. 11 patients died of intercurrent disease and two from fatal complications

	Surgery patients (n=170)		p
	≤4 cm (n=114)	>4 cm (n=55)	
Risk factor			
Surgical stage >pT2a	22 (19%)	19 (35%)	0·04
Safe stroma <3 mm	44 (39%)	25 (45%)	0·50
Cut-through	7 (6%)	12 (22%)	0·007
Positive lymph nodes	28 (25%)	17 (31%)	0·49
Capillary-like space inadequate	65 (57%)	41 (75%)	0·03
Adjuvant therapy	62 (54%)	46 (84%)	0·0002

Table 2: **Pathological risk factors in surgery-group patients by cervical diameter**

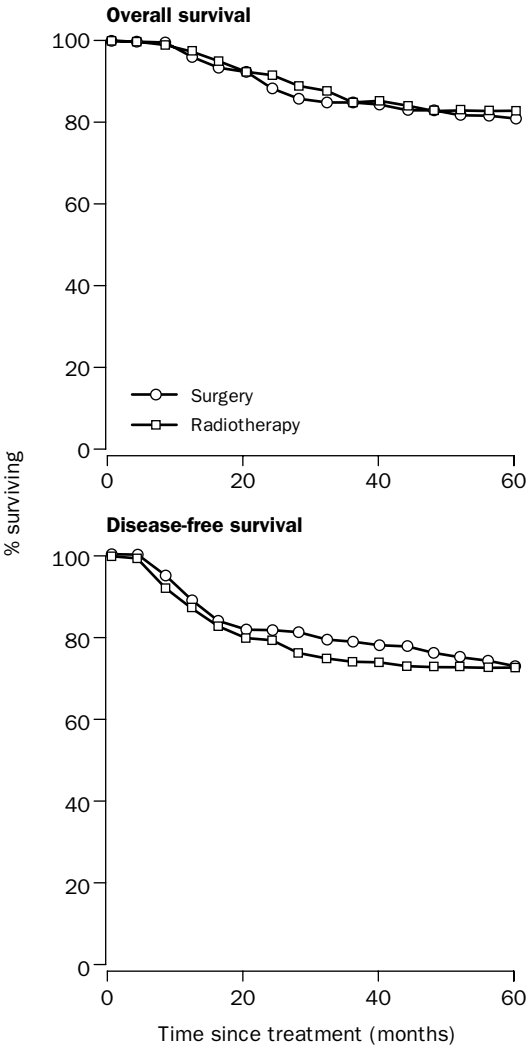

Figure 2: **Overall and disease-free actuarial survival by treatment group**

(bowel perforation and pulmonary embolism). The overall crude survival for all patients included in the intention-to-treat analysis was 76·5% (258 of 337). The status of the patients according to primary therapy and cervical diameter is shown in table 3.

The overall and disease-free actuarial 5-year survival for all patients were 83% and 74%, respectively, and did not differ significantly between the groups (figure 2).

5-year actuarial survival stratified by cervical diameter was similar in the surgery and radiotherapy groups (diameter ≤4 cm: 87% *vs* 90%; diameter >4 cm: 70% *vs* 72%; figure 3, table 3). 5-year actuarial disease-free survival for the surgery and radiotherapy groups was 80% and 82%, respectively, for patients whose cervical diameter was 4 cm or smaller, and 63% and 57% for those with a diameter larger than 4 cm; the between-group differences were not significant. The two groups did not differ significantly as regards squamous histotype: overall 5-year survival rates were 84% in surgery-group patients and 88% in radiotherapy-group patients; overall disease-free survival was 76% and 78%, respectively. For rates of adenocarcinoma there was a significant advantage for patients who had surgery compared with those who had radiotherapy in both overall survival (70% *vs* 59%, p=0·05) and disease-free survival (66% *vs* 47%, p=0·02).

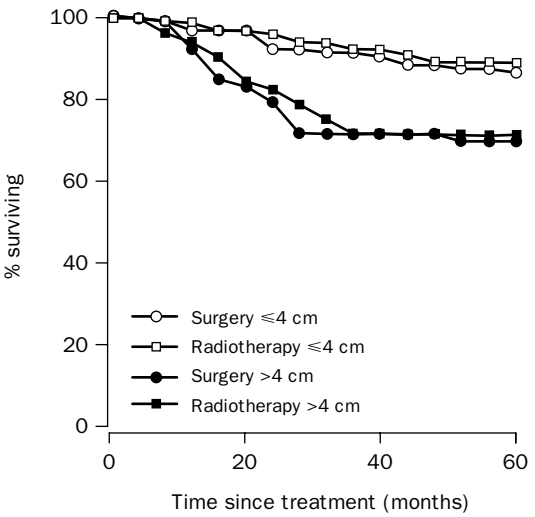

Figure 3: **Overall actuarial survival by treatment group and cervical diameter**

