

Carcinoma of the Cervix Uteri

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STAGING

Anatomy

Primary site

The cervix is the lower third of the uterus. It is roughly cylindrical in shape, projects through the upper, anterior vaginal wall and communicates with the vagina through an orifice called the external os. Cancer of the cervix may originate on the vaginal surface or in the canal.

Nodal stations

The cervix is drained by preureteral, postureteral, and uterosacral routes into the following first station nodes: parametrial, internal (obturator – hypogastric), external iliac, presacral and common iliac. Para-aortic nodes are second station and are considered metastases.

Metastatic sites

The most common sites of distant spread include the aortic and mediastinal nodes, the lungs and skeleton.

Table 1

Carcinoma of the cervix uteri: FIGO nomenclature (Montreal, 1994)

Stage 0	Carcinoma <i>in situ</i> , cervical intraepithelial neoplasia Grade III.
Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded).
Ia	Invasive carcinoma which can be diagnosed only by microscopy. All macroscopically visible lesions – even with superficial invasion – are allotted to Stage Ib carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.0 mm and a horizontal extension of not >7.0 mm. Depth of invasion should not be >5.0 mm taken from the base of the epithelium of the original tissue – superficial or glandular. The involvement of vascular spaces – venous or lymphatic – should not change the stage allotment.
Ia1	Measured stromal invasion of not >3.0 mm in depth and extension of not >7.0 mm.
Ia2	Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not >7.0 mm.
Ib	Clinically visible lesions limited to the cervix uteri or preclinical cancers greater than Stage Ia.
Ib1	Clinically visible lesions not >4.0 cm.
Ib2	Clinically visible lesions >4.0 cm.
Stage II	Cervical carcinoma invades beyond uterus, but not to the pelvic wall or to the lower third of vagina.
Ila	No obvious parametrial involvement.
Ilb	Obvious parametrial involvement.
Stage III	The carcinoma has extended to the pelvic wall. On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. The tumor involves the lower third of the vagina. All cases with hydronephrosis or nonfunctioning kidney are included, unless they are known to be due to other cause.
IIla	Tumor involves lower third of the vagina, with no extension to the pelvic wall.
IIlb	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney.
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum.
	A bullous edema, as such, does not permit a case to be allotted to Stage IV.
IVa	Spread of the growth to adjacent organs.
IVb	Spread to distant organs.

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Rules for classification

Clinical–diagnostic staging

Staging of cervical cancer is based on clinical evaluation; therefore, careful clinical examination should be performed in all cases, preferably by an experienced examiner and under anesthesia. The clinical staging must not be changed because of subsequent findings. When there is doubt as to which stage a particular cancer

should be allocated, the earlier stage is mandatory. The following examinations are permitted: palpation, inspection, colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, intravenous urography, and X-ray examination of the lungs and skeleton. Suspected bladder or rectal involvement should be confirmed by biopsy and histologic evidence. Conization or amputation of the cervix is regarded as a clinical examination. Invasive cancers so identified are to be included in

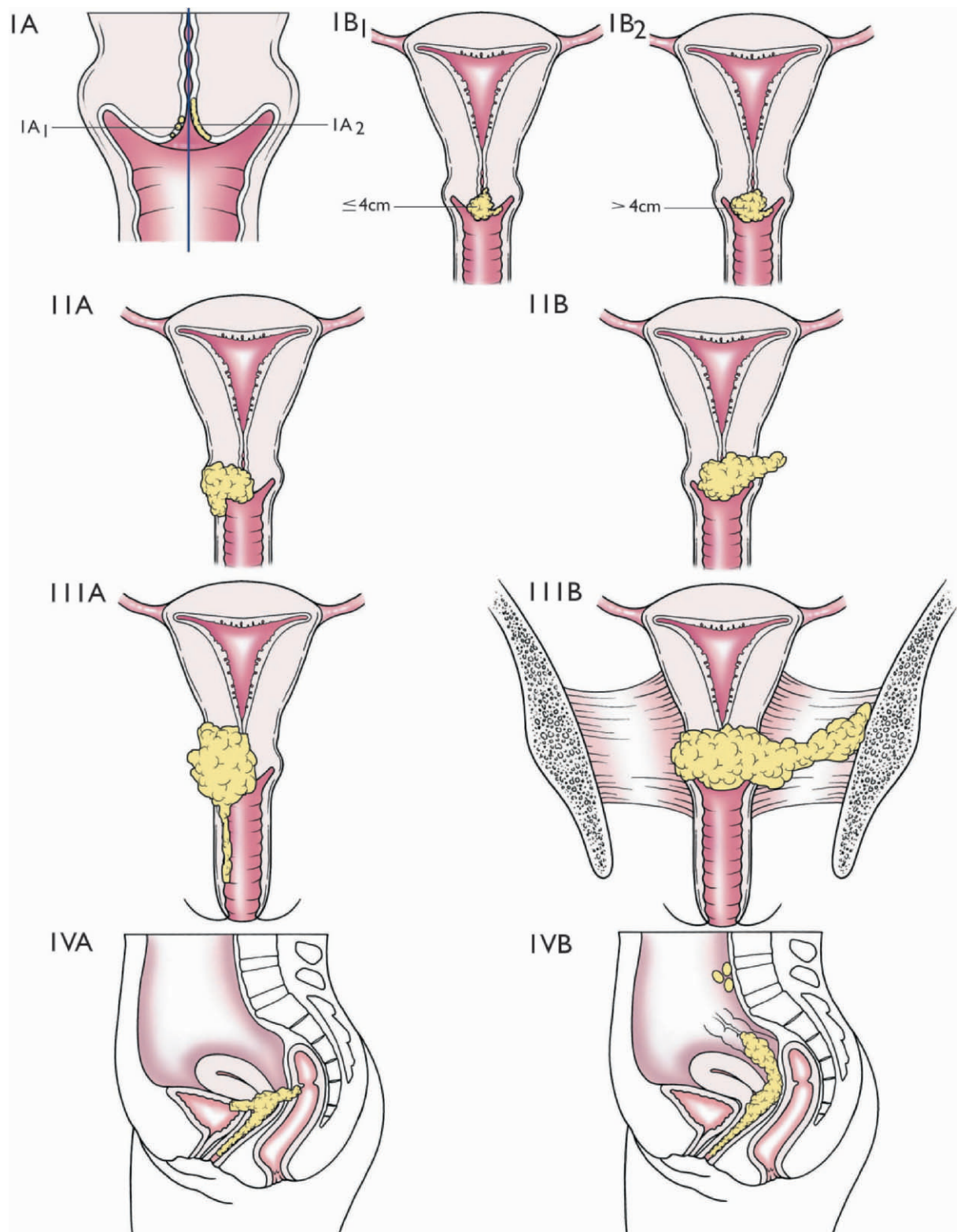


Fig. 1. Carcinoma of the cervix uteri: staging cervical cancer (primary tumor and metastases).

the reports. Findings of optional examinations e.g. lymphangiography, arteriography, venography, laparoscopy, ultrasound, computed tomography scan, and MRI are of value for planning therapy but, because these are not generally available and the interpretation of results is variable, the findings of such studies should not be the basis for changing the clinical staging. Fine needle aspiration (FNA) of scan-detected suspicious lymph nodes may be helpful in treatment planning.

Postsurgical treatment – pathologic staging

In cases treated by surgical procedures, the pathologist's findings in the removed tissues can be the basis for extremely accurate statements on the extent of disease. The findings should not be allowed to change the clinical staging but should be recorded in the manner described for the pathologic staging of disease. The TNM nomenclature is appropriate for this purpose. Infrequently it happens that hysterectomy is carried out in the presence of unsuspected extensive invasive cervical carcinoma. Such cases cannot be clinically staged or included in therapeutic statistics, but it is desirable that they be reported separately.

As in all gynecological cancers, staging is determined at the time of the primary diagnosis and cannot be altered, even at recurrence.

Only if the rules for clinical staging are strictly observed will it be possible to compare results among clinics and by differing modes of therapy.

Staging classification

Notes about the staging

Stage 0 comprises those cases with full-thickness involvement of the epithelium with atypical cells, but with no signs of invasion into the stroma.

The diagnosis of both Stage Ia1 and Ia2 should be based on microscopic examination of removed tissue, preferably a cone biopsy, which must include the entire lesion. The depth of invasion should not be >5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. The second dimension, the horizontal spread, must not exceed 7 mm. Vascular space involvement, either venous or lymphatic, should not alter the staging, but should be specifically recorded because it may affect treatment decisions in the future. Larger lesions should be staged as Ib.

As a rule, it is impossible to clinically estimate if a cancer of the cervix has extended to the corpus. Extension to the corpus should therefore be disregarded.

A patient with a growth fixed to the pelvic wall by a short and indurated, but not nodular, parametrium should

be allotted to Stage IIb. It is impossible, at clinical examination, to decide whether a smooth and indurated parametrium is truly cancerous or only inflammatory. Therefore, the case should be placed in Stage III only if the parametrium is nodular to the pelvic wall or if the growth itself extends to the pelvic wall.

The presence of hydronephrosis or non-functioning kidney resulting from stenosis of the ureter by cancer permits a case to be allotted to Stage III even if, according to the other findings, the case should be allotted to Stage I or Stage II.

The presence of bullous edema, as such, should not permit a case to be allotted to Stage IV. Ridges and furrows into the bladder wall should be interpreted as signs of submucous involvement of the bladder if they remain fixed to the growth at rectovaginal examination. Finding malignant cells in cytologic washings from the urinary bladder requires further histological confirmation in order to be considered for Stage IVa.

Histopathology

Cases should be classified as carcinomas of the cervix if the primary growth is in the cervix. All histologic types must be included. Grading by any of several methods is encouraged, but is not a basis for modifying the stage groupings. When surgery is the primary treatment, the histologic findings permit the case to have pathologic staging, as described above. In this situation, the TNM nomenclature may be used. All tumors are to be microscopically verified.

Histopathologic types

- Cervical intraepithelial neoplasia, Grade III
- Squamous cell carcinoma *in situ*
- Squamous cell carcinoma
 - Keratinizing
 - Nonkeratinizing
 - Verrucous
- Adenocarcinoma *in situ*
- Adenocarcinoma *in situ*, endocervical type
- Endometrioid adenocarcinoma
- Clear cell adenocarcinoma
- Adenosquamous carcinoma
- Adenoid cystic carcinoma
- Small cell carcinoma
- Undifferentiated carcinoma

Histopathologic grade (G)

- GX: Grade cannot be assessed
- G1: Well differentiated
- G2: Moderately differentiated
- G3: Poorly or undifferentiated

Table 2
Carcinoma of the cervix uteri: Stage grouping for cervix uteri

FIGO stage	UICC		
	T	N	M
0	Tis	N0	M0
Ia1	T1a1	N0	M0
Ia2	T1a2	N0	M0
Ib1	T1b1	N0	M0
Ib2	T1b2	N0	M0
IIa	T2a	N0	M0
IIb	T2b	N0	M0
IIIa	T3a	N0	M0
IIIb	T1	N1	M0
	T2	N1	M0
	T3a	N1	M0
	T3b	any N	M0
IVa	T4	any N	M0
IVb	any T	any N	M1

DEFINITIONS OF TREATMENTS

Treatment definitions are given in Table 3.

Table 3
Carcinoma of the cervix uteri: Definitions of treatments

Treatment	Definition
None	No treatment.
Surgery alone	Surgery as first therapy and no other therapy(ies) within 90 days from the date of surgery. Subsequently, patients can be given any further treatment.
Radiotherapy alone	External radiotherapy and/or intracavitary irradiation as first therapy(ies) and no other therapy(ies) within 90 days from the end of teletherapy/brachytherapy. Subsequently, patients can be given any further treatment.
Radio-surgery	External radiotherapy/intracavitary irradiation as first therapy and then surgery within 90 days from the end of teletherapy/brachytherapy. Subsequently, patients can be given any further treatment. (Chemotherapy can be associated within 120 days from the date of surgery.)
Neoadjuvant chemotherapy + surgery	Chemotherapy as first therapy and then surgery within 42 days from the end of chemotherapy. Subsequently, patients can be given any further treatment.
Surgery + adjuvant radiotherapy	Surgery as first therapy and then radiotherapy within 90 days from the date of surgery. Subsequently, patients can be given any further treatment. (Chemotherapy can be associated within 120 days from the date of surgery.)
Surgery + adjuvant chemotherapy	Surgery as first therapy and then chemotherapy within 90 days from the date of surgery or of the end of radiotherapy.
Chemo-radiotherapy	Radiotherapy with chemotherapy (either neoadjuvant, concomitant or sequential) administered together or at least within 90 days from the end of either therapy.
Chemotherapy alone	Chemotherapy as first therapy and no other therapy(ies) within 90 days from the end of chemotherapy. Subsequently, patients can be given any further treatment.

DATA ANALYSIS

Summary and comments

Volume 26 of the Annual Report contains information on 15081 patients characterized by a mean age ranging from 37 to 69 years, depending on stage and histologic type, and treated between the years 1999 and 2001. Of these, 11775 (mean age 51.7 years) are eligible for the survival analysis (see section on Materials and Methods). The number of cases reported reflects an overall increase by 7.8% of contributions to the Annual Report, with an 11.8% increase of cases eligible for survival analysis. New contributors from South Africa, Brazil, India, Japan, Korea, Thailand, Turkey, Pakistan, Sri Lanka, Germany, Greece, Italy, Slovenia, Sweden and the United Kingdom have added enormously to the value of this data collection (Table 4).

Figure 2 shows the distribution of patients according to age and stage, with early disease more common in women less than 50 years old.

Figure 3 shows the distribution of patients by stage and mode of treatment. As expected most patients with early disease were treated with surgery (\pm adjuvant therapy), while more advanced cases were mostly treated with radiotherapy. A three-fold increase in the number of patients treated with combined chemotherapy/radiation is

Table 4

Carcinoma of the cervix uteri: patients treated in 1999–2001. Distribution of patients by center and stage

		All	Not available	Stage I	Stage II	Stage III	Stage IV
All centers		15081	180	6353	4458	3220	870
Nigeria	Ibadan (IF Adewole)	60	2	4	26	24	4
South Africa	Cape Town (L van Wijk)	440	–	73	110	189	68
	Pretoria (G Lindeque)	381	3	67	57	190	64
Argentina	Buenos Aires (J Sardi)	200	–	93	79	20	8
	Buenos Aires (R Testa)	32	–	19	10	2	1
	Santa Fe (A Ellena)	74	–	17	23	31	3
Brazil	Belo Horizonte (A Moraes de Souza)	219	1	45	113	58	2
	Porto Alegre (G Py Gomez da Silveira)	7	–	5	2	–	–
	São Paulo (RL Rangel Costa)	71	–	30	22	15	4
	São Paulo (RL Rangel Costa)	382	–	201	100	74	7
Canada	Montreal (L Gilbert)	111	1	61	29	9	11
Chile	Santiago (E Suarez)	80	–	63	10	5	2
	Temuco (I Capurro)	151	1	95	25	24	6
Peru	Arequipa (L Medina Fernandez)	115	–	29	35	34	17
United States	Baltimore, MD (RE Bristow)	85	1	37	23	16	8
	Jacksonville, FL (B-E Sevin)	22	–	15	2	–	5
	Nashville, TN (HW Jones)	107	2	61	22	19	3
	Orange, CA (PJ DiSaia)	81	1	42	21	15	2
China	Guangzhou (Z Liu)	536	12	195	228	96	5
	Hong Kong (H Ngan)	233	1	138	65	23	6
	Wuhan (S Yu)	135	3	3	14	106	9
India	Karad (R Ranade)	27	2	7	8	9	1
Indonesia	Medan (M Fauzie Sahil)	119	–	23	43	47	6
Japan	Amagasaki (K Ito)	23	–	10	11	1	1
	Chiba (S Kato)	163	–	27	55	54	27
	Fukuoka (N Tsukamoto)	159	–	88	38	18	15
	Gunma (T Kanuma)	54	7	31	15	–	1
	Kochi (S Takeuchi)	34	–	19	5	7	3
	Kumamoto (H Katabuchi)	90	–	51	24	10	5
	Kurashiki-City (K Fujiwara)	20	–	13	5	1	1
	Nagasaki (T Ishimaru)	77	–	38	28	4	7
	Niigata (Y Aoki)	77	–	46	16	6	9
	Sapporo (N Sakuragi)	60	1	27	19	9	4
	Yonago (J Kigawa)	69	–	34	21	9	5

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Table 4, *continued*

		All	Not available	Stage I	Stage II	Stage III	Stage IV
Korea	Gyeonggi-do (S-Y Park)	45	–	24	17	4	–
	Kyunggi-do (SJ Kim)	91	–	42	40	5	4
	Seoul (HP Lee)	255	1	168	67	7	12
	Seoul (JE Mok)	461	–	310	109	22	20
	Seoul (H-S Saw)	42	–	22	16	1	3
Taiwan	Tao-Yuan (TC Chang)	1174	2	710	305	107	50
Thailand	Bangkok (D Tresjukosol)	463	7	151	142	152	11
	Bangkok (C Vipupinyo)	437	1	189	144	73	30
	Songkhla (V Wootipoom)	764	–	177	321	210	56
Turkey	Ankara (A Ayhan)	85	–	72	13	–	–
Pakistan	Islamabad (R Shaheen)	5	–	1	–	4	–
Sri Lanka	Galle (H Samarage)	2	–	–	–	2	–
Austria	Graz (M Lahousen)	109	–	55	38	11	5
	Innsbruck (C Marth)	109	–	63	22	15	9
Croatia	Rijeka (H Haller)	129	–	94	9	24	2
	Zagreb (S Jukic)	371	–	63	141	131	36
Czech Republic	Brno (A Dörr)	77	–	14	16	36	11
	Prague (E Kmonicková)	141	–	52	42	32	15
Finland	Oys (P Vuolo-Merilä)	44	–	26	12	2	4
	Turku (T Salmi)	41	–	18	15	6	2
France	Bordeaux (ML Campo)	111	–	41	49	14	7
Germany	Essen (R Callies)	41	–	20	11	5	5
	Greifswald (G Koehler)	118	3	41	16	40	18
	Hannover (H Kühnle)	139	11	62	33	25	8
	Wiesbaden (A du Bois)	69	–	39	12	16	2
	Würzburg (J Dietl)	159	75	42	19	16	7
Greece	Athens (G Magiakos)	62	–	32	14	13	3
	Athens (A Rodolakis)	231	–	99	56	62	14
Italy	Brescia (SM Magrini)	73	–	15	41	10	7
	Brescia (S Pecorelli)	65	–	43	12	2	8
	Latina (F Maneschi)	7	–	5	2	–	–
	Trento (E Arisi)	18	–	13	4	–	1
Netherlands	Amsterdam (MPM Burger)	250	–	151	53	35	11
Poland	Krakow (K Urbanski)	448	1	217	163	62	5
	Łódź (J Sobotkowski)	350	1	52	158	112	27
	Warsaw (M Bidzinski)	927	12	204	335	341	35

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Table 4, *continued*

		All	Not available	Stage I	Stage II	Stage III	Stage IV
Portugal	Coimbra (O Campos)	49	–	14	9	23	3
	Coimbra (C Freire de Oliveira)	62	–	12	18	25	7
	Coimbra (D Pereira da Silva)	98	–	71	12	15	–
	Lisboa (MA Roldão)	409	1	93	242	65	8
Slovakia	Bratislava (L Kállay)	229	3	157	43	22	4
Slovenia	Ljubljana (M Primic Zakelj)	345	–	170	64	94	17
	Maribor (I Takac)	78	–	37	20	16	5
Spain	Barcelona (S Dexeus)	23	–	16	7	–	–
	Barcelona (A Gil Moreno)	107	–	72	20	13	2
	Barcelona (J Pahisa Fabregas)	66	–	29	16	19	2
	Las Palmas de Gran Canaria (O Falcon-Vizcaino)	126	–	83	33	7	3
	Madrid (A de Armas Serra)	47	–	33	5	8	1
	Madrid (P de La Fuente)	44	–	31	7	3	3
Sweden	Gothenburg (G Horvath)	136	1	47	32	42	14
	Örebro (B Sorbe)	97	–	63	23	6	5
	Umeå (K Boman)	106	4	63	11	17	11
Switzerland	Basel (E Wight)	20	–	5	8	4	3
UK	Birmingham (KK Chan)	62	6	51	3	2	–
	Cambridge (LT Tan)	135	–	60	27	37	11
	Gateshead (T Lopes)	91	5	57	12	13	4
	Northwood (PJ Hoskin)	64	6	21	18	12	7
Yugoslavia	Nis (M Stanojevic)	189	–	78	64	41	6
Australia	Carlton (MA Quinn)	91	2	56	13	14	6

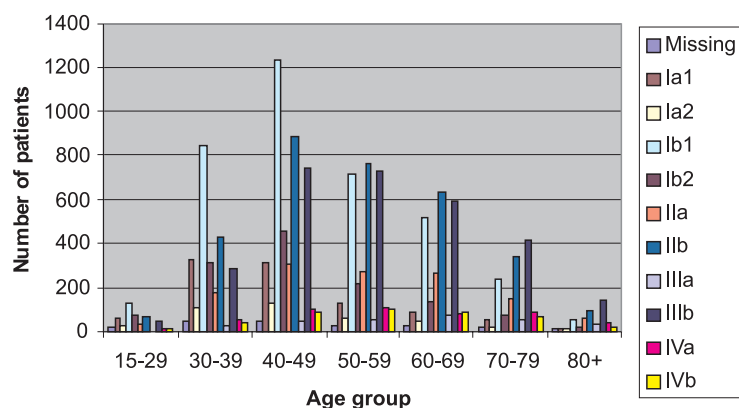
noted in this volume, with 14.2% of cases receiving the combination as opposed to only 4.5% recorded in the years 1996–1998. In Volume 26, the survival benefit from this treatment modality is becoming clear: the 5-year overall survival rate has moved from 49.1% to 59.3% (refer to Fig. 10 – Carcinoma of the Cervix Uteri, FIGO Annual Report, Vol. 25). This improvement observed in the combination treatment is, however, not apparent in the global analysis of overall survival. One out of five patients presented with Stage III disease, which disappointingly is a slightly lower figure to the last two reports and presumably reflects a lack of screening programs in many of the countries contributing to the Report.