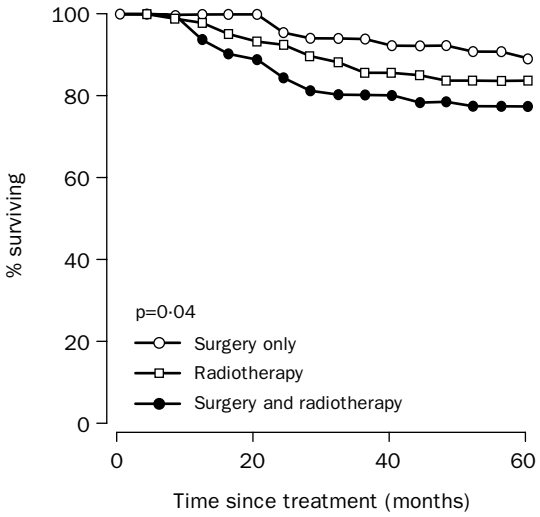

Figure 4: **Overall actuarial survival by treatment group**

Results of univariate and multivariate analysis are shown in table 4. Significant factors in both univariate and multivariate analyses were cervical diameter, positive lymphangiography, and adenocarcinomatous histotype. Overall survival for the 108 surgery-group patients who received adjuvant treatment (high-risk group) compared with the patients with surgery alone (low-risk group) or radiotherapy alone (unknown risk) is shown in figure 4,

Overall, 86 (25·5%) patients developed recurrent disease: 42 (25%) in the surgery group and 44 (26%) in the radiotherapy group. Of these 86 patients, 60 (70%) died of disease. Six patients were still alive with disease 4–18 months after the diagnosis of relapse. Three patients with recurrence died of intercurrent disease (one after successful treatment of the recurrence). Among the patients who developed recurrent disease, six (14%) in the surgery group and 13 (30%) in the radiotherapy group were cured; this difference was not significant (p=0·15). The median time to recurrence did not differ significantly between the surgery and radiotherapy groups (20 *vs* 18 months, p=0·24).

82% of pelvic recurrences and 61% of the distant ones became evident within 2 years of the primary treatment. Of the 86 patients who developed a recurrence, 50 (58%) had local or pelvic recurrence (22 [52%] in the surgery group *vs* 28 [64%] in the radiotherapy group, p=0·42), and 36 (42%) had distant metastases (20 [48%] *vs* 16 [36%], p=0·62); five of these 36 patients also had a pelvic recurrence. However, when cervical diameter was taken into account, there were substantial between-group differences in pelvic recurrence. In particular, among radiotherapy-group patients with cervical diameter larger than 4 cm, the rate of pelvic relapse was more than two-fold the rate of distant relapses (30% *vs* 13%). In addition, among women with a cervical diameter larger than 4 cm, there was a significantly higher rate of pelvic relapse among those who had radiotherapy than among those who had surgery plus adjuvant irradiation (16 [70%] *vs* 9 [53%], p=0·46).

Complications

Patients who had a treatment crossover were excluded from the analysis because the same factors that induced the treatment crossover could have affected the subsequent morbidity. Thus, 169 patients in the surgery group and 158 in the radiotherapy group were included in this analysis. Complications were classified according to the glossary of Chassagne and colleagues.[10] In the surgery group, 48 (28%) patients showed severe (grade 2–3) morbidity that required medical or surgical treatment, compared with 19 (12%) patients in the radiotherapy group, (p=0·0004; table 3). Grade 2 or 3 complications affected 19 (31%) patients who had surgery alone and 29 (27%) patients who received surgery and adjuvant radiotherapy (p=0·71). The sum of the short-term and long-term complications exceeds the total number of complications because some of the patients had multiple morbidity.

Two deaths were related to the primary treatment, both in the surgery group: ileal spontaneous perforation (11 months after adjuvant radiotherapy) and pulmonary embolism (17 days after surgery). This accounts for an overall mortality rate of 0·6%. Three (1·7%) surgery-

	Surgery						Radiotherapy group	
	Surgery only		Surgery plus radiotherapy		Total		⩽4 cm	>4 cm
	⩽4 cm	>4 cm	⩽4 cm	>4 cm	⩽4 cm	>4 cm		
Number of patients	53 (52)	9 (9)	62 (62)	46 (46)	115 (114)	55 (55)	113 (105)	54 (53)
Relapses	7 (13%)	2 (22%)	15 (26%)	17 (37%)	23 (20%)	19 (34%)	21 (18%)	23 (42%)
Pelvic	4	2	7	9	11	11	12	16
Distant	3	. .	9	8	12	8	9	7
Morbidity								
Grade 2–3†	16 (31%)	3 (33%)	18 (29%)	11 (24%)	34 (30%)	14 (25%)	13 (12%)	6 (11%)
Short-term	10 (16%)		22 (20%)		32 (19%)		11 (7%)	
Long-term	15 (24%)		31 (29%)		46 (27%)		25 (16%)	

*Parentheses show number of patients who actually received this treatment instead of intention to treat. †% calculated for number of patients who actually received treatment.