Overall five-year survival by age group and stage is shown in Table 9. It is clear that the decision

Table 5

Carcinoma of the cervix uteri: Review of the 5-year survival rates reported in volumes 18–26

Vol.	Year	Patients	Survival (%)
18	1973–75	34178	55.7
19	1976–78	32428	55.0
20	1979–81	31543	53.5
21	1982–86	32052	59.8
22	1987–89	22428	65.0
23	1990–92	12153	65.4
24	1993–95	11709	72.2
25	1996–98	10525	69.9
26	1999–2001	15081	69.6
Total		202097	



Age group	Missing	Ia1	Ia2	Ib1	Ib2	IIa	IIb	IIIa	IIIb	IVa	IVb	Total
15-29	18	61	25	127	74	27	67	3	41	5	8	456
30-39	47	326	111	846	311	177	429	24	284	52	36	2643
40-49	46	310	126	1235	453	307	882	43	747	103	86	4338
50-59	25	126	58	717	218	267	763	50	729	112	101	3166
60-69	25	90	42	520	134	265	638	76	587	79	86	2542
70-79	14	51	18	230	72	149	334	51	417	85	64	1485
80+	5	4	4	51	13	57	96	27	141	36	17	451

Fig. 2. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Distribution of patients by stage and age groups.

to sub-divide Stage Ib into Ib1 and Ib2 according to the size of the tumor has been a good one, with a substantial difference in survival rates – for all age groups – according to this breakdown in categories. Women over 80 clearly have an inferior survival, but the better survival for women under the age of 50 which is seen in other malignancies of the female genital tract is not apparent in carcinoma of the cervix, reflecting the uniform biology of the disease (Figs. 6–9).

Figure 4 depicts the sites of relapse by stage with significant differences in the proportion of relapses by site between early and advanced stages, with a preponderance of local recurrence in early stages (3 out of 4) and a preponderance of distant (\pm local) recurrence in advanced stages (3 out of 4). The drop-off in complete response rates with advancing stage can be seen in Fig. 50, with 10 percent of patients with Stage III disease having tumor progression through treatment.

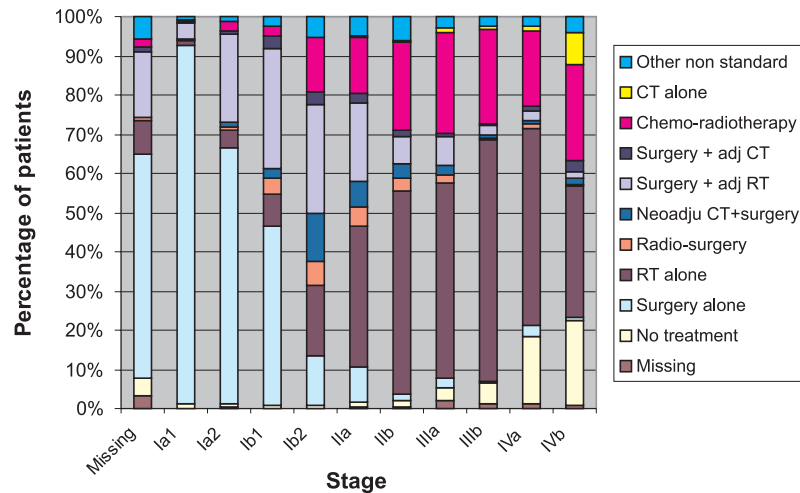
Tables 6 and 7 supply information about histological sub-types, with, as in the previous Report, 80% of patients having epidermoid tumors, 11% adenocarcinomas, and 6% adenosquamous carcinomas. The consistency of these histological patterns once again reflects almost certainly the lack of impact of screening in reducing squamous disease in countries where such facilities are not

available. There is an increase in age with stage across all histological types, reflecting the biology of the disease.

Table 8 compares FIGO stage which is clinically assessed and the TNM classification in patients treated with up-front surgery with or without adjuvant radiation and/or chemotherapy. As expected the correlation between the two systems is good ($r=0.76$) and highest in early-stage disease and then falls off, reflecting the difficulty in accurately assessing parametrial spread. The use of modern imaging may well improve this correlation and will be the subject of a future Annual Report analysis.

The overall survival in this cohort was almost 70% and remains unchanged compared with the overall survival rates in the last decade. Though, if we compare the AR survival rates collected in 1980s, there is an increase by approximately 10%. Because of the different methodology in collecting the data and in the number of contributing centers, it cannot be concluded that such an increase reflects a true improvement in the management of cervical cancer.

Cancer of the cervix uteri continues to be the only major gynecological malignancy that is not surgically staged. The FIGO Committee on Gynecologic Oncology constantly evaluates all current evidence-based medicine on staging of gynecological cancer. Up till now the



Treatment	Missing	Ia1	Ia2	Ib1	Ib2	IIa	IIb	IIIa	IIIb	IVa	IVb	Total
Missing	6	1	2	7	2	5	12	6	40	6	3	90
No treatment	8	9	3	23	7	14	49	8	150	81	87	439
Surgery alone	103	888	251	1702	164	111	52	7	9	14	2	3303
Radiotherapy alone	15	9	17	299	228	453	1665	137	1820	237	134	5014
Radio-surgery	2	4	3	165	79	57	103	5	18	4	1	441
Neoadjuvant CT + surgery	—	2	4	83	155	83	127	7	23	5	7	496
Surgery + adjuvant RT	30	39	86	1145	355	250	221	20	74	12	6	2238
Surgery + adjuvant CT	2	6	4	127	42	30	46	2	11	6	12	288
Chemo-radiotherapy	4	1	9	77	177	180	726	71	709	89	98	2141
Chemotherapy alone	—	1	—	—	—	6	14	3	22	7	31	84
Other non-standard treatment	10	8	5	98	66	60	194	8	70	11	17	547
Total	180	968	384	3726	1275	1249	3209	274	2946	472	398	15081

Fig. 3. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Distribution of patients by stage and mode of treatment.

Committee has decided not to modify the present clinical staging which is employed on a world-wide basis and, in particular, in countries with limited resources where cervical cancer is the major neoplasm affecting women.

Stage is the most important predictor of survival, reflecting the extent and aggressiveness of the disease with the risk of death being almost three times more likely in Stage IIb compared to Ib disease, five times more likely for Stage III disease and ten to twenty times more likely for Stage IV (Fig. 11).

Figure 12 depicts survival by treatment mode, and of interest is the lower hazards ratio (surgery alone as a reference) observed in women treated with chemo-radiation compared with those treated with radiation alone, even when adjusted for age, stage and country of origin. A further detailed analysis in survival according to these modalities of treatment by FIGO stage is provided in

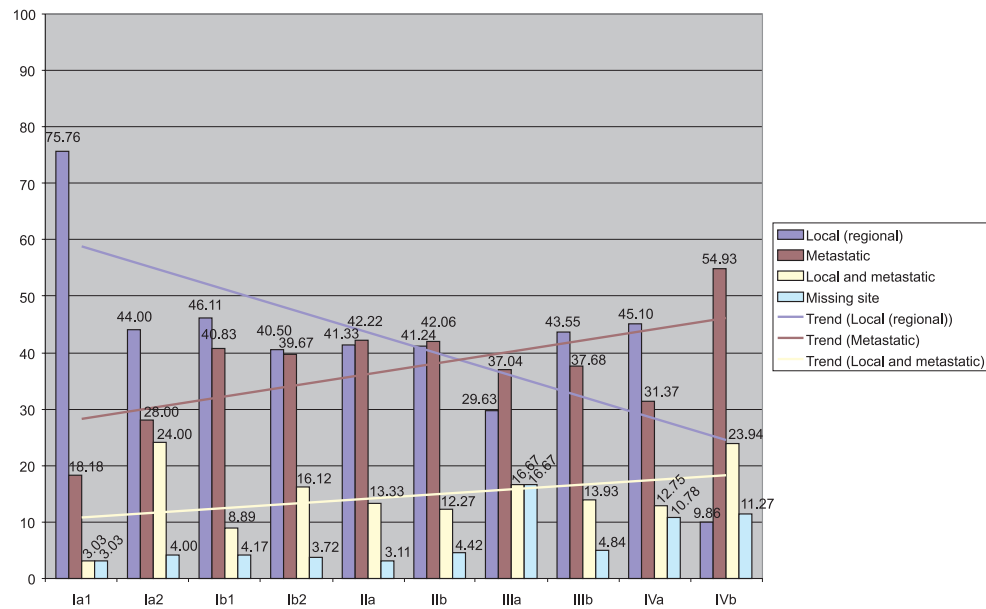
Figs. 13–18. Figure 19 once again stresses the accuracy of the FIGO staging, showing survival curves by pTNM (UICC Classification) which are superimposable on those drawn in Fig. 11 (FIGO classification).

Figures 20 and 21 depict survival stage for stage across histological sub-types. Stage by stage, there are no major differences between the two major histological sub-types (epidermoid vs. adenocarcinoma) in univariate analysis, while in the multivariate analysis adenocarcinoma shows a worse prognosis in all stages (Table 12).

Lymph node spread has always been noted to be a poor prognostic factor in cancer of the cervix. Figure 22 shows the survival of the 4317 patients in whom node status was available, with node-positive tumors being associated with a slightly younger age, and the presence of positive nodes increasing the risk of dying by more than three overall and four in all Stage Ib1 disease (Fig. 23). The

Table 6
Carcinoma of the cervix uteri: patients treated in 1999–2001. Mean age by stage and histologic type

Histotype	Missing	Ia1	Ia2	Ib1	Ib2	IIa	IIb	IIa	IIIb	IVa	IVb
Missing	52.8	37.0	44.0	54.2	—	43.0	64.3	57.3	54.3	69.7	—
No biopsy	67.0	46.4	53.1	49.1	48.7	57.5	50.6	57.0	58.7	67.8	56.0
Epidermoid	53.1	44.7	46.5	49.3	46.8	55.2	53.7	60.7	55.5	56.8	55.8
Adenocarcinoma	46.1	43.9	42.2	47.2	47.2	51.4	51.9	60.6	59.0	58.5	60.6
Adenosquamous	50.3	45.3	39.4	46.2	46.5	50.0	52.4	58.6	55.6	57.3	56.3
Clear cell	79.0	31.0	58.0	45.9	47.8	58.2	55.7	61.5	64.7	51.3	57.0
Other	41.6	47.2	37.5	48.4	46.0	50.0	56.4	61.8	58.1	62.9	59.1



Site of relapse	Ia1	Ia2	Ib1	Ib2	IIa	IIb	IIIa	IIIb	IVa	IVb
Local (regional)	25	11	166	98	93	252	16	297	46	7
Metastatic	6	7	147	96	95	257	20	257	32	39
Local and metastatic	1	6	32	39	30	75	9	95	13	17
Missing site	1	1	15	9	7	27	9	33	11	8
Total	33	25	360	242	225	611	54	682	102	71

Fig. 4. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Site of relapse by stage.

outcome by FIGO stage in the 2792 patients who had negative nodes at the time of surgery is depicted in Fig. 24, and the survival (by FIGO stage) of those (608) with positive nodes in Fig. 25. Lymph node positivity was associated with an inferior outcome across all stages. The incidence of lymph node positivity in micro-invasive disease (3.9% in Ia1 disease and 9.7% in Ia2 disease)

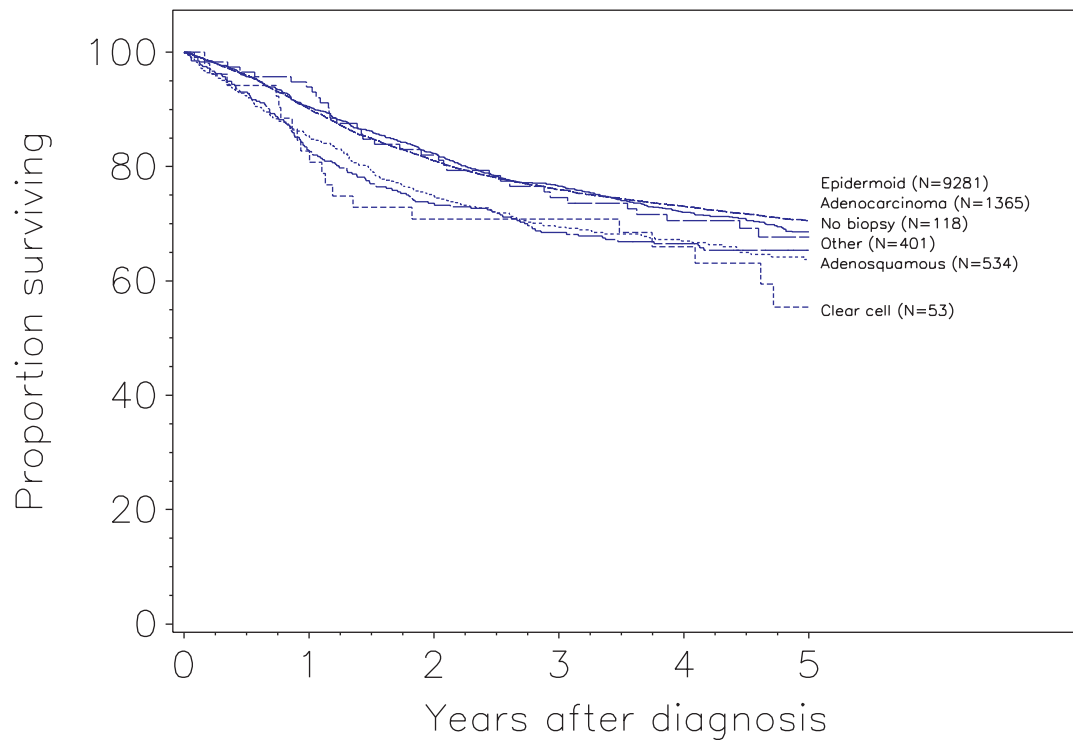
reflects current literature (Table 11). Lymphadenectomy was performed in 2057 patients with surgical Stage Ib1 disease. Of these, 296 (14%) were lymph node positive and their overall survival was only 78% in comparison to 95% when the nodes were negative (Figs. 24, 25).

The presence of lymphovascular space involvement (LVI) is a poor prognostic variable. Figure 26 depicts the

Table 7

Carcinoma of the cervix uteri: patients treated in 1999–2001. Number of patients by stage and histologic type

Histotype	Missing	Ia1	Ia2	Ib1	Ib2	IIa	IIb	IIa	IIIb	IVa	IVb	Total	%
Missing/not stated	6	24	11	36	18	14	36	6	40	8	9	208	1.4
Epidermoid	69	820	307	2675	934	1021	2671	209	2531	389	281	11907	79.0
Adenocarcinoma	21	57	37	681	168	110	267	17	175	30	50	1613	10.7
Adenosquamous	6	35	16	231	98	69	148	24	136	29	30	822	5.5
Clear cell	1	1	2	20	13	6	9	2	7	3	1	65	0.4
Other	77	31	11	83	44	29	78	16	57	13	27	466	3.1
Total	180	968	384	3726	1275	1249	3209	274	2946	472	398	15081	100.0



Histotype	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
No biopsy	118	52.1	93.9	82.1	74.6	70.5	67.6	1.3 (0.9–1.8)
Epidermoid	9281	52.1	90.2	81.1	76.0	73.0	70.5	Reference
Adenocarcinoma	1365	49.7	90.6	82.3	76.6	71.9	68.7	1.1 (1.0–1.2)
Adenosquamous	534	49.6	85.5	74.9	69.4	66.9	63.8	1.4 (1.2–1.6)
Clear cell	53	53.9	82.9	70.9	70.9	66.0	56.3	1.2 (0.8–1.8)
Other	401	50.6	83.2	73.8	68.7	66.7	65.2	1.5 (1.2–1.8)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for countryFig. 5. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Survival by histologic type, $n = 11752$.

Table 8

Carcinoma of the cervix uteri: patients treated in 1999–2001. Correlation % (number of patients) between FIGO stage (clinically assessed) and pT (TNM) in patients treated with upfront surgery (surgery alone \pm adj RT/CT)

pT (TNM)	FIGO									
	Ia1	Ia2	Ib1	Ib2	IIa	IIb	IIIa	IIIb	IVa	IVb
Ia1	95% (608)	10% (24)	3% (69)	3% (16)	3% (13)	4% (19)	8% (3)	7% (10)	6% (3)	7% (2)
Ia2	1% (8)	82% (192)	1% (29)	1% (7)	0% (2)	1% (5)	0% (0)	0% (0)	0% (0)	0% (0)
Ib1	2% (16)	5% (12)	82% (1947)	15% (92)	11% (45)	14% (61)	3% (1)	6% (9)	2% (1)	3% (1)
Ib2	0% (1)	1% (2)	3% (73)	61% (380)	7% (30)	6% (25)	8% (3)	6% (8)	0% (0)	0% (0)
IIa	0% (3)	0% (0)	1% (31)	5% (30)	60% (252)	6% (25)	14% (5)	1% (2)	0% (0)	0% (0)
IIb	0% (1)	1% (2)	3% (73)	6% (38)	7% (30)	59% (258)	5% (2)	6% (8)	4% (2)	0% (0)
IIIa	0% (0)	0% (0)	0% (2)	0% (1)	0% (2)	0% (2)	54% (20)	1% (2)	0% (0)	0% (0)
IIIb	1% (4)	1% (2)	6% (141)	9% (56)	8% (35)	7% (31)	5% (2)	70% (100)	0% (0)	7% (2)
IVa	0% (0)	0% (0)	0% (2)	0% (1)	1% (5)	1% (5)	3% (1)	0% (0)	84% (43)	7% (2)
IVb	0% (0)	0% (0)	0% (6)	0% (2)	1% (6)	2% (7)	0% (0)	2% (3)	4% (2)	77% (23)

$r = 0.76$ (Spearman).

poorer outcome in Stage Ia2 disease of the 14 patients with LVI-positive tumors and negative nodes compared with the 41 patients with LVI-negative tumors and negative nodes. This can also be observed in the analysis of more advanced disease (Figs. 27–30).

The importance of LVI is further depicted in Figs. 31 through 34. Lymphovascular space involvement is consistently associated with worse outcome when comparing early vs. advanced stages both clinically and surgically staged.

Table 10 depicts the types of surgery undertaken in patients with micro-invasive disease, ranging from conization through to simple hysterectomy to radical hysterectomy and lymphadenectomy. Much of this (one out of three) seems to be over-treatment.

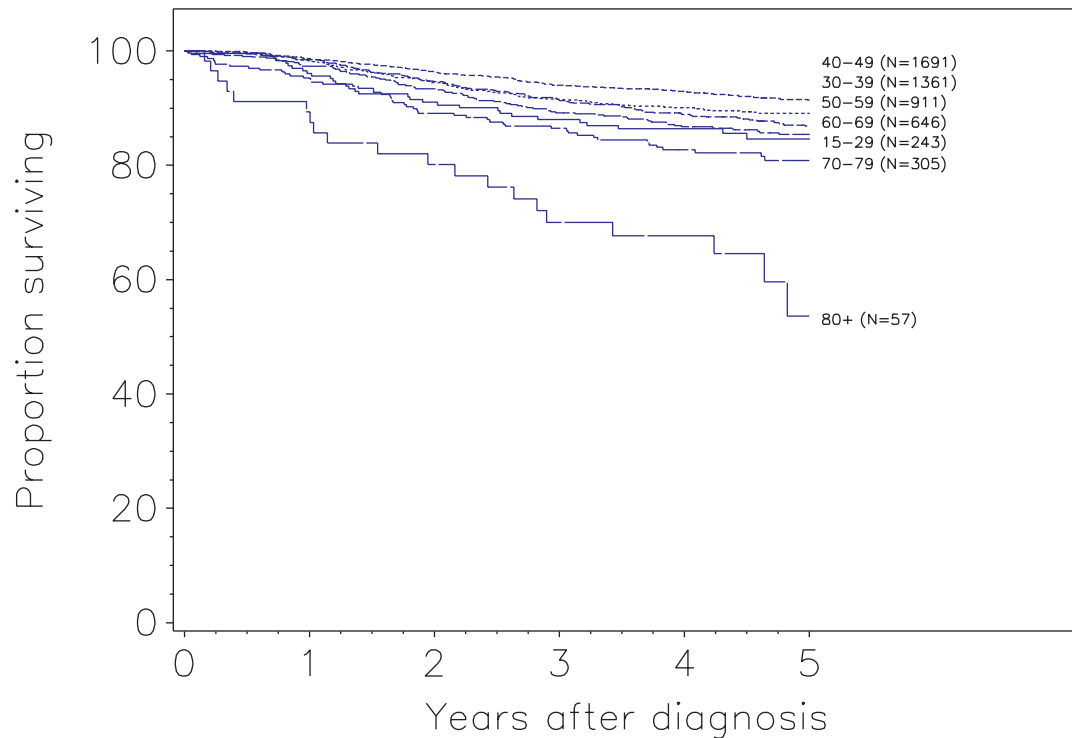
The survival of patients treated with either neoadjuvant or adjuvant chemotherapy followed by surgery, or by chemo-radiation is depicted in Figs. 35 and 36, showing no obvious benefit for multiple drug administration over single drug administration, although this observation for platinum versus non-platinum treatments is not quite so clear (Fig. 37). The importance of number of lymph nodes involved is depicted in Figs. 38–45, and that of site of spread in Figs. 46–48, with local spread alone carrying

a better prognosis. These data hold true in surgically staged disease.

Figure 49 shows the survival from the time of recurrence according to mode of primary treatment. Patients treated with surgery alone under these circumstances fared better presumably due to more localized disease. Those treated with radiation alone had a median survival of just less than a year.

Table 12 depicts a multivariate analysis by FIGO stage of all patients treated in 1999–2001, stratified by age, histological type, grade, tumor size, lymphovascular space involvement, and lymph node status. Age had a negative impact only in Stage I disease. Non-epidermoid tumors carried a significantly worse prognosis stage for stage, but tumor de-differentiation only seemed important in Stage I disease, whilst tumor size and lymph node status were predictors of poor outcome with increasing stage as expected, except for stage IV where the size of the primary tumor impacts on prognosis to a lower extent compared to the presence of metastases.

Carcinoma of the cervix remains the second most common cancer affecting women world-wide. More than 99% of cases are associated with HPV infection (with only clear cell and serous papillary tumors and



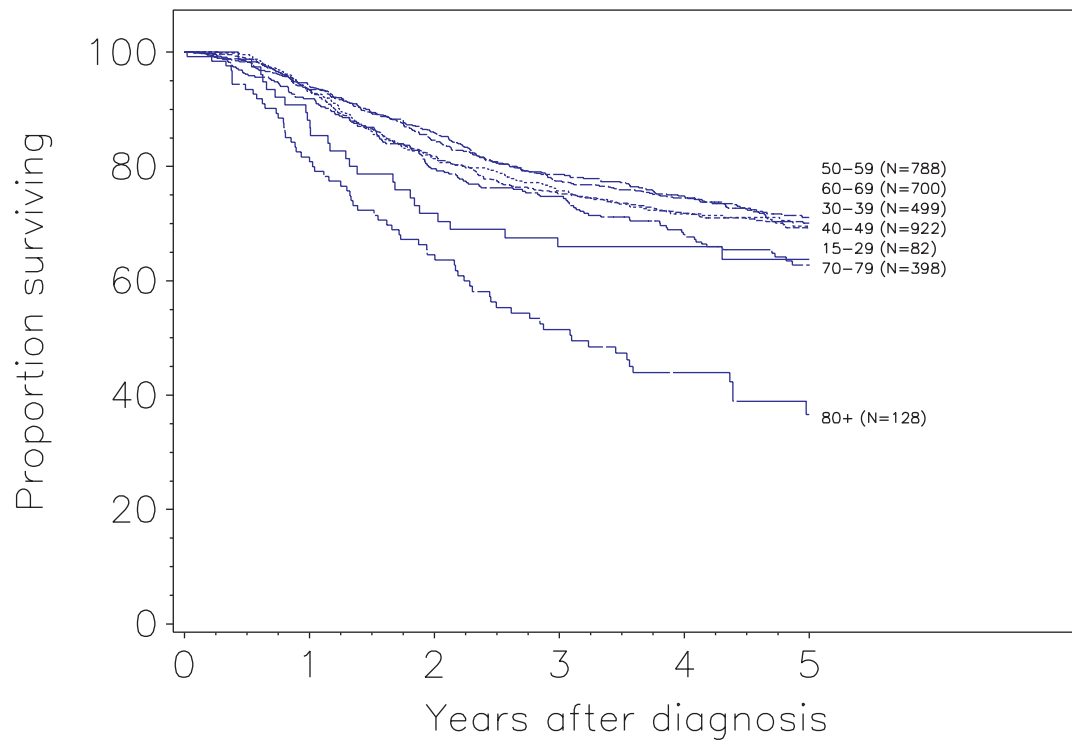
Age group	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
15-29	243	26.6	96.2	91.1	88.1	86.3	84.6	1.2 (0.8-1.8)
30-39	1361	35.2	98.3	94.5	91.5	90.0	89.0	0.8 (0.6-1.1)
40-49	1691	44.3	98.7	96.3	94.0	93.0	91.3	0.6 (0.5-0.8)
50-59	911	54.0	98.5	94.7	91.5	88.9	86.9	Reference
60-69	646	64.1	97.3	93.5	89.2	86.7	85.5	1.2 (0.9-1.6)
70-79	305	73.6	95.3	89.1	86.4	82.6	80.7	1.6 (1.2-2.2)
80+	57	83.7	89.3	80.0	70.0	67.6	56.7	3.2 (2.0-5.2)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for country

Fig. 6. Carcinoma of the cervix uteri: Patients treated in 1999-2001. Survival by age (Stage I), $n = 5214$.

minimal deviation cancers being HPV negative); the introduction of HPV vaccination against HPV 16 and 18 has the potential to reduce the burden by 70%. This is especially important in poorly resourced countries where more than 80% of new cases of cervix cancer occur. There are, however, still huge logistical problems to be

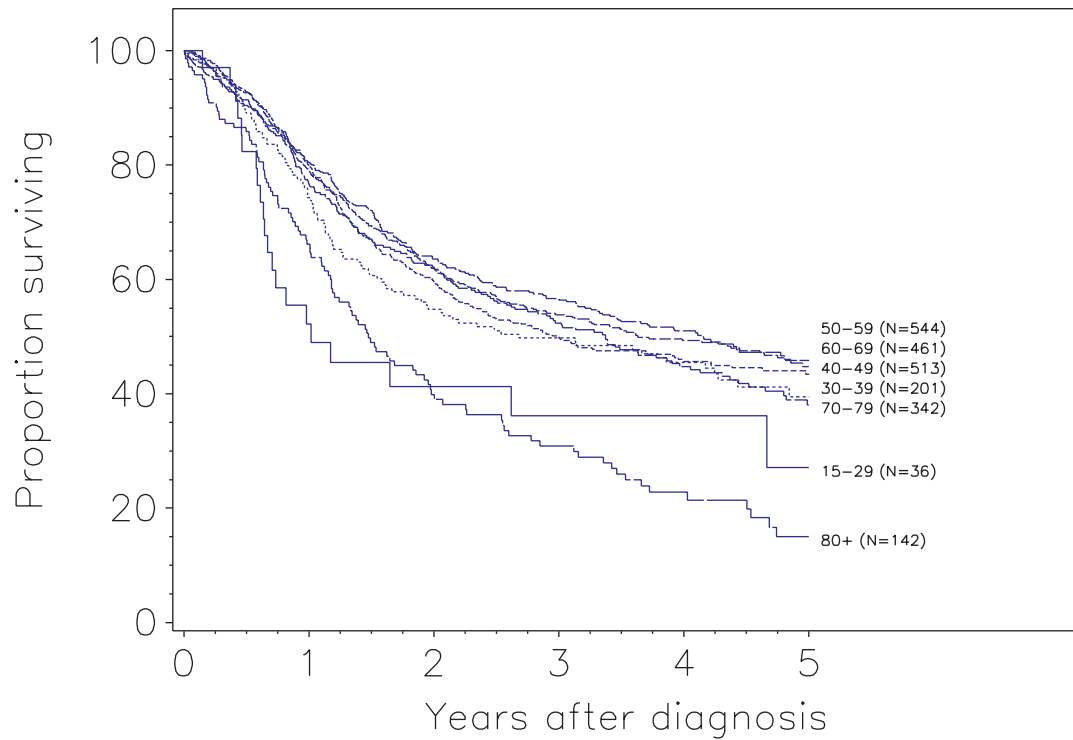
solved before the vaccines reach the communities most at need. Until then, innovative screening strategies are still needed. Treatment of established malignancy needs to involve a multi-disciplinary team and attention to the enormous psychosocial impact on women and their families should be prioritized.



Age group	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
15-29	82	26.9	88.5	72.2	66.4	66.4	63.8	1.4 (0.9-2.1)
30-39	499	35.6	93.2	81.5	75.9	71.7	69.8	1.1 (0.8-1.3)
40-49	922	44.7	93.6	81.8	75.2	71.8	69.3	1.1 (0.9-1.3)
50-59	788	54.3	93.5	84.7	77.6	74.5	71.2	Reference
60-69	700	64.2	94.2	86.0	78.6	74.8	70.1	1.0 (0.8-1.2)
70-79	398	74.1	91.9	79.7	74.8	68.0	62.8	1.2 (1.0-1.5)
80+	128	83.9	82.1	64.6	51.5	43.7	37.1	2.5 (1.8-3.3)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for country

Fig. 7. Carcinoma of the cervix uteri: Patients treated in 1999-2001. Survival by age (Stage II), $n=3517$.



Age group	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
15-29	36	26.6	52.9	41.2	36.0	36.0	28.0	1.8 (1.1-2.8)
30-39	201	35.4	74.9	55.1	50.0	45.5	39.8	1.2 (0.9-1.5)
40-49	513	44.8	80.3	59.9	50.0	45.8	43.7	1.0 (0.9-1.2)
50-59	544	54.1	79.4	62.1	53.9	49.3	45.9	Reference
60-69	461	64.4	80.6	63.6	56.7	50.8	44.9	0.9 (0.8-1.1)
70-79	342	73.9	77.0	62.4	52.5	44.9	38.6	1.1 (0.9-1.3)
80+	142	84.4	66.3	39.6	30.7	22.1	14.5	1.6 (1.3-2.1)

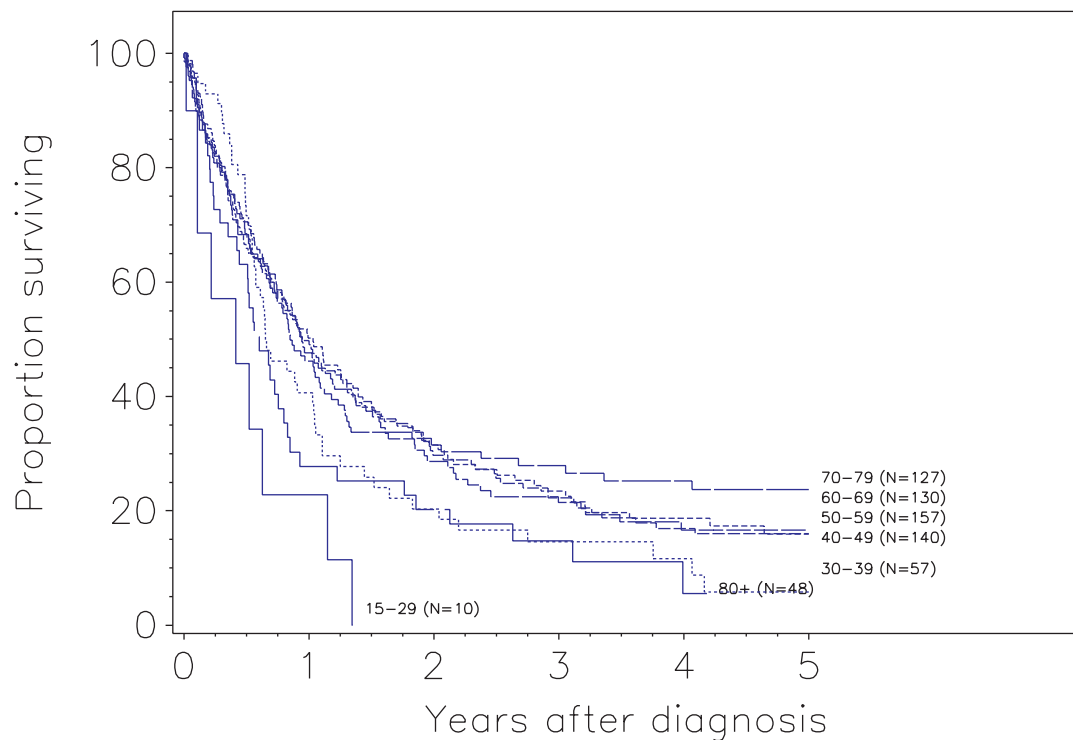
^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for country

Fig. 8. Carcinoma of the cervix uteri: Patients treated in 1999-2001. Survival by age (Stage III), $n = 2239$.

Table 9

Carcinoma of the cervix uteri: patients treated in 1999–2001. Overall survival (%) after 5 years by age group and FIGO stage

Age at diagnosis	Overall 5-year survival (%)									
	Ia1	Ia2	Ib1	Ib2	IIa	IIb	IIIa	IIIb	IVa	IVb
15–29	100.0	91.7	88.5	62.8	80.1	57.5	–	27.9	–	–
30–39	98.4	95.1	89.9	74.5	72.6	68.7	39.8	40.3	13.8	–
40–49	99.5	96.4	93.4	79.3	74.5	67.4	40.4	43.9	23.5	10.0
50–59	96.7	100.0	87.1	78.0	79.8	68.1	56.0	45.3	22.4	10.8
60–69	92.7	84.5	86.5	75.9	73.3	68.7	38.1	46.0	19.5	15.0
70–79	90.7	100.0	81.5	67.9	69.0	60.0	38.0	38.7	35.1	9.2
80+	–	66.7	58.1	53.3	46.2	31.4	25.4	12.2	–	–
All age groups	97.5	94.8	89.1	75.7	73.4	65.8	39.7	41.5	22.0	9.3



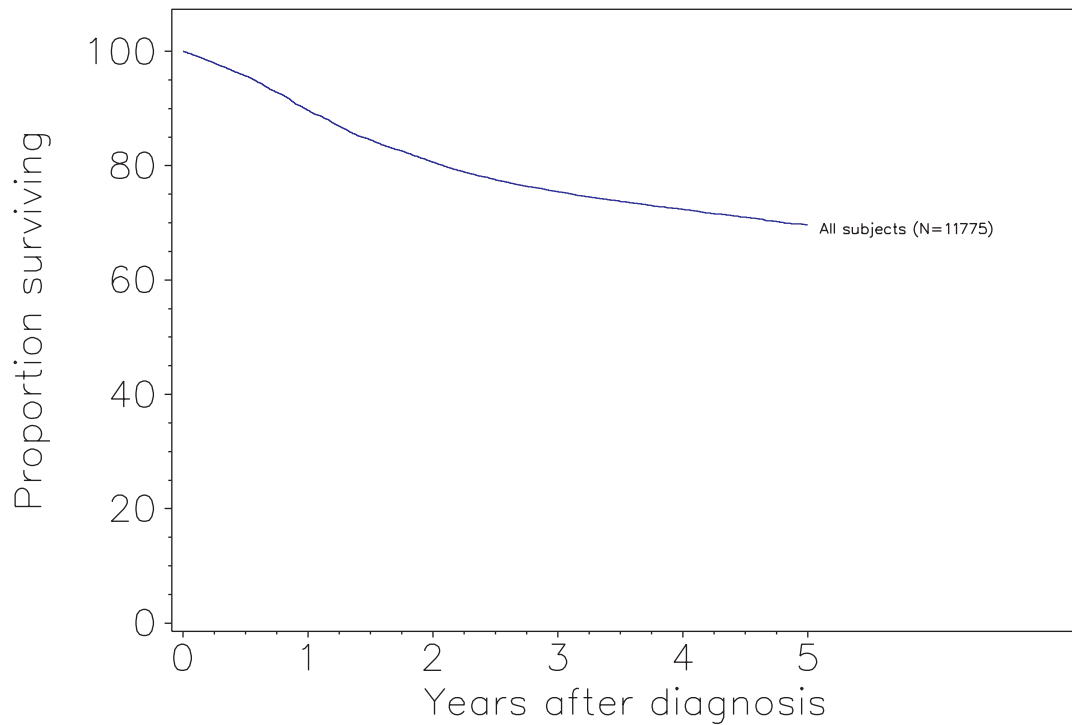
Age group	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
15–29	10	27.0	26.3	–	–	–	–	4.0 (2.0–8.0)
30–39	57	36.0	41.1	20.5	14.7	12.2	5.2	1.1 (0.8–1.6)
40–49	140	44.8	50.9	31.9	23.8	18.6	16.0	0.9 (0.7–1.2)
50–59	157	54.1	49.5	30.0	22.5	17.1	16.0	Reference
60–69	130	64.4	49.2	29.7	22.4	17.4	17.4	1.0 (0.8–1.3)
70–79	127	74.0	46.7	31.4	27.9	25.1	22.9	1.1 (0.8–1.4)
80+	48	84.4	32.6	23.7	16.9	7.3	–	1.6 (1.1–2.4)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for countryFig. 9. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Survival by age (Stage IV), *n* = 669.

Table 10

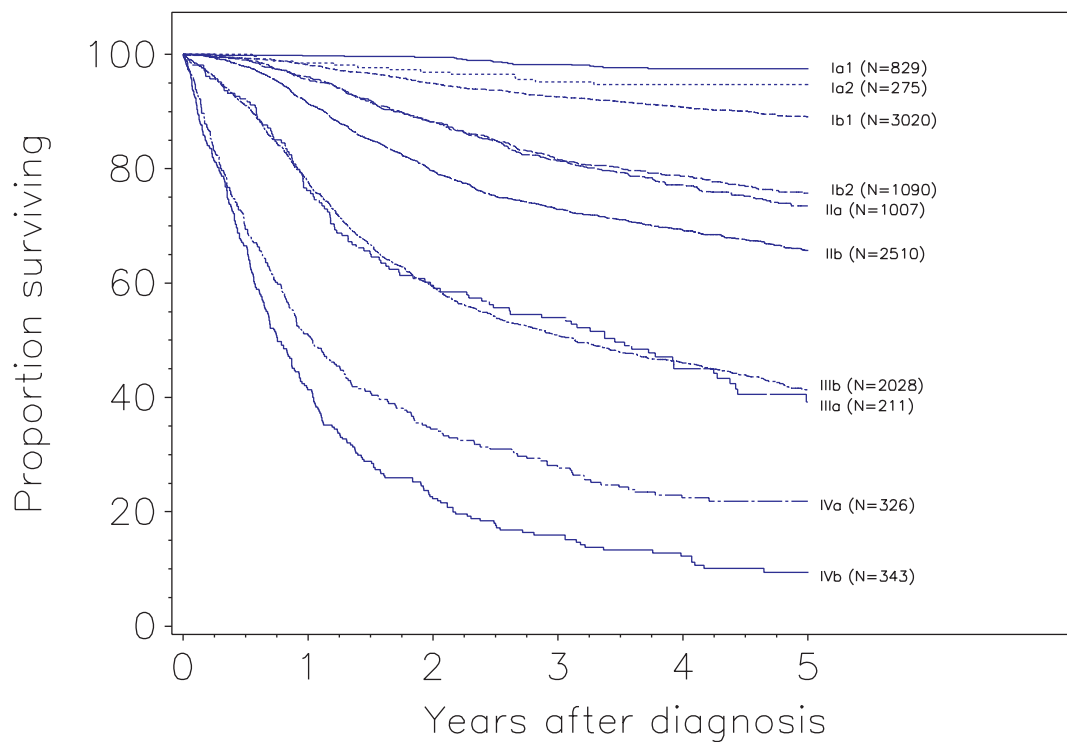
Carcinoma of the cervix uteri: Patients treated in 1999–2001. Distribution of Stage Ia1 and Ia2 patients submitted to up-front surgery (surgery or surgery + adj RT or surgery + adj CT) by type of surgery

Type of treatment	All patients	Missing	No treatment	Surgery alone	RT alone	Radio-surgery	Neoadj CT + surg	Surg + adj RT	Surg + adj CT	CT-RT	CT alone	Other non-standard
All	1352	3	12	1139	26	7	6	125	10	10	1	13
Missing	86	2	12	28	26	2	–	3	1	10	1	1
Conization and other types of trachelectomy	214	1	–	209	–	–	–	2	–	–	–	2
Simple abdominal hysterectomy without lymphadenectomy	359	–	–	314	–	1	–	41	1	–	–	2
Simple abdominal hysterectomy with lymphadenectomy	114	–	–	106	–	1	–	5	–	–	–	2
Simple vaginal hysterectomy without lymphadenectomy	75	–	–	68	–	–	–	7	–	–	–	–
Simple vaginal hysterectomy with lymphadenectomy	41	–	–	9	–	–	–	32	–	–	–	–
Radical abdominal hysterectomy without lymphadenectomy	57	–	–	46	–	–	–	5	1	–	–	5
Radical abdominal hysterectomy with lymphadenectomy	353	–	–	308	–	3	6	28	7	–	–	1
Radical vaginal hysterectomy without lymphadenectomy	7	–	–	7	–	–	–	–	–	–	–	–
Radical vaginal hysterectomy with lymphadenectomy	20	–	–	19	–	–	–	1	–	–	–	–
Other type of surgery	26	–	–	25	–	–	–	1	–	–	–	–



	Patients (n)	Mean age (yrs)	Overall survival (%) at				
			1 year	2 years	3 years	4 years	5 years
All subjects	11775	51.7	89.8	80.7	75.5	72.3	69.6

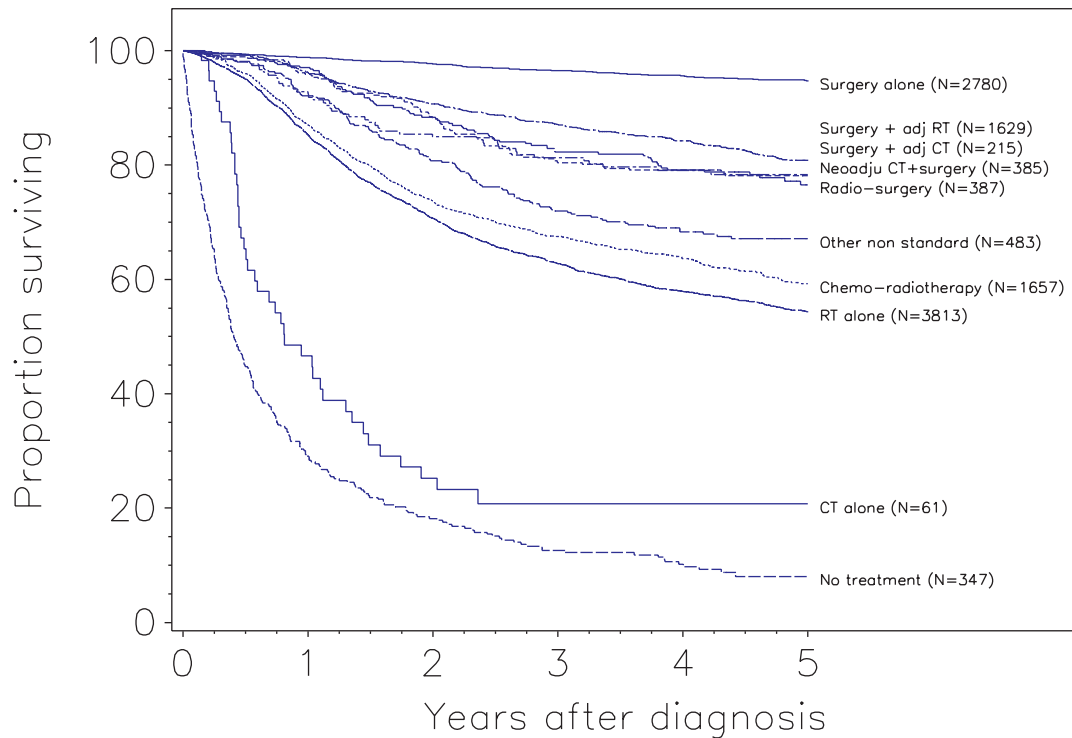
Fig. 10. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Overall survival, $n = 11775$.



Stage	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Ia1	829	44.5	99.8	99.5	98.3	97.5	97.5	} Reference
Ia2	275	45.4	98.5	96.9	95.2	94.8	94.8	
Ib1	3020	48.6	98.2	95.0	92.6	90.7	89.1	
Ib2	1090	46.8	95.8	88.3	81.7	78.8	75.7	
IIa	1007	54.4	96.1	88.3	81.5	77.0	73.4	
IIb	2510	53.5	91.7	79.8	73.0	69.3	65.8	2.7 (2.4–3.0)
IIIa	211	60.3	76.7	59.8	54.0	45.1	39.7	5.3 (4.3–6.5)
IIIb	2028	56.6	77.9	59.5	51.0	46.0	41.5	5.3 (4.7–5.9)
IVa	326	59.5	51.9	35.1	28.3	22.7	22.0	11.7 (9.9–13.8)
IVb	343	56.8	42.2	22.7	16.4	12.6	9.3	20.3 (17.4–23.7)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

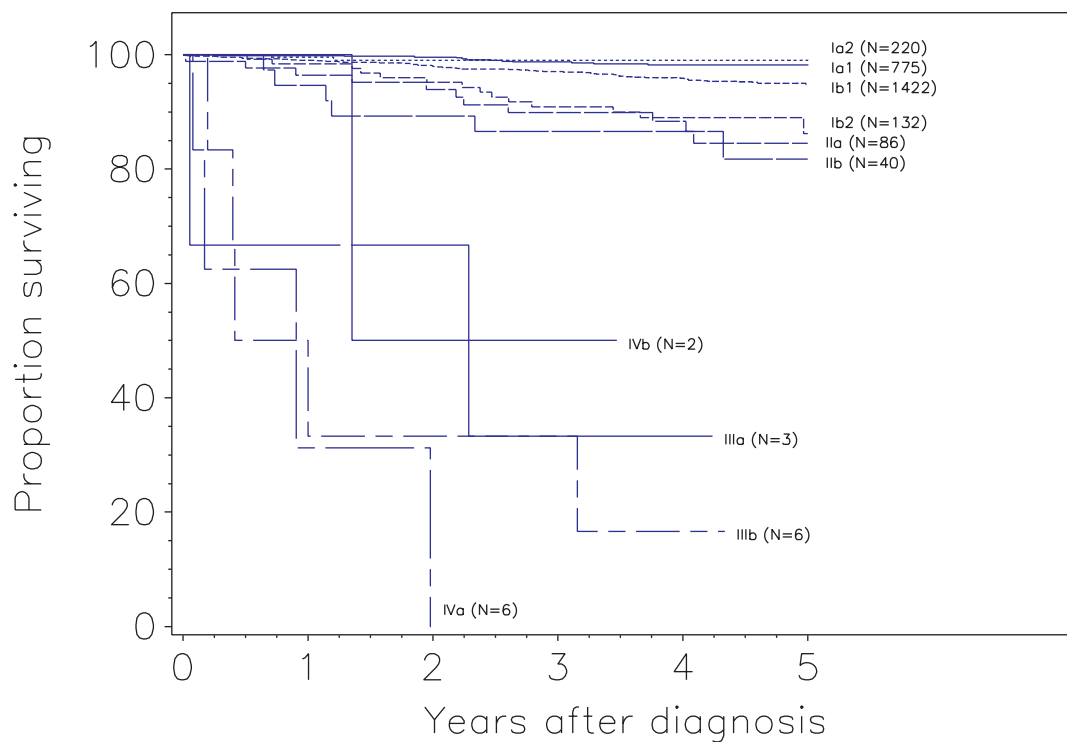
Fig. 11. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Survival by FIGO stage, $n = 11639$.