Table 3: **Relapses and morbidity**

	Number of patients	Univariate p	Unadjusted hazard ratio (95% CI)	Multivariate p	Adjusted hazard ratio (95% CI)
Treatment group					
Surgery	170	0·8	1·2 (0·7–2·3)	0·6	0·8 (0·5–1·2)
Radiotherapy	167				
Cervical diameter					
⩽4 cm	228	0·0003	2·1 (1·2–3·8)	0·0005	2·6 (1·9–3·5)
>4 cm	109				
Age (years)					
⩽50	159	0·4	0·9 (0·5–1·6)	0·2	1·4 (1–1·9)
>50	178				
Lymphangiography					
Negative	291	0·0004	5·4 (2·6–11·2)	0·002	3·6 (2·5–5·1)
Positive	46				
FIGO stage					
Ib	298	0·3	1 (0·4–2·6)	0·99	1 (0·6–1·6)
IIa	39				
Histological type					
Squamous	287	0·007	2·9 (1·4–6)	0·0008	2·68 (1·9–3·8)
Adenocarcinomeatous	50				
Histological grade					
1–2	180	0·2	1·3 (0·5–2·9)	0·3	1·3 (0·4–1·5)
3	157				

Table 4: **Univariate and multivariate analysis of overall survival**

group patients had perioperative complications: one vascular lesion during lymphadenectomy, one postoperative ureterovaginal fistula, and one fatal pulmonary embolism.

Hydroureteronephrosis was recorded in: two (3%) of 61 patients who had surgery alone; 11 (10%) of 108 patients who had surgery plus radiotherapy; and eight (5%) of 158 patients who had radiotherapy alone (p=0·1). The relative risk of this complication for surgery plus radiotherapy versus surgery alone was 3·11 (95% CI 0·71–13·56) and was 2·01 (95% CI 0·84–4·8%) for surgery plus radiotherapy versus radiotherapy alone. Positioning of ureteral catheter or nephtostomy was needed, respectively, in two (100%), three (27%), and five (62%) patients with hydroureteronephrosis in the three above-mentioned groups.

Chronic neurological bladder was observed in eight (13%) patients who had surgery alone and in five (5%) patients who had surgery plus radiotherapy. Other vesical complications (severe actinic cystitis, stress incontinence, high-pressure bladder) were recorded in two (3%) patients after surgery, 11 (10%) after surgery plus radiotherapy, and in eight (5%) after radiotherapy alone. Ileal obstruction occurred in six (5%) patients who underwent surgery plus radiotherapy and in two (1%) who received radical radiotherapy. In the radiotherapy group, one patient had intestinal perforation, one rectovaginal fistula, and 12 severe proctites.

Severe oedema of the legs occurred in ten (9%) patients who had surgery plus radiotherapy, in one (0·6%) patient who had radiotherapy alone, and in none of the patients who had surgery alone. Pelvic lymphocyst occurred in five (8%) patients after surgery and in five (15%) after surgery plus radiotherapy. Abdominal hernia occurred in seven patients, of whom four received surgery alone and three received surgery plus radiotherapy.

Discussion

Our review of the published research suggests that cure rates are similar for patients with stage-I cervical cancers who undergo surgery or radiotherapy. Newton[5] reported that the 5-year survival rate for 119 patients with stage-I disease accrued over 10 years in a partly randomised study was 81% for radical surgery and 74% for radiotherapy; this difference was not significant. Morley and Seski's[11] study, of 446 patients with stage-Ib disease recruited between 1945 and 1975 and treated with radical hysterectomy and bilateral pelvic lymphadenectomy or external irradiation and brachyradiotherapy, reported crude 5-year survival of 87% and 83%, respectively. These rates suggest that both treatments are equally effective for early-stage cancers (Ib and IIa).