Treatment	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
No treatment	347	58.8	31.5	19.7	13.6	11.1	8.7	19.5 (15.2–25.1)
Surgery	2780	45.3	98.9	97.7	96.5	95.6	94.7	Reference
Radiotherapy	3813	58.0	85.5	70.9	62.9	57.9	54.4	4.7 (3.8–5.9)
Radio-surgery	387	48.0	97.1	88.4	82.3	79.3	76.8	3.1 (2.3–4.2)
Neoadjuvant CT + surgery	385	46.5	96.0	88.2	80.5	79.1	78.1	3.4 (2.5–4.7)
Surgery + adj RT	1629	49.7	96.2	90.8	87.1	84.2	80.7	2.8 (2.3–3.5)
Surgery + adj CT	215	47.4	92.9	84.9	81.3	79.0	78.1	3.2 (2.3–4.6)
Chemo-radiotherapy	1657	52.3	87.1	73.8	67.6	63.6	59.3	3.5 (2.8–4.4)
Chemotherapy alone	61	57.5	49.1	26.6	21.5	21.5	21.5	9.4 (6.4–13.7)
Other non-standard treatment	483	46.8	92.3	80.9	72.1	68.3	66.9	3.2 (2.5–4.2)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age, FIGO stage and country

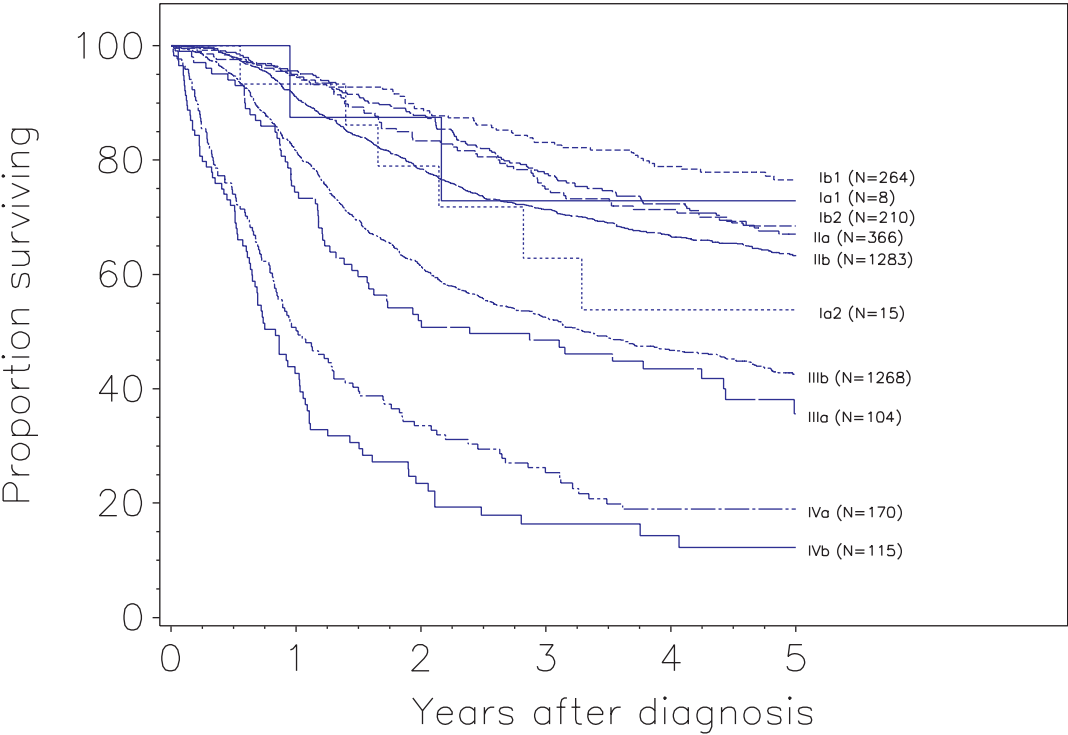
Fig. 12. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Survival by mode of treatment, $n=11757$.



Stage	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Ia1	775	43.8	99.9	99.6	98.7	98.2	98.2	0.4 (0.2–0.7)
Ia2	220	44.7	99.5	99.0	99.0	99.0	99.0	0.3 (0.1–0.8)
Ib1	1422	45.9	99.1	98.0	97.0	95.8	94.8	} Reference
Ib2	132	45.3	98.4	95.2	90.9	89.0	87.4	
IIa	86	49.8	96.4	93.9	89.9	88.3	83.8	2.6 (1.4–5.1)
IIb	40	47.7	94.8	89.4	86.6	86.6	82.1	2.6 (1.0–6.8)
IIIa	3	46.3	66.7	66.7	33.3	33.3	–	28.6 (6.2–132.0)
IIIb	6	73.0	50.0	33.3	33.3	16.7	–	10.1 (3.3–30.6)
IVa	6	61.8	40.0	–	–	–	–	40.3 (9.9–164.0)
IVb	2	51.0	100.0	50.0	50.0	–	–	13.8 (1.6–119.8)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

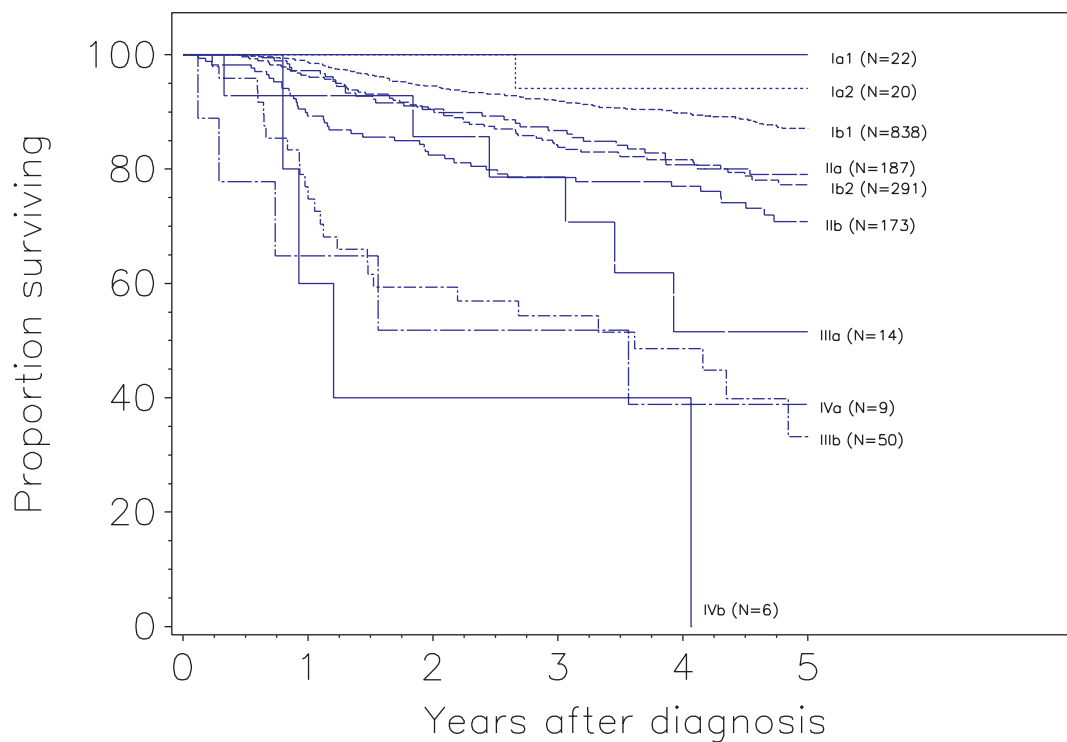
Fig. 13. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Survival by FIGO stage (surgery alone), $n=2692$.



Stage	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Ia1	8	69.0	87.5	87.5	72.9	72.9	72.9	} Reference
Ia2	15	58.4	93.3	79.5	63.6	53.8	53.8	
Ib1	264	63.5	94.9	89.1	83.1	78.9	76.5	
Ib2	210	52.1	95.1	83.4	75.0	71.4	68.3	} Reference
IIa	366	59.7	95.8	88.0	77.6	72.2	66.9	
IIb	1283	56.1	91.3	78.5	71.4	66.7	63.4	1.6 (1.3–2.0)
IIIa	104	63.3	75.0	52.2	48.7	43.5	36.3	3.3 (2.3–4.5)
IIIb	1268	58.0	81.9	61.8	52.8	46.9	42.8	3.0 (2.4–3.6)
IVa	170	62.9	51.4	34.3	25.8	19.2	19.2	7.3 (5.6–9.5)
IVb	115	57.7	44.6	24.1	17.0	15.2	12.5	12.5 (9.4–16.8)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

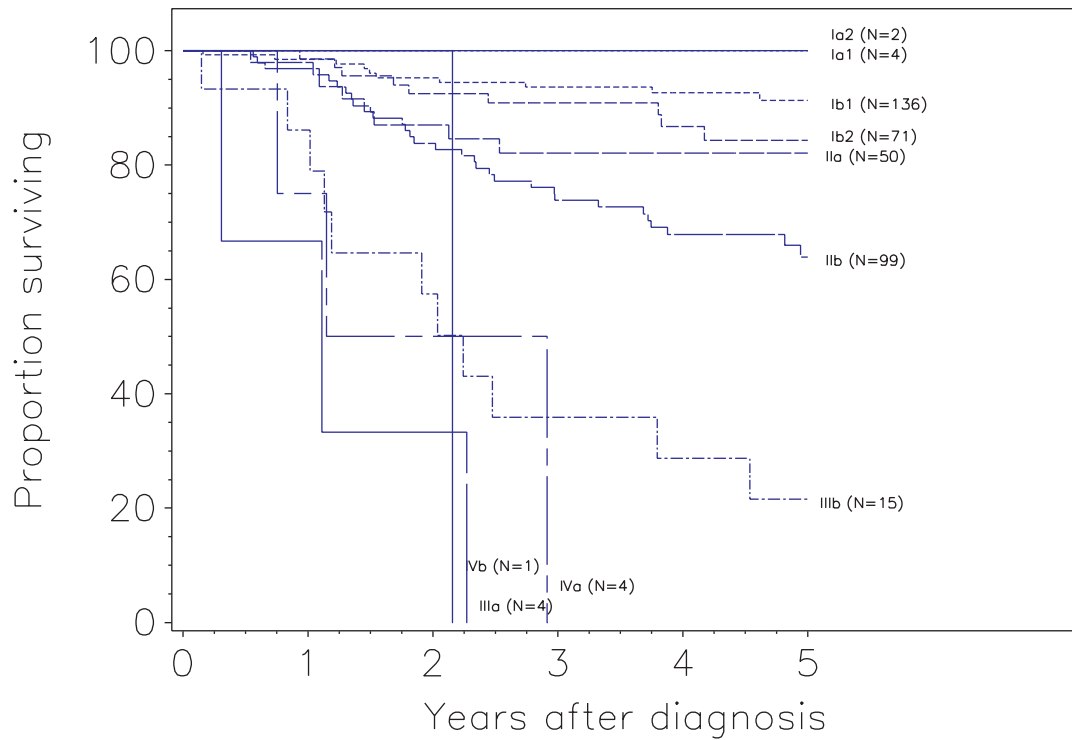
Fig. 14. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Survival by FIGO stage (radiotherapy), n = 3803.



Stage	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Ia1	22	53.5	100.0	100.0	100.0	100.0	100.0	—
Ia2	20	47.8	100.0	100.0	94.3	94.3	94.3	0.4 (0.1–3.2)
Ib1	838	49.4	98.7	94.5	91.9	89.7	87.0	} Reference
Ib2	291	47.5	96.5	90.6	84.3	81.7	77.2	
IIa	187	52.1	97.3	90.4	86.7	80.6	78.8	1.4 (0.9–2.0)
IIb	173	49.3	89.4	82.5	78.6	77.1	70.8	2.8 (2.0–4.0)
IIIa	14	60.5	92.9	85.7	78.3	52.2	52.2	6.9 (3.1–15.5)
IIIb	50	52.5	77.3	59.4	54.3	48.3	34.5	5.2 (3.2–8.4)
IVa	9	61.2	64.7	51.8	51.8	37.0	37.0	10.7 (4.1–28.2)
IVb	6	59.7	63.6	42.4	42.4	42.4	—	10.5 (3.6–30.6)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

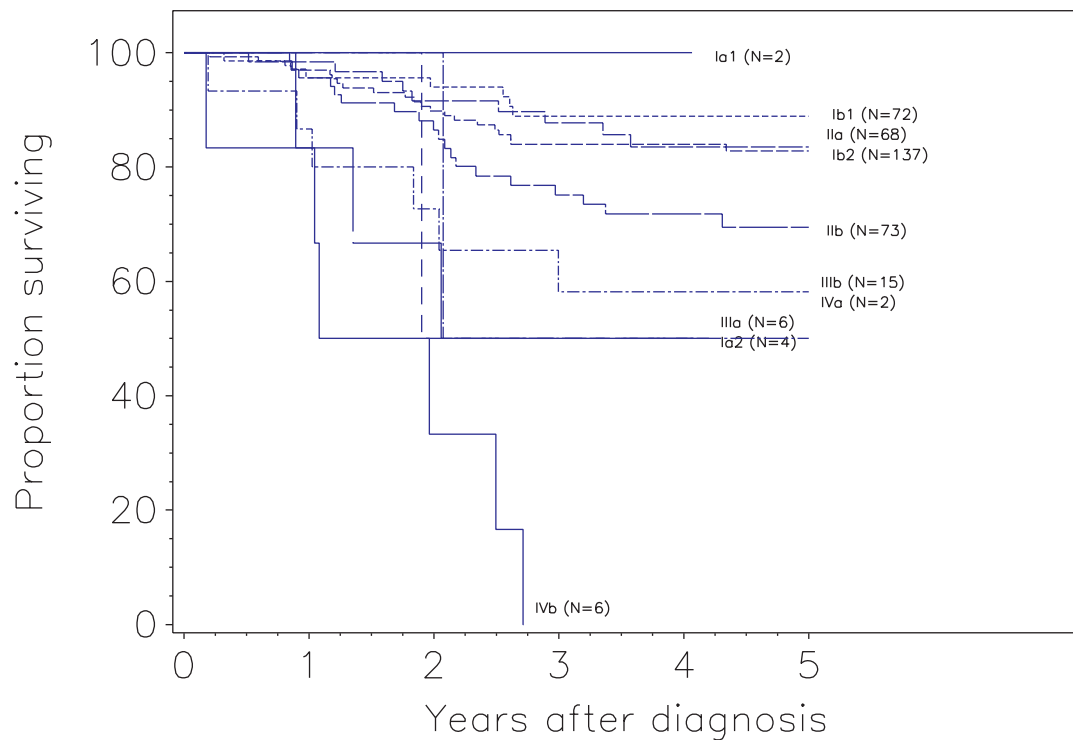
Fig. 15. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Survival by FIGO stage (surgery + adjuvant radiotherapy), $n=1610$.



Stage	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Ia1	4	53.5	100.0	100.0	100.0	100.0	100.0	—
Ia2	2	54.5	100.0	100.0	100.0	100.0	100.0	—
Ib1	136	47.4	98.5	95.3	93.6	92.7	91.3	} Reference
Ib2	71	44.4	98.6	92.6	90.9	87.0	84.3	
IIa	50	50.7	97.9	86.7	81.7	81.7	81.7	2.6 (1.1–6.3)
IIb	99	48.4	96.9	84.1	74.0	67.9	64.6	3.0 (1.5–5.8)
IIIa	4	56.5	71.4	35.7	—	—	—	56.2 (13.6–232.8)
IIIb	15	52.5	86.2	57.5	35.9	28.7	19.2	9.2 (3.7–22.6)
IVa	4	53.5	75.0	50.0	—	—	—	19.9 (4.9–81.3)
IVb	1	42.0	100.0	100.0	—	—	—	14.0 (1.7–116.7)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

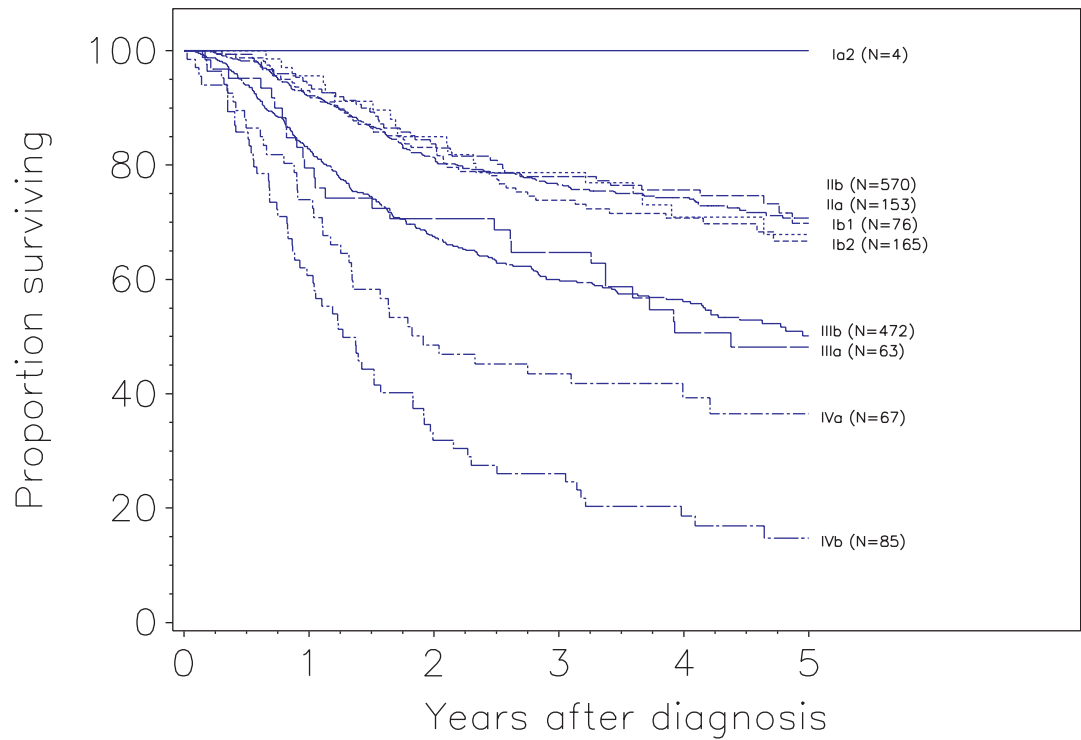
Fig. 16. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Survival by FIGO stage (radio-surgery), $n = 386$.



Stage	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Ia1	2	67.0	100.0	100.0	100.0	100.0	—	—
Ia2	4	39.3	100.0	60.0	60.0	60.0	—	3.9 (0.4–33.5)
Ib1	72	45.1	95.7	94.1	89.1	89.1	89.1	} Reference
Ib2	137	43.0	97.0	89.9	84.1	84.1	82.8	
IIa	68	47.3	98.4	91.7	88.0	83.7	83.7	1.0 (0.4–2.3)
IIb	73	50.7	95.7	86.6	75.1	71.4	68.8	2.2 (1.1–4.6)
IIIa	6	58.8	83.3	66.7	47.6	47.6	—	3.3 (0.7–15.1)
IIIb	15	52.0	86.7	72.8	58.2	58.2	58.2	3.9 (1.4–10.9)
IVa	2	46.0	100.0	100.0	50.0	50.0	50.0	6.2 (0.5–73.4)
IVb	6	55.0	83.3	33.3	—	—	—	16.6 (5.8–48.0)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country.

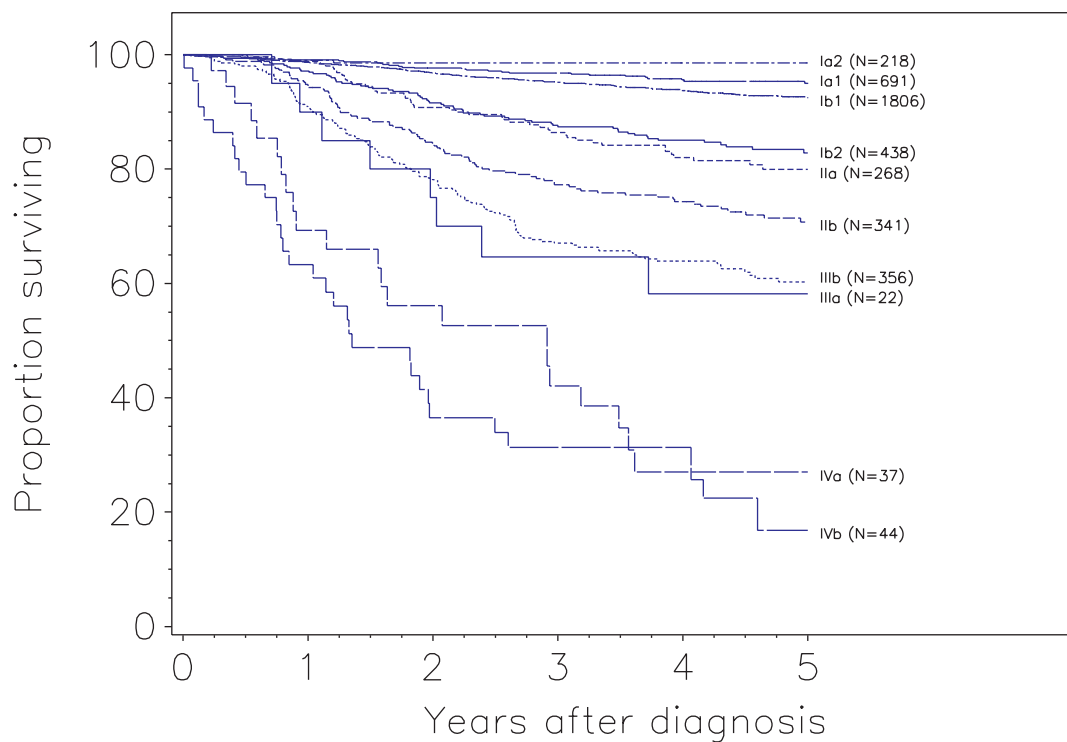
Fig. 17. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Survival by FIGO stage (chemotherapy + surgery), $n = 385$.



Stage	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Ia1	—	—	—	—	—	—	—	—
Ia2	4	40.5	100.0	100.0	100.0	100.0	100.0	—
Ib1	76	52.0	95.8	85.2	78.7	71.0	68.1	} Reference
Ib2	165	45.7	93.1	83.1	73.9	70.7	66.9	
IIa	153	54.0	94.0	83.7	78.0	75.6	70.6	0.9 (0.6–1.4)
IIb	570	52.2	92.2	81.5	76.7	74.3	70.5	0.8 (0.6–1.1)
IIIa	63	55.8	80.0	70.8	65.0	50.8	48.2	1.6 (1.0–2.5)
IIIb	472	53.1	82.9	67.4	59.8	55.9	50.2	1.7 (1.2–2.3)
IVa	67	54.5	74.0	48.6	43.5	39.5	36.2	2.6 (1.7–3.9)
IVb	85	54.0	60.5	31.9	26.3	18.5	14.6	4.8 (3.3–6.9)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

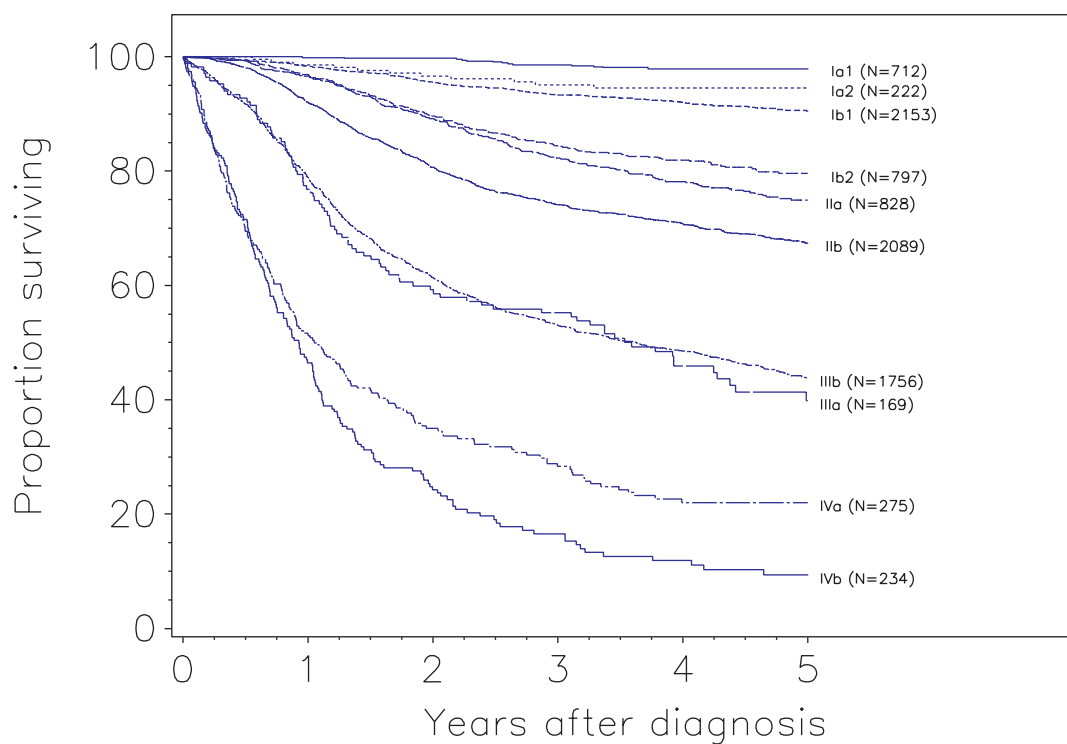
Fig. 18. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Survival by FIGO stage (chemo-radiotherapy), $n = 1655$.



pT (UICC-TNM)	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
PT Ia1	691	45.3	99.1	97.6	96.8	95.6	95.1	0.5 (0.4–0.8)
PT Ia2	218	46.5	99.1	98.6	98.6	98.6	98.6	0.2 (0.1–0.5)
PT Ib1	1806	47.3	98.7	96.8	95.2	93.8	92.5	} Reference
PT Ib2	438	46.3	97.2	91.6	87.7	85.0	82.9	
PT IIa	268	50.4	98.9	90.8	86.4	82.0	79.9	
PT IIb	341	50.1	94.9	84.4	77.3	74.3	70.6	2.0 (1.4–2.8)
PT IIIa	22	53.5	90.5	75.4	64.6	58.5	58.5	2.9 (2.2–3.8)
PT IIIb	356	47.7	91.1	78.2	67.0	63.8	60.2	3.5 (1.5–7.8)
PT IVa	37	54.4	70.6	56.8	42.6	26.4	26.4	5.2 (4.0–6.6)
PT IVb	44	55.2	63.2	37.0	31.9	31.9	17.7	9.8 (6.2–15.6)
								15.7 (10.5–23.5)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

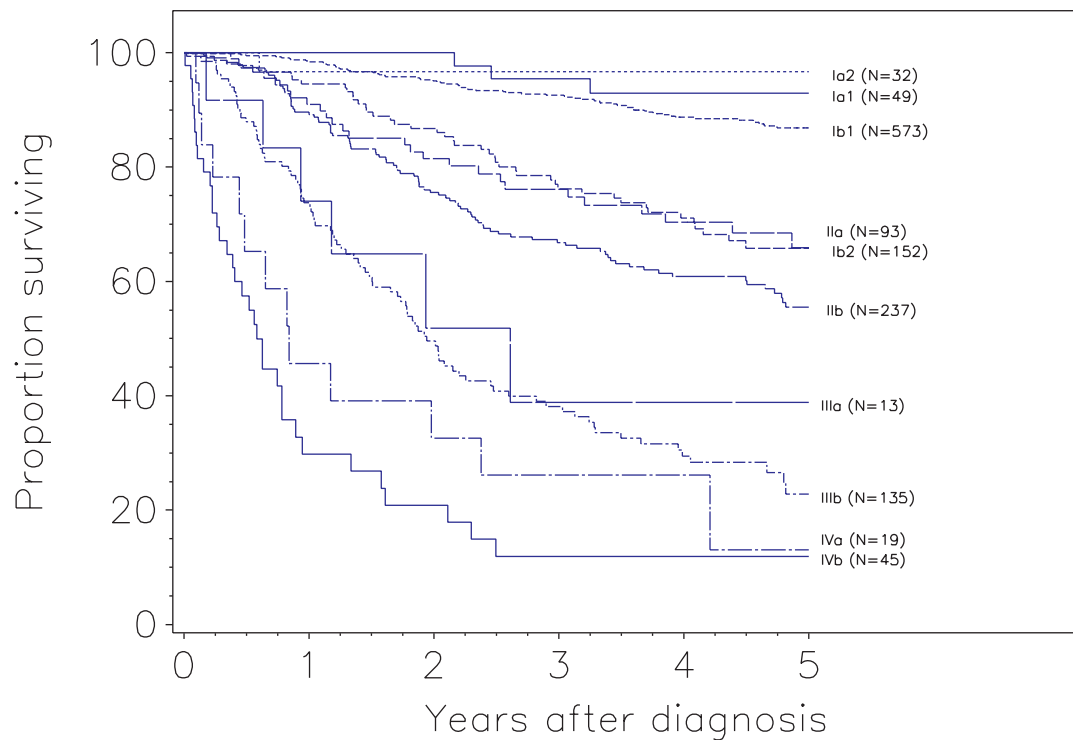
Fig. 19. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Survival by pT(UICC-TNM), $n=4221$.



Stage	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Ia1	712	44.3	99.9	99.7	98.6	97.9	97.9	0.2 (0.1–0.3) 0.6 (0.3–1.0) Reference
Ia2	222	46.1	98.6	96.6	95.1	94.6	94.6	
Ib1	2153	49.3	98.4	95.6	93.3	92.0	90.5	
Ib2	797	46.6	96.9	89.7	84.5	81.9	79.5	2.1 (1.8–2.6) 3.0 (2.6–3.4) 6.2 (4.9–8.0)
IIa	828	55.1	96.6	89.2	82.3	78.1	74.8	
IIb	2089	53.6	92.2	80.8	74.2	70.8	67.4	
IIIa	169	60.8	77.2	59.4	55.3	46.0	40.5	5.8 (5.1–6.7) 13.9 (11.5–16.7)
IIIb	1756	56.3	79.1	61.5	53.2	48.5	44.0	
IVa	275	59.1	52.3	35.7	28.9	22.3	22.3	21.6 (17.9–26.0)
IVb	234	56.2	47.0	24.5	16.8	11.9	9.3	

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

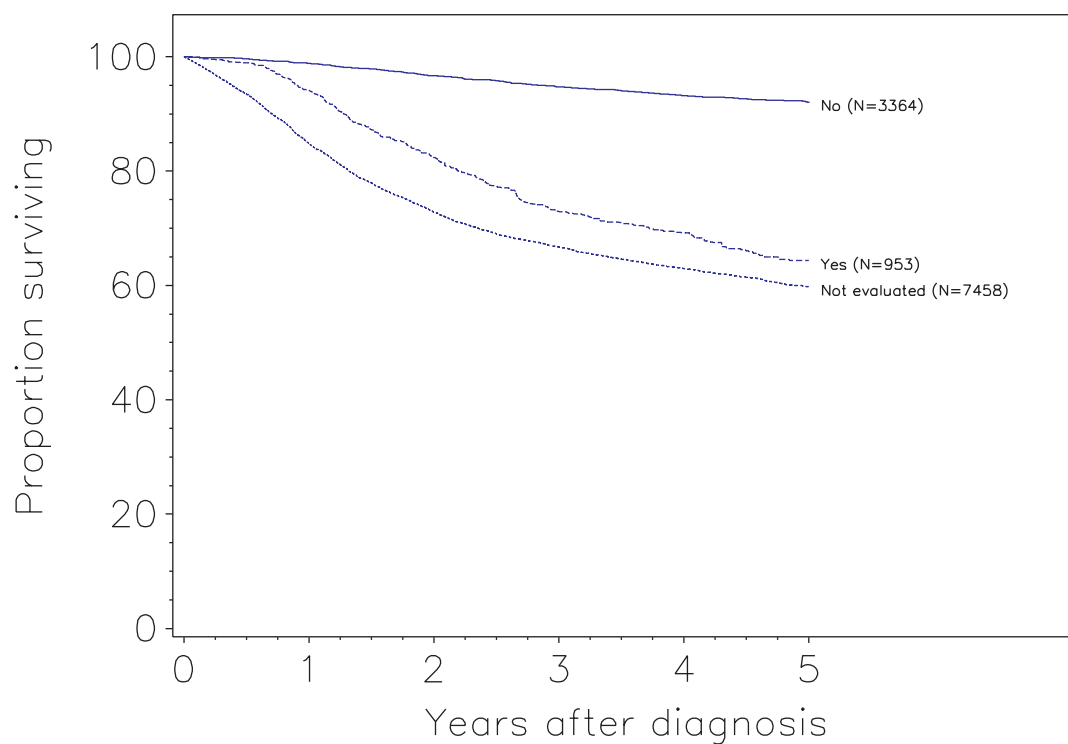
Fig. 20. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Survival by FIGO stage (epidermoid), $n=9235$.



Stage	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Ia1	49	43.8	100.0	100.0	95.5	92.8	92.8	Reference
Ia2	32	42.4	96.8	96.8	96.8	96.8	96.8	
Ib1	573	46.8	98.4	95.1	92.6	88.6	86.8	
Ib2	152	46.9	94.6	86.7	76.2	71.2	65.3	Reference
IIa	93	50.7	91.2	81.7	76.5	70.5	66.4	
IIb	237	52.0	89.9	75.8	67.0	60.9	55.9	
IIIa	13	56.2	75.0	53.6	40.2	40.2	40.2	5.5 (2.3–13.1)
IIIb	135	59.2	73.9	49.9	38.3	29.4	23.7	5.9 (4.3–8.1)
IVa	19	61.6	48.6	34.7	27.8	27.8	16.7	10.0 (5.2–19.1)
IVb	45	60.3	32.5	22.8	13.0	13.0	13.0	18.0 (11.7–27.6)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

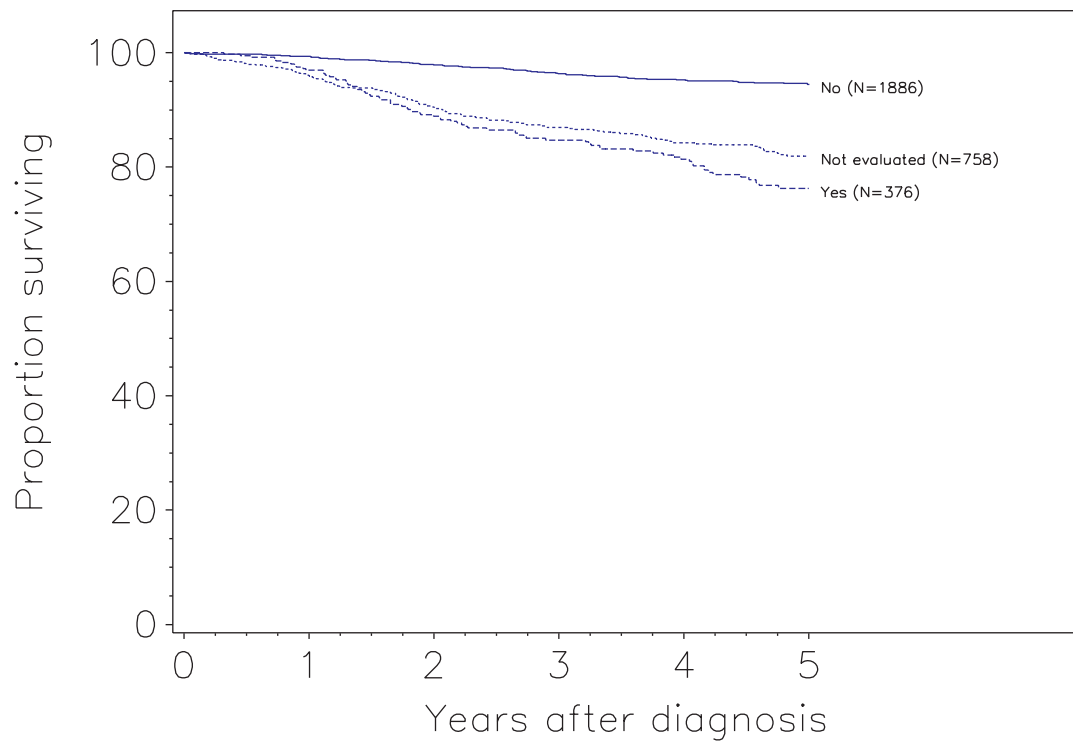
Fig. 21. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Survival by FIGO stage (adenocarcinoma), $n = 1348$.



Lymph nodes	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Negative	3364	46.9	98.8	96.7	94.7	93.2	92.1	Reference
Positive	953	46.1	94.3	82.4	73.0	69.1	64.1	3.3 (2.8–4.0)
Unknown	7458	54.6	85.0	73.0	66.8	62.9	59.8	3.0 (2.6–3.5)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age, FIGO stage and country

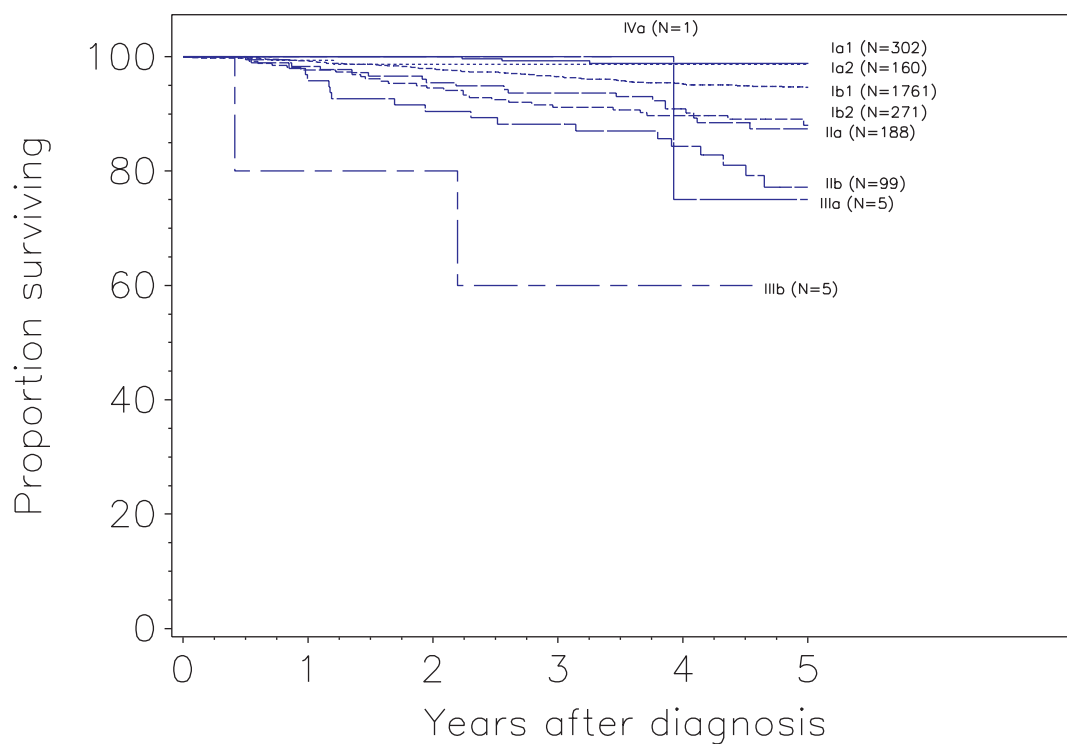
Fig. 22. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Survival by lymphnodal status, $n = 11775$.



Stage	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Negative	1886	46.6	99.3	97.9	96.4	95.2	94.5	Reference
Positive	376	46.2	97.0	88.9	84.8	81.4	75.9	4.7 (3.5–6.4)
Unknown	758	54.8	95.9	90.6	86.9	84.2	82.1	3.4 (2.5–4.6)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age, FIGO stage and country

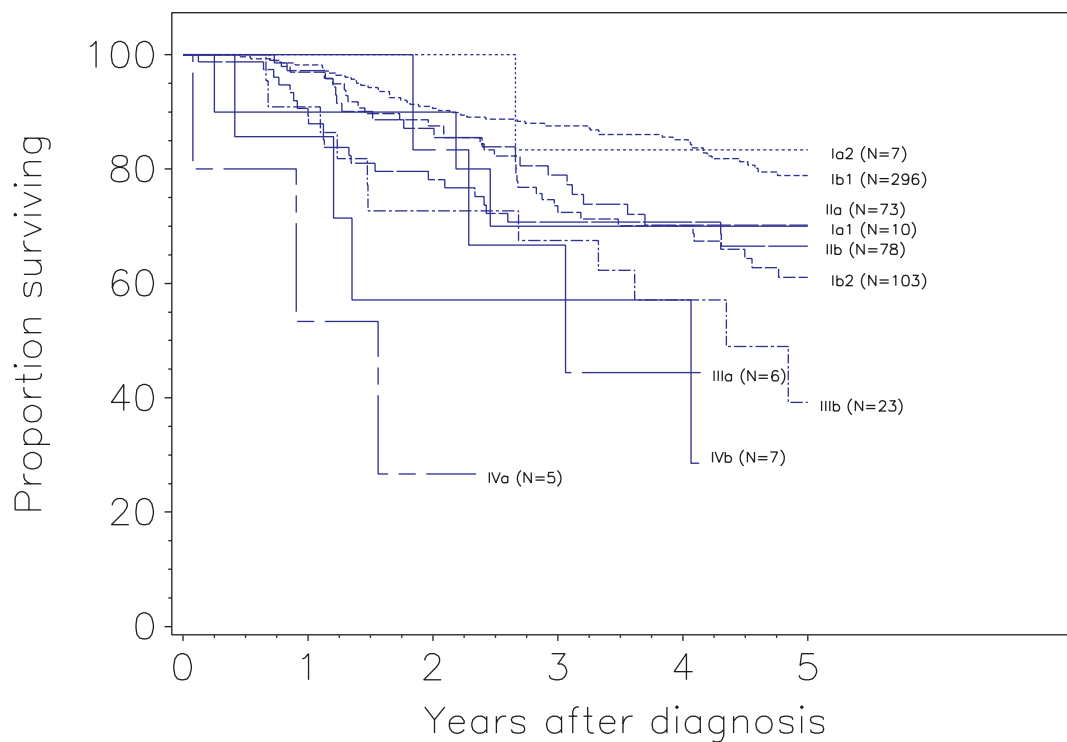
Fig. 23. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Survival in FIGO Stage Ib1 patients by lymphodal status, $n=3020$.



Stage	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Ia1	302	46.3	100.0	100.0	99.3	98.8	98.8	0.2 (0.1–0.6)
Ia2	160	45.5	99.4	98.7	98.7	98.7	98.7	0.2 (0.1–0.9)
Ib1	1761	46.7	99.3	97.9	96.5	95.3	94.6	} Reference
Ib2	271	46.7	97.7	94.6	91.2	89.8	88.4	
IIa	188	51.3	98.4	95.5	93.7	90.9	87.1	1.6 (1.0–2.7)
IIb	99	47.3	95.9	90.5	88.2	84.4	76.9	4.1 (2.4–7.0)
IIIa	5	55.0	100.0	100.0	100.0	77.8	77.8	6.7 (1.4–31.3)
IIIb	5	39.0	80.0	80.0	60.0	60.0	–	10.3 (2.4–43.2)
IVa	1	42.0	100.0	100.0	100.0	–	–	–
IVb	–	–	–	–	–	–	–	–

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

Fig. 24. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Survival by FIGO stage (up-front surgery, negative nodes), $n=2792$.