In our study, 5-year actuarial survival was the same in the surgery and radiation groups (83%), which suggests that there is no treatment of choice with respect to local control of disease. Apart from survival, optimum treatment strategies depend on the benefits and disadvantages of each treatment and on prognostic factors (cervical diameter, histotype, and lymph-node status). Age is also an important factor; in most cases, cervical carcinomas occur in middle-aged women. Radical hysterectomy allows the gonadal function of at least one ovary to be saved, thereby avoiding the effects of early menopause in younger women. Shortening and fibrosis of the vagina can be limited if the woman is sexually active. Most complications can be easily corrected. Surgery also offers other advantages: pelvic relapses can be successfully cured by radiotherapy, whereas salvage surgery after primary irradiation carries a high rate of failures and severe morbidity. Furthermore, surgery allows the status of the lymph nodes, the most dependent variable associated with survival, to be assessed accurately.

By contrast, radiotherapy is easier to deliver for patients who are obese, are elderly, or have severe illness—major contraindications to the surgical approach. Radiotherapy also avoids the risks of anaesthesia and the laparotomy scar, and iatrogenic mortality is rare. Complications after radiotherapy arise later than after surgery, although radiotherapy-related complications are often permanent.

Morbidity is associated with both treatment strategies, though the most severe complications, such as operative mortality, urological complications, and tissue damage from irradiation, have been reduced during the past 20 years. In our experience, the combination of surgery and adjuvant radiotherapy carries the worst morbidity, especially long-term (delayed in onset) complications,

that are difficult to record during the follow-up. Hydroureteronephroses, oedema of the lower limbs, various vesical complications, and bowel morbidity are more common and compromising in women who undergo surgery plus radiotherapy. On the other hand, the low rate of major complications after radiotherapy (12%) suggests that this approach is well-tolerated by most patients.

25% of the surgery-group patients and 26% patients in the radiotherapy group developed neoplastic recurrence. The pelvic area (including vagina and cervix, when present) was involved in 22 (52%) of 42 relapses after surgery and in 28 (64%) of 44 relapses after radiotherapy. The women with a cervical diameter larger than 4 cm had the most unfavourable pathological prognostic factors and were at risk of a relapse independently from any other clinical factor. These data are confirmed by other previous studies.[12,13]

Adjuvant radiotherapy was prospectively planned in patients at high risk of relapse. Our study was not aimed to assess the usefulness of the postoperative treatment, though our finding that patients treated with surgery plus radiotherapy were exposed to early and late complications of both treatments is important. Clinical prognostic factors can prove useful to select those patients who should be treated primarily by irradiation, reserving surgery for patients who do not need adjuvant treatment. In Italy, a prospective randomised trial has been under way since 1993 to assess the best adjuvant treatment (chemotherapy or radiotherapy) for high-risk patients after radical surgery for FIGO stage Ib–IIa cancer.

Improvements in local control and survival could be achieved by combined treatments, which would avoid the discomforting complications associated with surgery plus radiotherapy. The most important clinical risk factors that could indicate benefit of combined treatments are cervical diameter and lymph node status as assessed by lymphangiography.

Most women with stage Ib–IIa cervical cancer can be treated successfully with radiotherapy, whereas a judicious selection of patients is necessary before planning primary radical surgery. Histological type should be included in the selection criteria, because our data show that radiotherapy was less effective than surgery for adenocardinoma of the cervix. This finding should resolve some of the conflicting approaches to this issue.[14–16] Our results suggest that the optimum candidates for primary radical surgery are women with normal ovarian function and cervical diameters of 4 cm or smaller, whereas radiotherapy is preferable for postmenopausal women. Women whose cervical diameters are larger than 4 cm should be identified before surgery so that they can benefit from tailored treatment: radical radiotherapy, with the option of concomitant radiosensitising chemotherapy to improve the local control of the disease, or cisplatin-based chemotherapy followed by radical surgery. The latter approach offers the advantages of surgery, and the neoadjuvant chemotherapy will keep to a minimum the risk of extracervical spread of the tumour without combining surgery and radiotherapy.[17,18] An Italian prospective randomised trial of radical radiotherapy versus neoadjuvant chemotherapy followed by surgery in patients with squamous neoplasia and cervical diameters larger than 4 cm has been in progress since 1991.

Contributors

F Landoni designed the trial, and was involved in the surgical procedures, follow-up, and the writing of the paper. A Maneo contributed to follow-up, data collection, statistical analysis, and writing the paper. A Colombo was involved in the design of the trial, radiotherapic procedures, follow-up, and writing the paper. F Placa took part in the radiotherapy procedures and follow-up. R Milani contributed to the surgical procedures, and follow-up and edited the paper. P Perego provided data from the surgical specimens. G Favini presented data from the radiological evaluations and edited the paper. L Ferri oversaw the design and conduct of the trial and took part in radiotherapy procedures. C Mangioni oversaw the design and conduct of the trial, took part in surgical procedures, and edited the paper.

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