Stage	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Ia1	10	40.9	90.0	90.0	68.8	68.8	68.8	3.7 (1.0–13.7)
Ia2	7	43.0	100.0	100.0	84.6	84.6	84.6	0.9 (0.1–6.5)
Ib1	296	46.6	98.3	90.7	87.6	85.1	78.4	} Reference
Ib2	103	43.5	97.0	87.7	73.6	70.0	61.0	
IIa	73	49.3	97.2	86.9	78.8	69.7	69.7	1.3 (0.8–2.2)
IIb	78	48.1	90.8	78.2	70.8	70.8	66.7	1.6 (1.0–2.7)
IIIa	6	48.8	100.0	83.3	64.8	43.2	–	2.6 (0.8–8.8)
IIIb	23	47.0	91.1	72.4	67.4	56.2	41.2	2.5 (1.2–5.2)
IVa	5	48.8	55.6	27.8	–	–	–	4.4 (1.0–19.0)
IVb	7	48.6	85.7	57.1	57.1	57.1	–	3.7 (1.1–12.8)

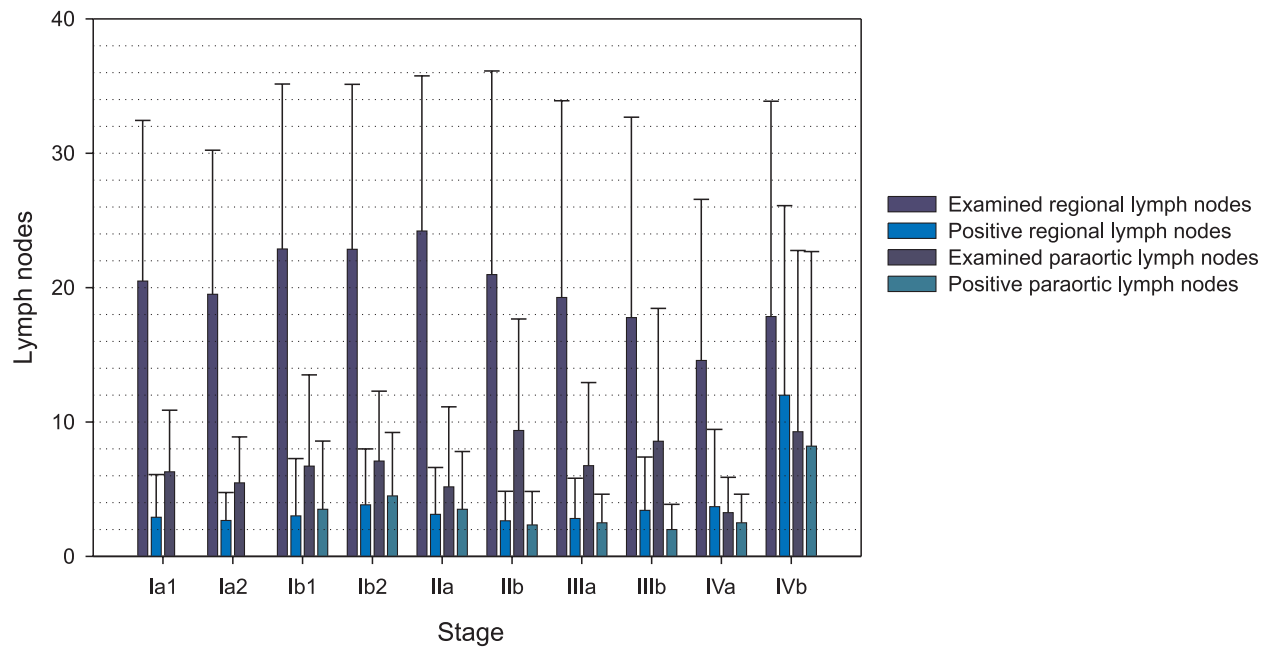
^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

Fig. 25. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Survival by FIGO stage (up-front surgery, positive nodes), $n = 608$.

Table 11

Carcinoma of the cervix uteri: Patients treated in 1999–2001. Distribution of patients with histologically proven lymphnodal involvement by FIGO stage

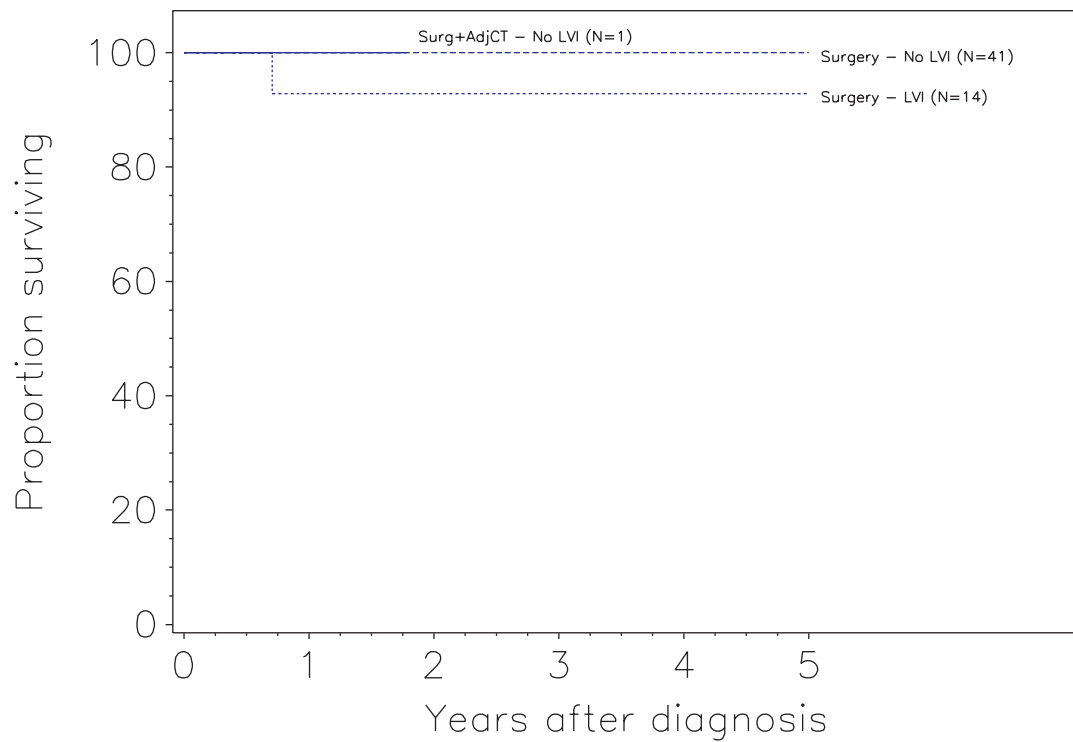
FIGO stage	Patients (n)	Lymphnodal involvement				FIGO stage	Patients (n)	Lymphnodal involvement			
		Positive		Negative				Positive		Negative	
		N	%	N	%			N	%	N	%
Total	5173	1161	22.4	4012	77.6	IIb	491	185	37.7	306	62.3
Ia1	356	14	3.9	342	96.1	IIIa	29	14	48.3	15	51.7
Ia2	238	23	9.7	215	90.3	IIIb	117	71	60.7	46	39.3
Ib1	2687	460	17.1	2227	82.9	IVa	28	16	57.1	12	42.9
Ib2	685	209	30.5	476	69.5	IVb	24	22	91.7	2	8.3
IIa	486	140	28.8	346	71.2	Missing	32	7	21.9	25	78.1



Stage	Regional lymphnodes						Paraortic lymphnodes					
	Examined			Positive			Examined			Positive		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Ia1	230	20.5	12.0	11	2.9	3.2	24	6.3	4.6	–	–	–
Ia2	209	19.5	10.7	18	2.7	2.1	15	5.5	3.4	–	–	–
Ib1	2122	22.9	12.3	376	3.0	4.3	309	6.7	6.8	24	3.5	5.1
Ib2	552	22.8	12.3	172	3.8	4.2	89	7.1	5.2	6	4.5	4.7
IIa	373	24.2	11.6	114	3.1	3.5	65	5.2	6.0	10	3.5	4.3
IIb	365	21.0	15.2	151	2.6	2.2	73	9.4	8.3	15	2.3	2.5
IIIa	23	19.3	14.6	11	2.8	3.0	4	6.7	6.2	2	2.5	2.1
IIIb	82	17.8	14.9	49	3.4	4.0	23	8.6	9.9	13	2.0	1.9
IVa	19	14.6	12.0	13	3.7	5.8	4	3.2	2.7	2	2.5	2.1
IVb	19	17.8	16.0	16	12.0	14.1	11	9.3	13.5	10	8.2	14.5

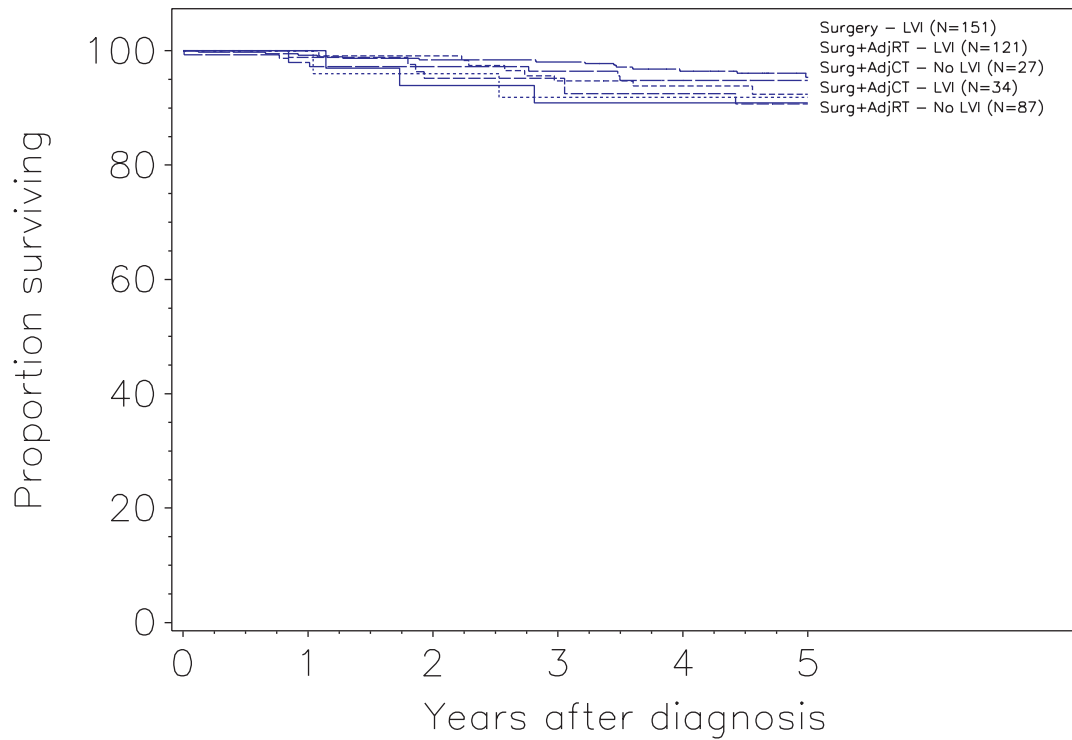
^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

Fig. 26. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Mean number (± standard deviation) of lymph nodes.



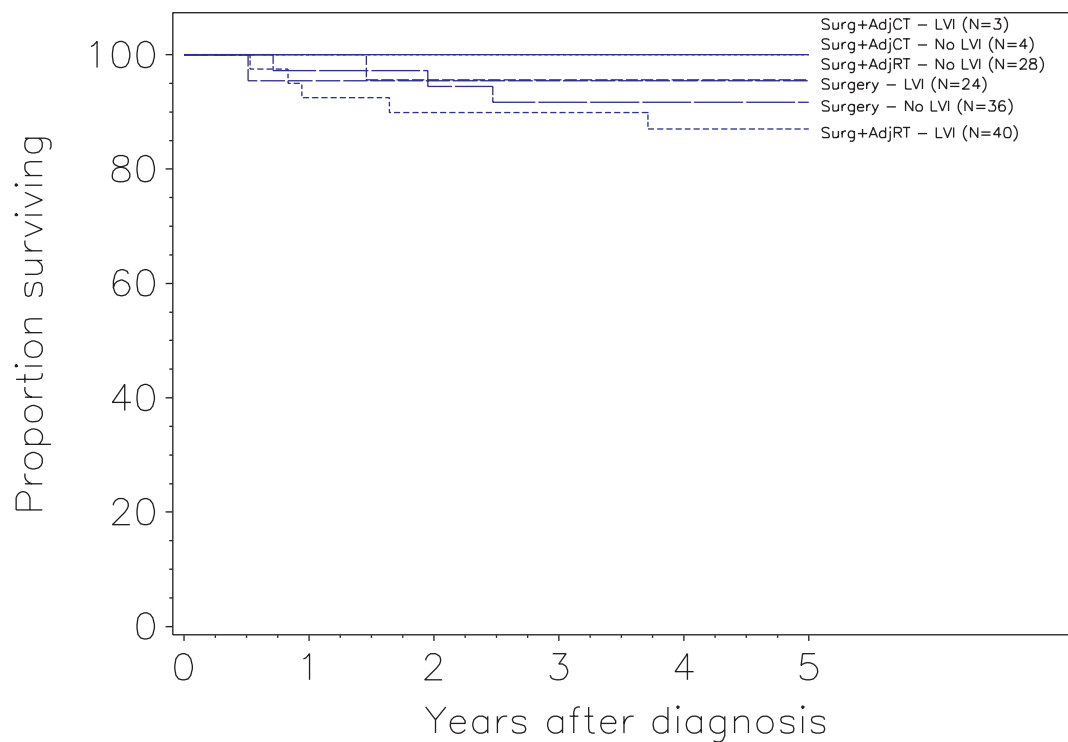
Treatment/LVI	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Surgery - No LVI	41	41.5	100.0	100.0	100.0	100.0	100.0	Reference
Surgery - LVI	14	41.9	92.3	92.3	92.3	92.3	92.3	—
Surgery + adjuvant CT - No LVI	1	43.0	100.0	—	—	—	—	—

Fig. 27. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Survival in FIGO Stage Ia2 patients submitted to up-front surgery (surgery or surgery + adjuvant RT or surgery + adjuvant CT) and with negative histologically proven lymphnodal involvement by lymphovascular space involvement (absent or present), $n = 56$.



Treatment/LVI	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Surgery - No LVI	388	45.2	99.2	98.4	98.1	96.5	95.5	Reference
Surgery - LVI	151	45.4	97.9	97.2	96.5	94.8	94.8	1.3 (0.5-3.3)
Surgery + adjuvant RT - No LVI	87	47.4	98.8	95.2	95.2	92.3	90.4	2.1 (0.8-5.5)
Surgery + adjuvant RT - LVI	121	48.8	100.0	99.1	94.7	93.8	92.4	1.7 (0.7-4.2)
Surgery + adjuvant CT - No LVI	27	43.4	100.0	96.0	91.9	91.9	91.9	1.6 (0.3-8.0)
Surgery + adjuvant CT - LVI	34	46.6	100.0	94.0	91.0	91.0	91.0	1.8 (0.5-7.0)

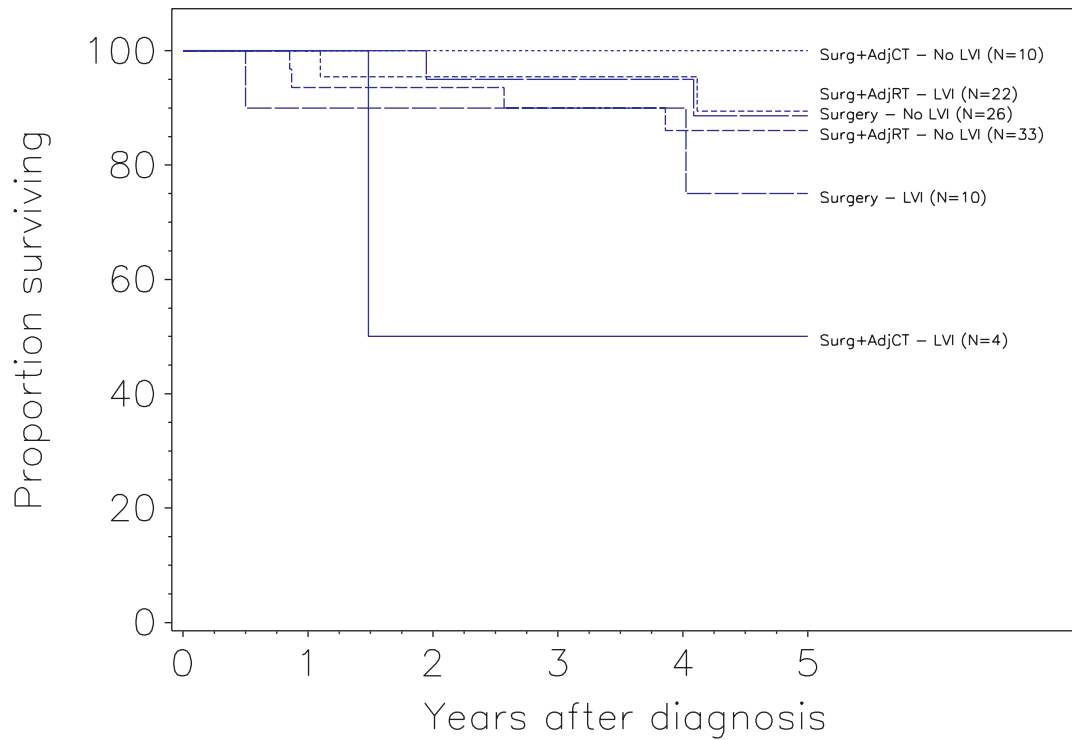
Fig. 28. Carcinoma of the cervix uteri: Patients treated in 1999-2001. Overall survival in Stage Ib1 patients submitted to upfront surgery (surgery or surgery + adjuvant RT or surgery + adjuvant CT) and with negative histologically proven lymphnodal involvement by lymphovascular space involvement (absent or present), $n = 808$.



Treatment/LVI	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Surgery - No LVI	36	45.4	97.2	94.4	91.7	91.7	91.7	Reference
Surgery - LVI	24	45.8	95.6	95.6	95.6	95.6	95.6	1.1 (0.0–32.5)
Surgery + adjuvant RT - No LVI	28	51.0	100.0	95.7	95.7	95.7	95.7	–
Surgery + adjuvant RT - LVI	40	47.7	92.5	90.0	90.0	87.1	87.1	2.4 (0.2–29.5)
Surgery + adjuvant CT - No LVI	4	47.5	100.0	100.0	100.0	100.0	100.0	–
Surgery + adjuvant CT - LVI	3	42.0	100.0	100.0	100.0	100.0	100.0	–

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

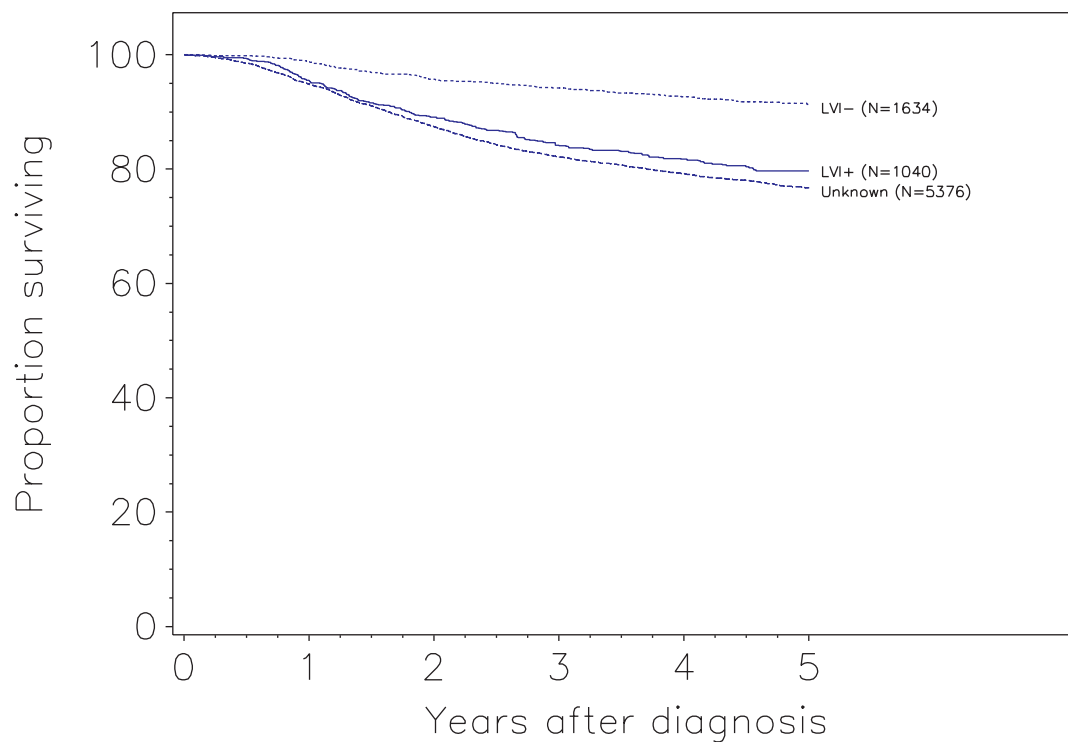
Fig. 29. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Overall survival in Stage Ib2 patients submitted to up-front surgery (surgery or surgery + adjuvant RT or surgery + adjuvant CT) and with negative histologically proven lymphnodal involvement by lymphovascular space involvement (absent or present), $n = 135$.



Treatment/LVI	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Surgery – No LVI	26	51.2	100.0	95.3	95.3	95.3	87.4	Reference
Surgery – LVI	10	48.7	89.5	89.5	89.5	89.5	73.2	7.4 (0.3–161.4)
Surgery + adjuvant RT – No LVI	33	52.7	93.8	93.8	90.2	86.4	86.4	4.3 (0.6–32.7)
Surgery + adjuvant RT – LVI	22	54.5	100.0	95.3	95.3	95.3	88.5	1.3 (0.2–11.5)
Surgery + adjuvant CT – No LVI	10	46.7	100.0	100.0	100.0	100.0	100.0	–
Surgery + adjuvant CT – LVI	4	52.0	100.0	50.0	50.0	50.0	50.0	7.2 (0.5–109.7)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

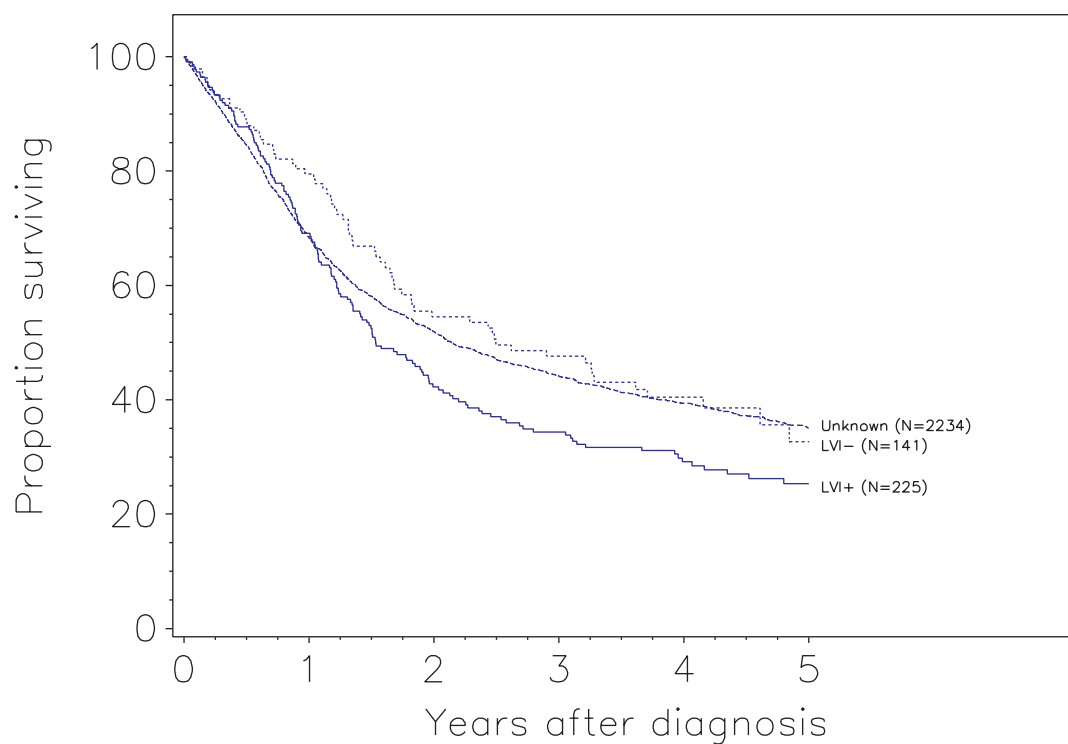
Fig. 30. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Overall survival in Stage IIa patients submitted to up-front surgery (surgery or surgery + adjuvant RT or surgery + adjuvant CT) and with negative histologically proven lymphnodal involvement by lymphovascular space involvement (absent or present), $n = 105$.



LVI	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
LVI-	1634	46.6	98.9	95.7	94.2	92.6	91.3	Reference
LVI+	1040	47.4	95.6	89.1	84.2	81.7	79.5	2.9 (2.3–3.7)
Unknown	5376	51.2	94.9	87.5	82.2	79.2	76.7	3.0 (2.4–3.7)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

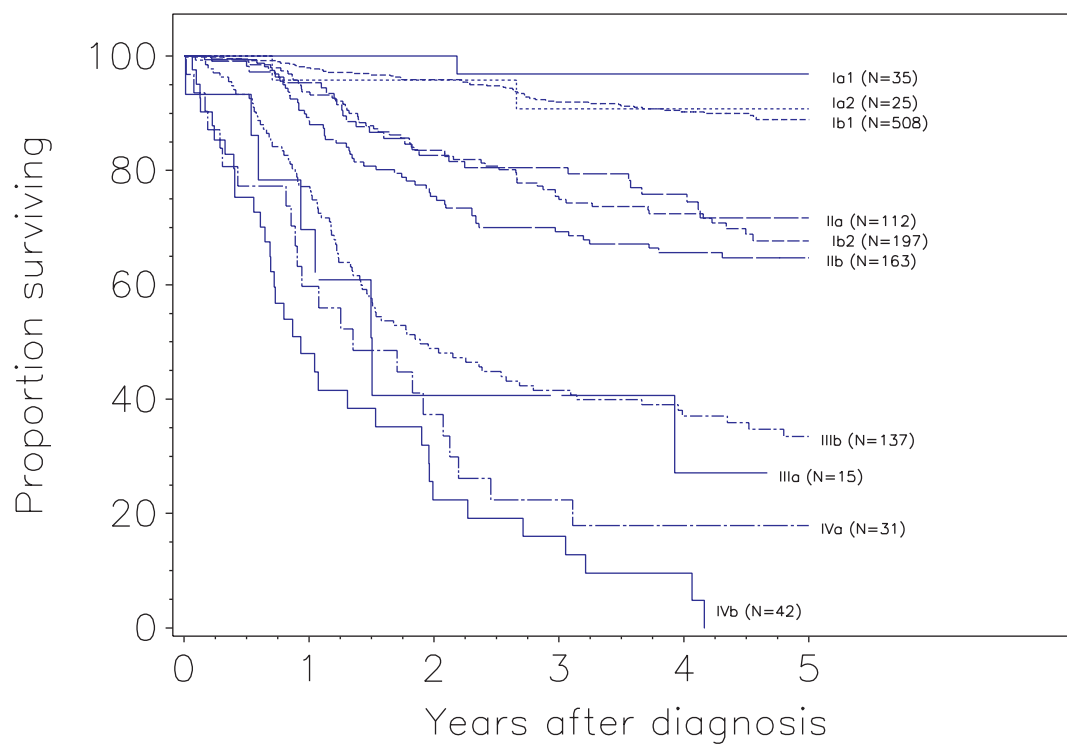
Fig. 31. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Overall survival of FIGO Stage I–II patients by lymphovascular space involvement (absent or present), $n=8050$.



LVI	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
LVI-	141	54.5	79.8	55.1	48.0	40.6	34.0	Reference
LVI+	225	53.4	69.2	42.3	34.5	29.2	25.4	1.4 (1.1–1.9)
Unknown	2234	57.5	68.7	52.1	44.3	39.3	35.3	1.3 (0.9–1.7)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

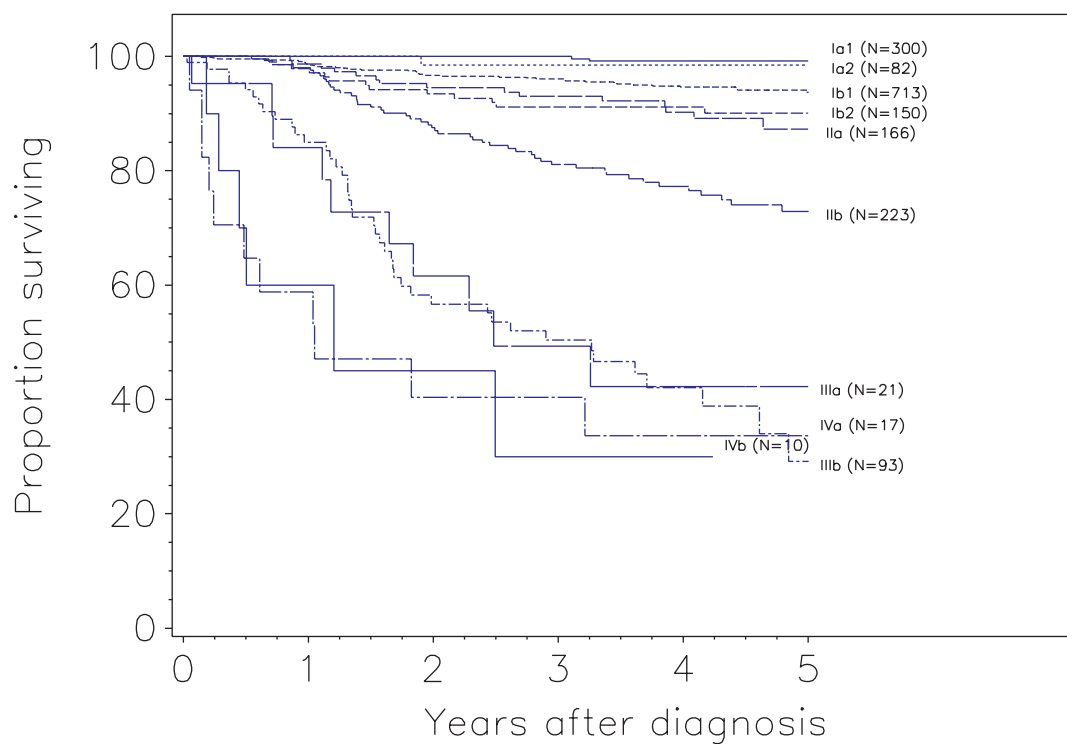
Fig. 32. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Overall survival of FIGO Stage III–IV patients by lymphovascular space involvement (absent or present), $n=2600$.



Strata	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Ia1	35	45.6	100.0	100.0	96.8	96.8	96.8	} Reference
Ia2	25	41.3	95.7	95.7	90.7	90.7	90.7	
Ib1	508	46.6	98.0	95.9	92.0	90.3	88.9	
Ib2	197	45.9	93.8	83.6	75.6	72.4	67.7	
IIa	112	51.6	95.4	82.5	80.4	75.6	71.0	1.8 (1.2–2.7)
IIb	163	50.2	89.3	75.5	69.4	65.6	64.6	2.5 (1.8–3.5)
IIIa	15	51.5	70.4	42.2	42.2	28.1	–	8.0 (3.3–19.6)
IIIb	137	52.5	77.4	49.0	41.7	37.2	33.8	4.7 (3.4–6.7)
IVa	31	58.6	59.3	37.1	21.5	16.7	16.7	7.9 (4.7–13.3)
IVb	42	53.2	48.1	22.4	16.0	8.9	–	15.9 (10.3–24.5)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

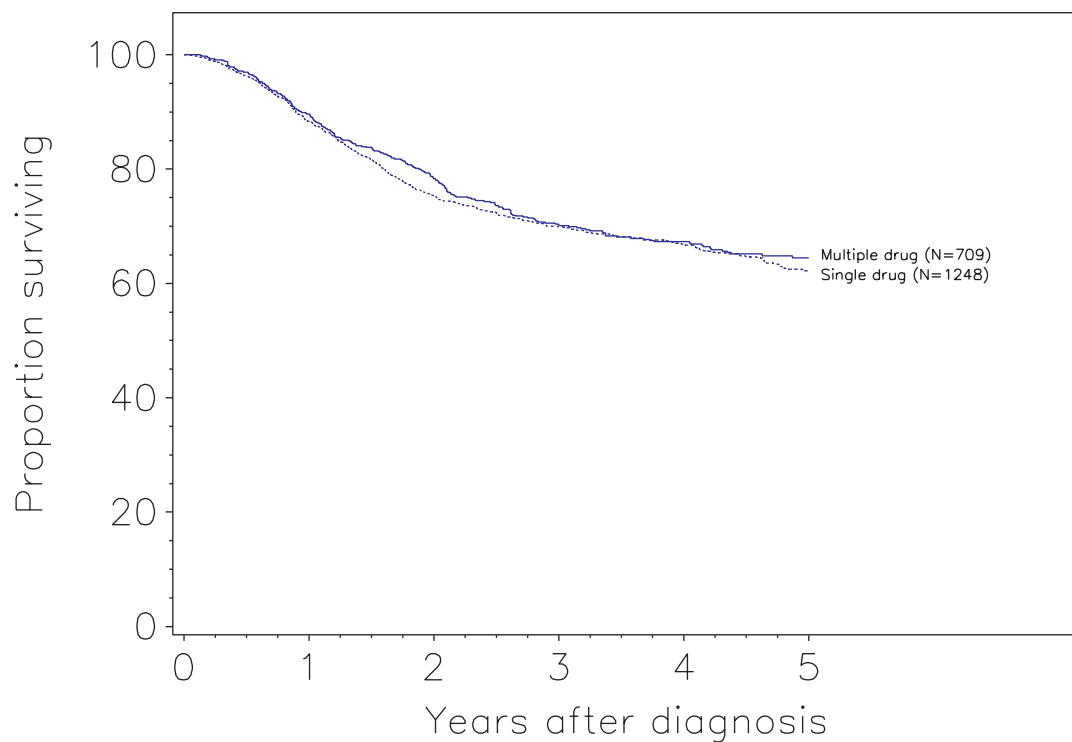
Fig. 33. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Overall survival of patients with lymphovascular space involvement by FIGO stage, $n = 1265$.



Strata	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Ia1	300	42.5	100.0	100.0	100.0	99.1	99.1	0.2 (0.1–0.5)
Ia2	82	42.5	100.0	98.6	98.6	98.6	98.6	0.5 (0.1–1.6)
Ib1	713	46.7	98.7	96.7	96.1	94.6	93.8	} Reference
Ib2	150	46.6	97.9	93.5	91.2	91.2	89.9	
IIa	166	51.3	98.7	94.5	93.0	90.4	87.5	1.9 (1.1–3.3)
IIb	223	50.0	98.1	87.6	81.1	77.3	72.8	3.8 (2.5–5.8)
IIIa	21	56.1	84.6	61.3	48.4	40.9	40.9	12.6 (6.0–26.6)
IIIb	93	52.6	85.6	58.1	51.6	43.3	31.0	11.2 (6.9–18.1)
IVa	17	58.2	58.8	40.2	40.2	32.9	32.9	36.9 (17.7–76.7)
IVb	10	62.2	55.6	41.7	27.8	27.8	–	36.3 (14.2–92.8)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

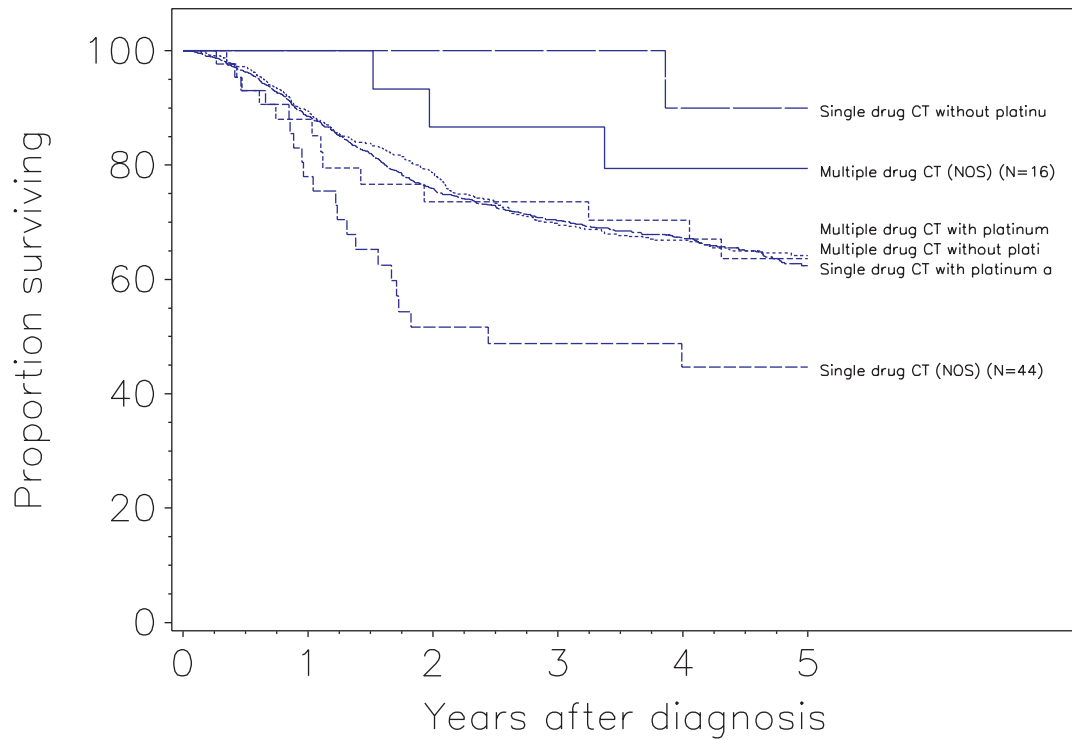
Fig. 34. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Overall survival of patients with no lymphovascular space involvement by FIGO stage, $n = 1775$.



Chemotherapy	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Single drug	1248	52.7	88.5	75.4	70.0	66.6	62.4	Reference
Multiple drug	709	48.3	89.6	78.4	70.3	67.2	64.1	1.1 (0.9–1.4)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

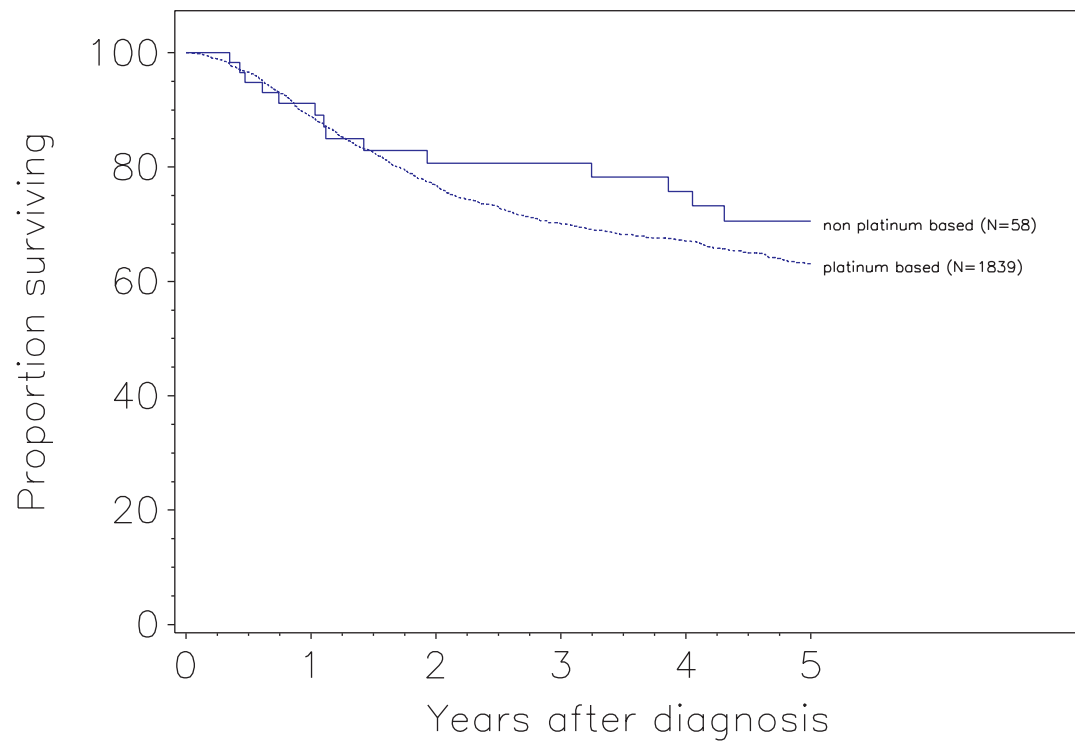
Fig. 35. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Overall survival of patients submitted to neoadjuvant CT + surgery or CT–RT by type of CT (grouping single drug CT vs. multiple drug), $n = 1957$.



Chemotherapy	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Single drug CT (NOS)	44	55.5	78.6	52.4	49.5	46.1	46.1	1.9 (1.1–3.3)
Single drug CT with platinum analogue	1189	52.7	88.7	75.9	70.3	67.1	62.7	Reference
Single drug CT without platinum analogue	15	46.7	100.0	100.0	100.0	90.5	90.5	0.2 (0.0–1.5)
Multiple drug CT (NOS)	16	44.1	100.0	86.7	86.7	79.4	79.4	0.6 (0.2–1.8)
Multiple drug CT with platinum analogue	650	48.4	89.5	78.5	69.7	66.8	63.9	1.2 (0.9–1.4)
Multiple drug CT without platinum analogue	43	47.7	87.3	72.8	72.8	69.6	61.9	1.4 (0.8–2.5)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

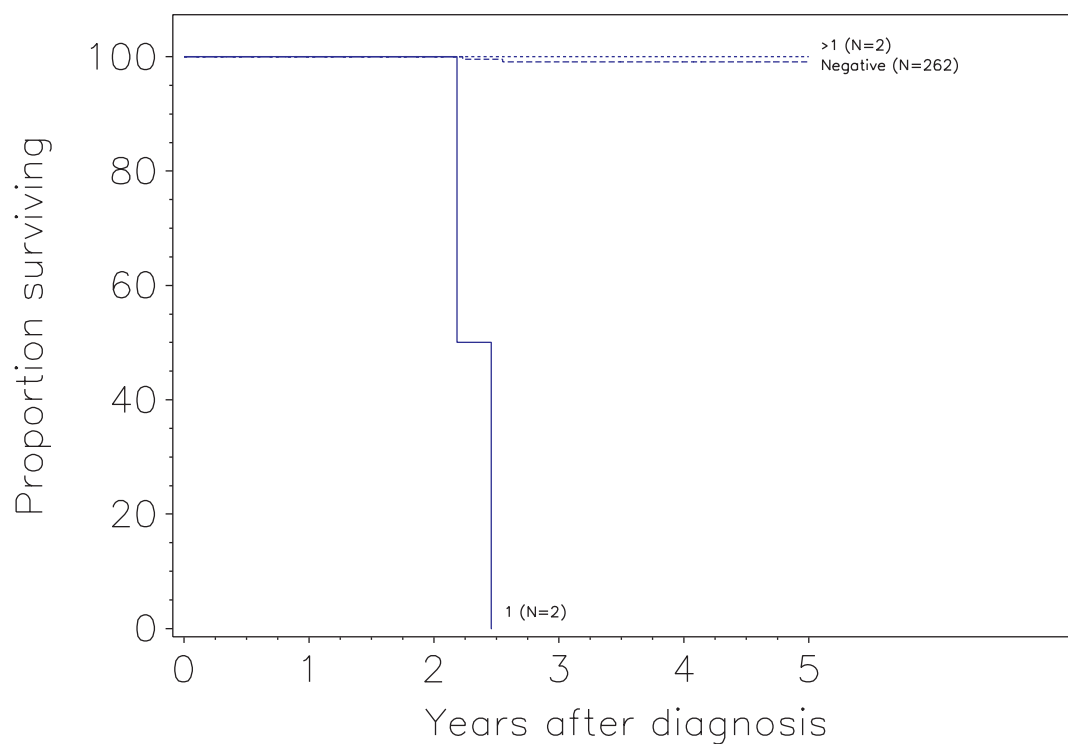
Fig. 36. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Overall survival of patients submitted to chemotherapy by type of chemotherapy (single vs. multiple drug), $n = 1957$.



Chemotherapy	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Platinum based	1839	51.1	89.0	76.9	70.1	67.0	63.1	Reference
Non platinum based	58	47.5	90.7	80.0	80.0	75.2	69.3	0.9 (0.5–1.6)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

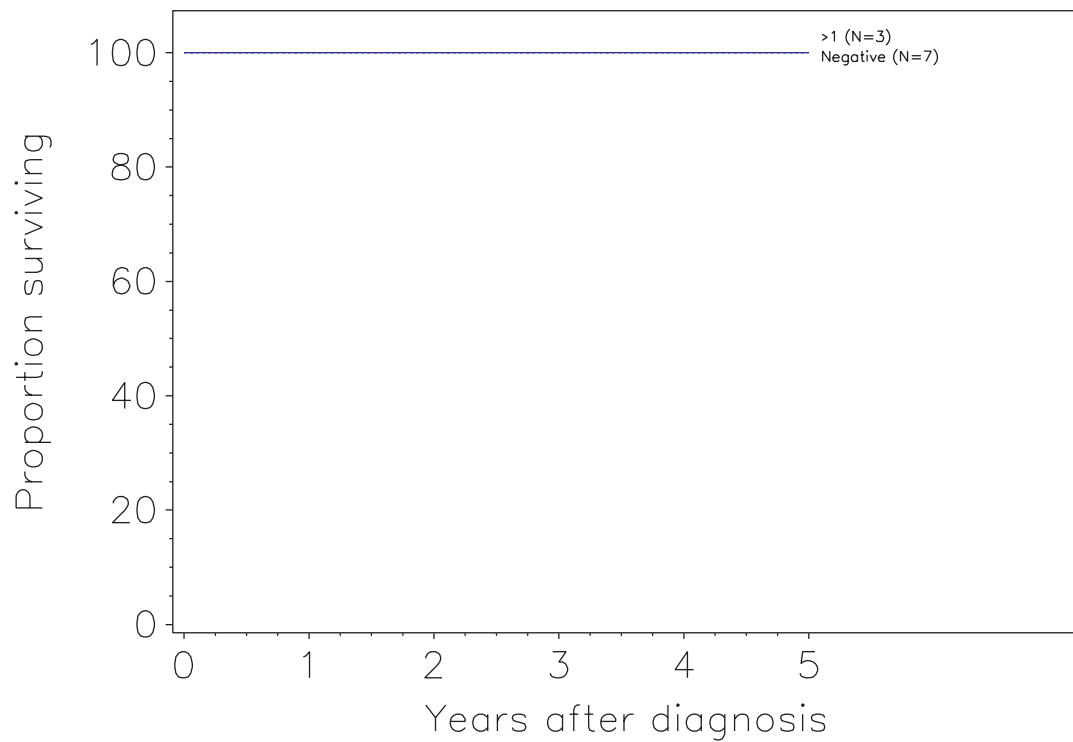
Fig. 37. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Overall survival of patients submitted to neoadjuvant CT + surgery or CT–RT by type of CT (grouping platinum-based CT vs. non-platinum-based CT), $n = 1897$.



Lymphnodal involvement	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Negative	262	45.5	100.0	100.0	99.1	99.1	99.1	Reference
1	2	45.5	100.0	100.0	—	—	—	—
>1	2	28.5	100.0	100.0	100.0	100.0	100.0	—

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

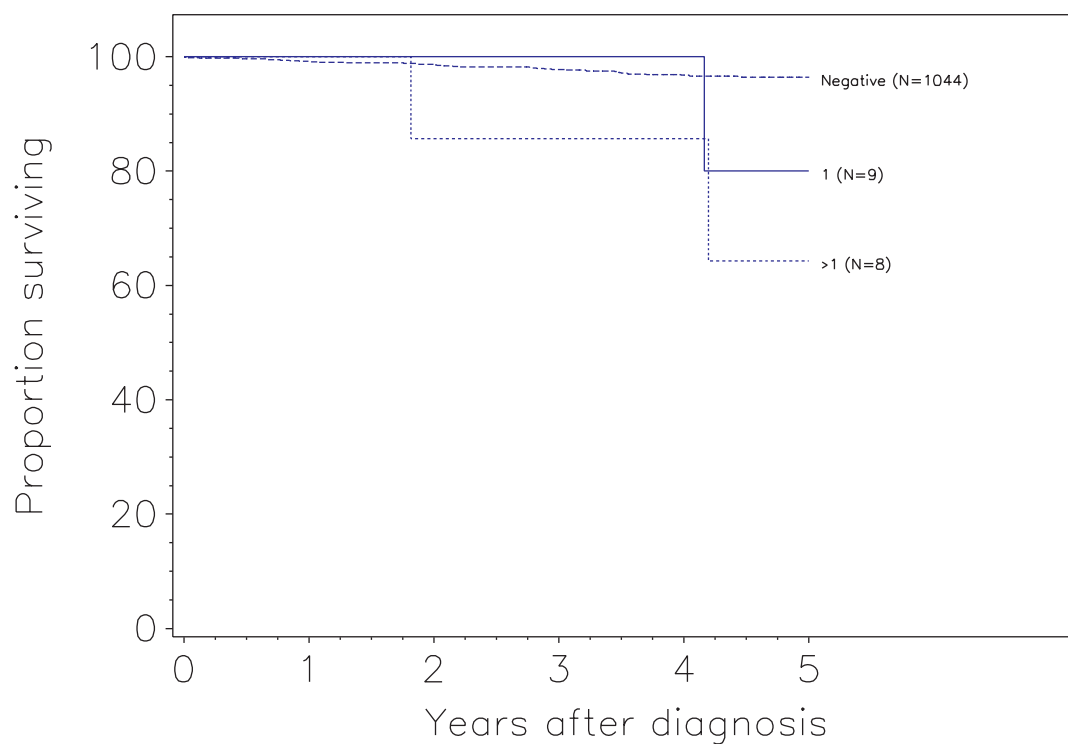
Fig. 38. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Overall survival of Stage Ia1 patients submitted to surgery alone by number of positive regional lymph nodes (cut-off 3 nodes), $n = 266$.



Lymphnodal involvement	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Negative	7	61.9	100.0	100.0	100.0	100.0	100.0	Reference
>1	3	46.7	100.0	100.0	100.0	100.0	100.0	–

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

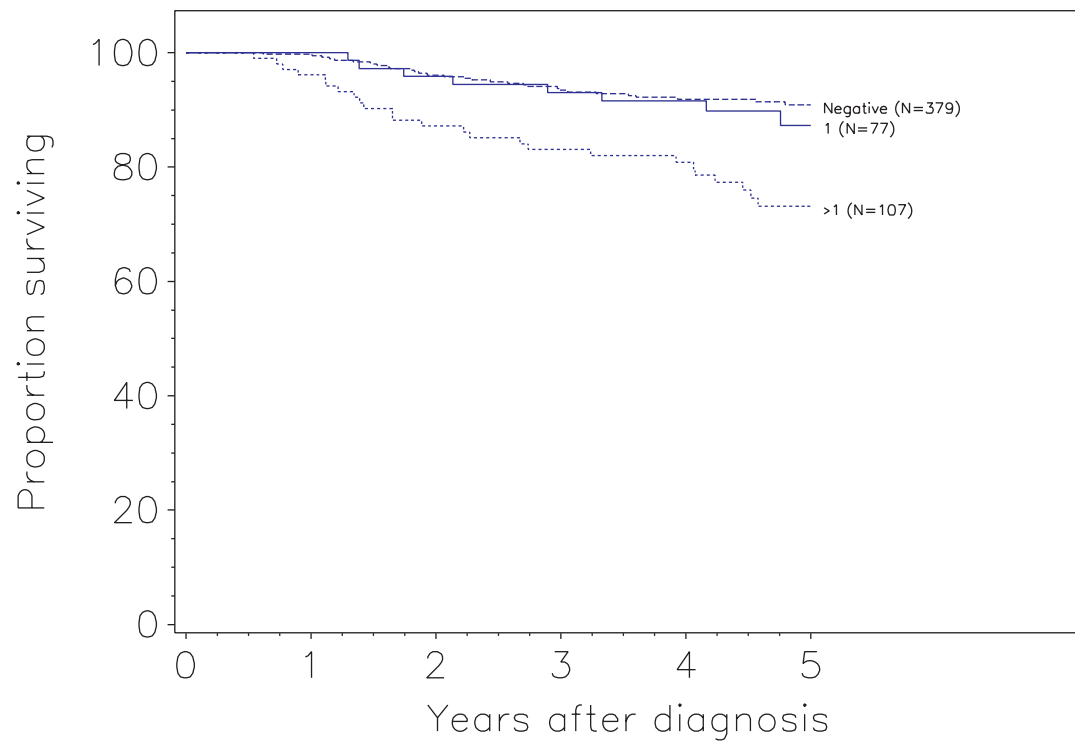
Fig. 39. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Overall survival of Stage Ia1 patients submitted to surgery + adjuvant RT by number of positive regional lymph nodes (cut-off 3 nodes), $n = 10$.



Lymphnodal involvement	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Negative	1044	46.0	99.2	98.6	97.8	96.7	96.4	Reference
1	9	48.3	100.0	100.0	100.0	100.0	81.8	7.0 (0.8–60.0)
>1	8	47.3	100.0	86.7	86.7	86.7	65.0	10.7 (2.3–49.4)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

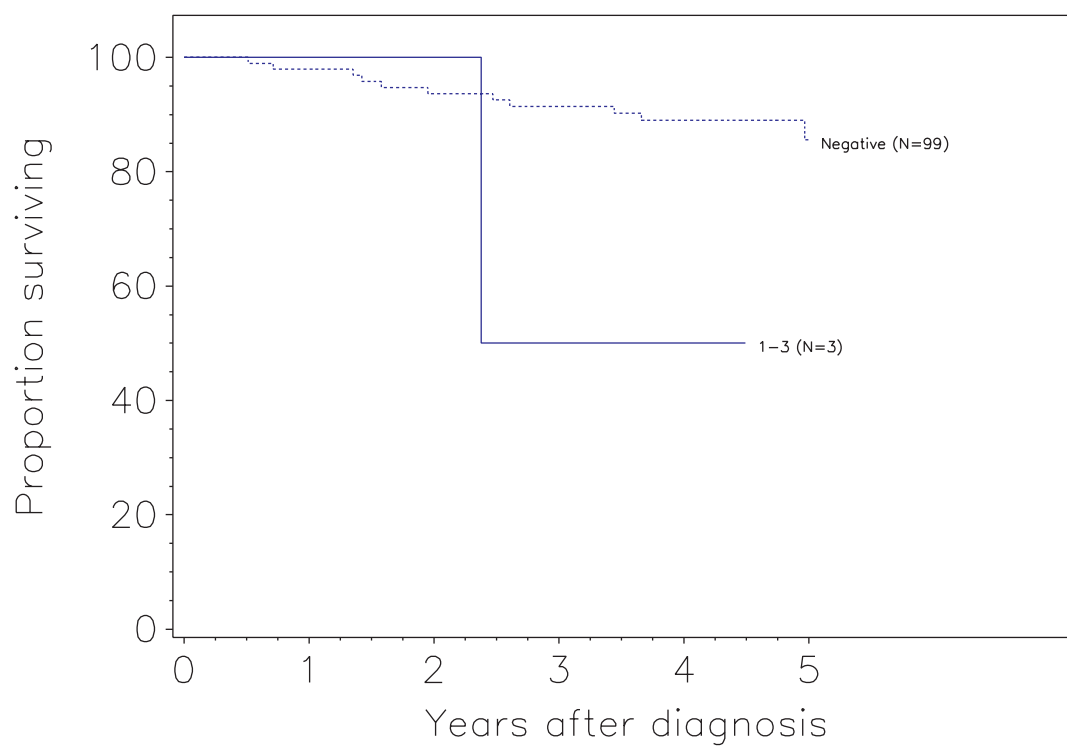
Fig. 40. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Overall survival of Stage Ib1 patients submitted to surgery alone by number of positive regional lymph nodes (cut-off 3 nodes), $n = 1061$.



Lymphnodal involvement	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Negative	379	49.7	99.7	96.1	93.5	91.8	91.0	Reference
1	77	47.5	100.0	95.9	93.1	91.5	87.4	1.1 (0.4–2.8)
>1	107	46.2	96.2	87.2	83.1	80.9	72.6	3.6 (2.0–6.4)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

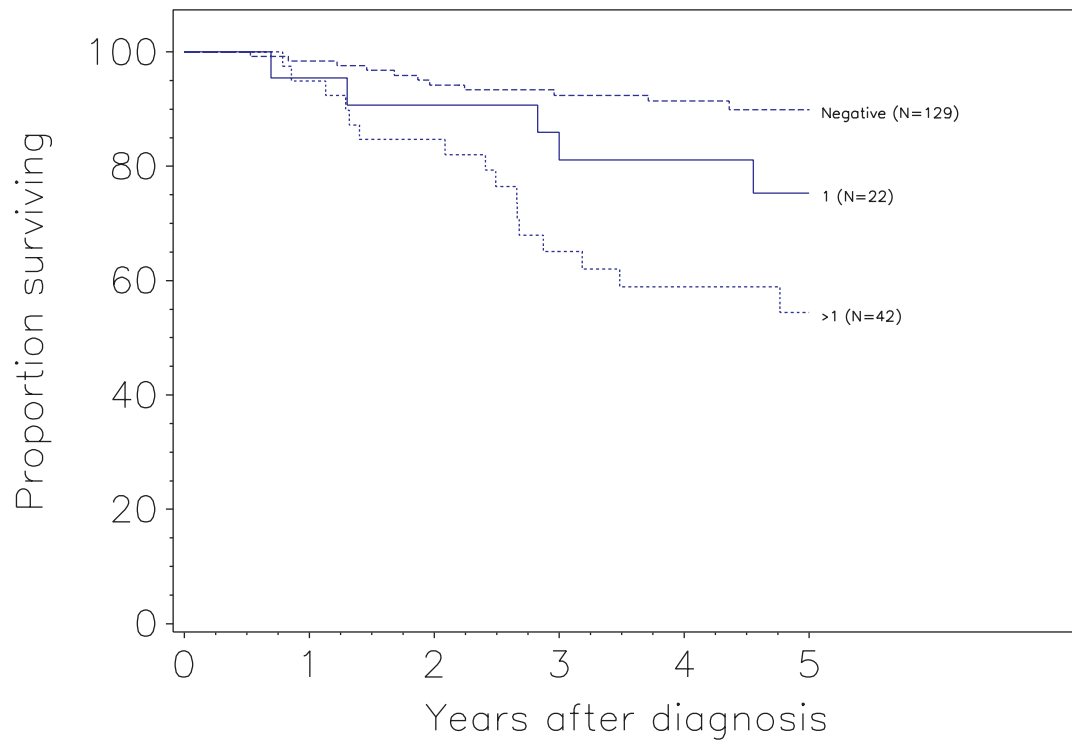
Fig. 41. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Overall survival of Stage Ib1 patients submitted to surgery + adjuvant RT by number of positive regional lymph nodes (cut-off 3 nodes), $n = 563$.



Lymphnodal involvement	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Negative	99	45.9	97.9	93.7	91.4	88.9	86.9	Reference
>1	3	39.3	100.0	100.0	50.0	50.0	—	—

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

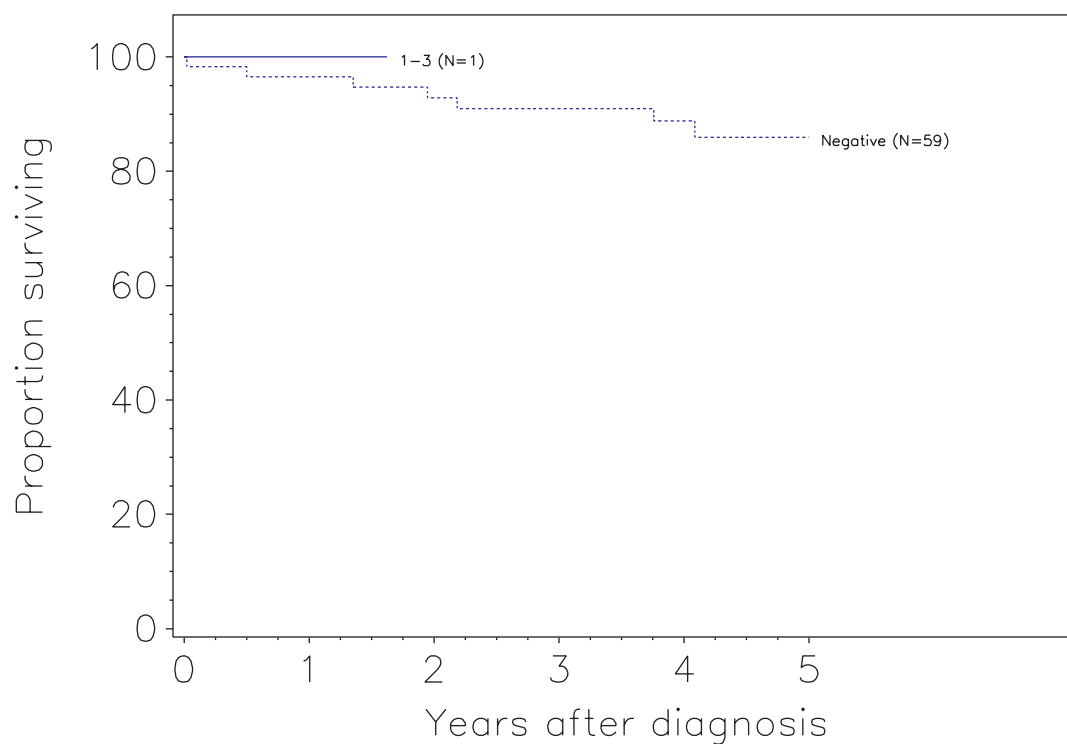
Fig. 42. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Overall survival of Stage Ib2 patients submitted to surgery alone by number of positive regional lymph nodes (cut-off 3 nodes), $n = 102$.



Lymphnodal involvement	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Negative	129	48.7	98.4	94.3	92.5	91.5	90.0	Reference
1	22	44.8	95.5	90.8	86.0	81.1	75.3	3.0 (1.0–9.3)
>1	42	44.7	95.1	84.6	65.2	58.9	54.8	5.5 (2.2–13.5)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

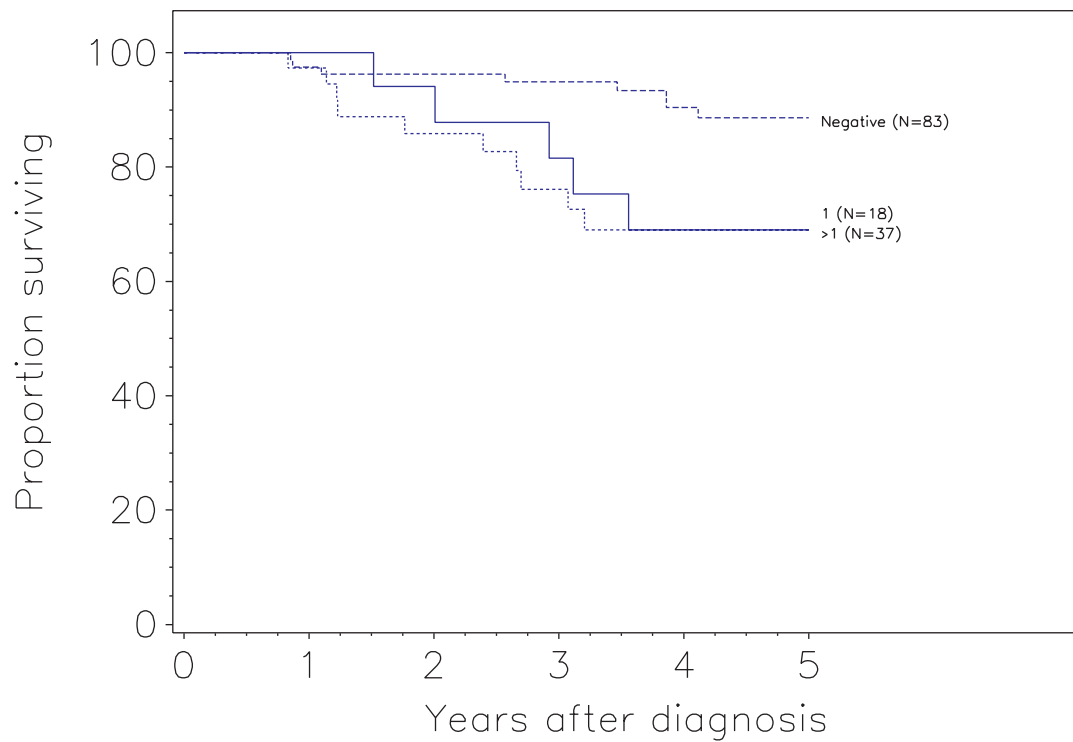
Fig. 43. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Overall survival of Stage Ib2 patients submitted to surgery + adjuvant RT by number of positive regional lymph nodes (cut-off 3 nodes), $n = 193$.



Lymphnodal involvement	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Negative	59	50.1	96.5	92.8	90.8	88.7	85.7	Reference
1	1	55.0	100.0	—	—	—	—	—

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

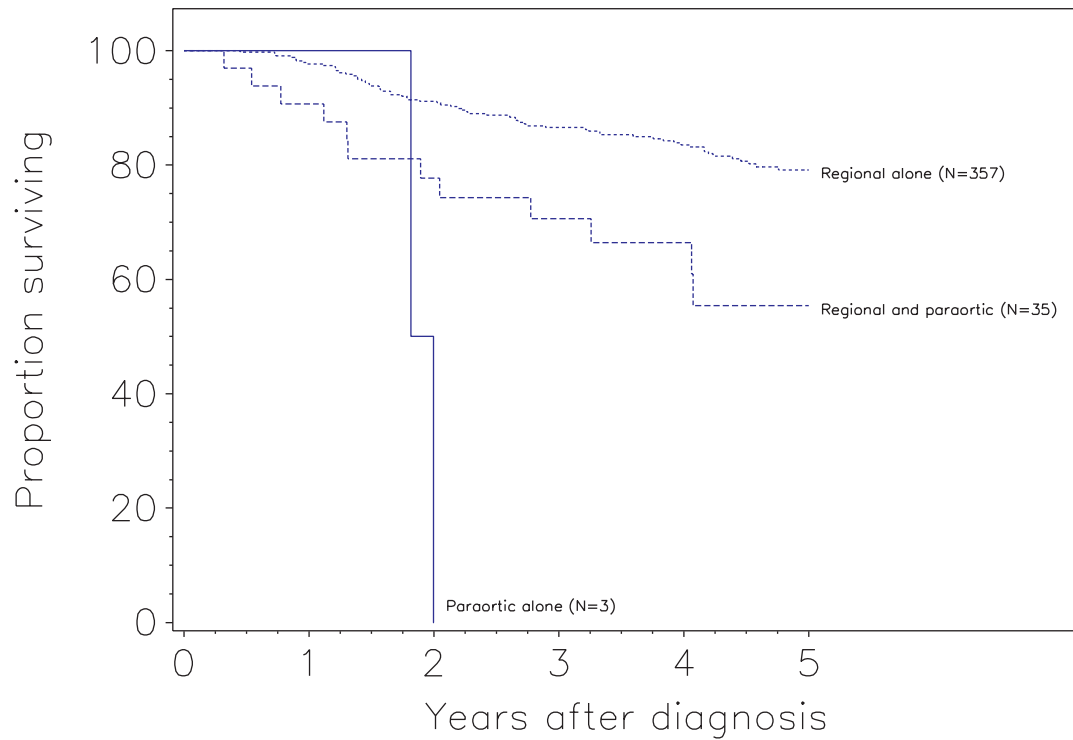
Fig. 44. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Overall survival of Stage IIa patients submitted to surgery alone by number of positive regional lymph nodes (cut-off 3 nodes), $n = 60$.



Lymphnodal involvement	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Negative	83	52.5	97.5	96.3	94.9	90.3	88.2	Reference
1	18	54.8	100.0	94.1	81.6	69.0	69.0	3.1 (0.9–11.3)
>1	37	47.9	97.3	85.9	76.1	68.5	68.5	3.8 (1.3–11.3)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

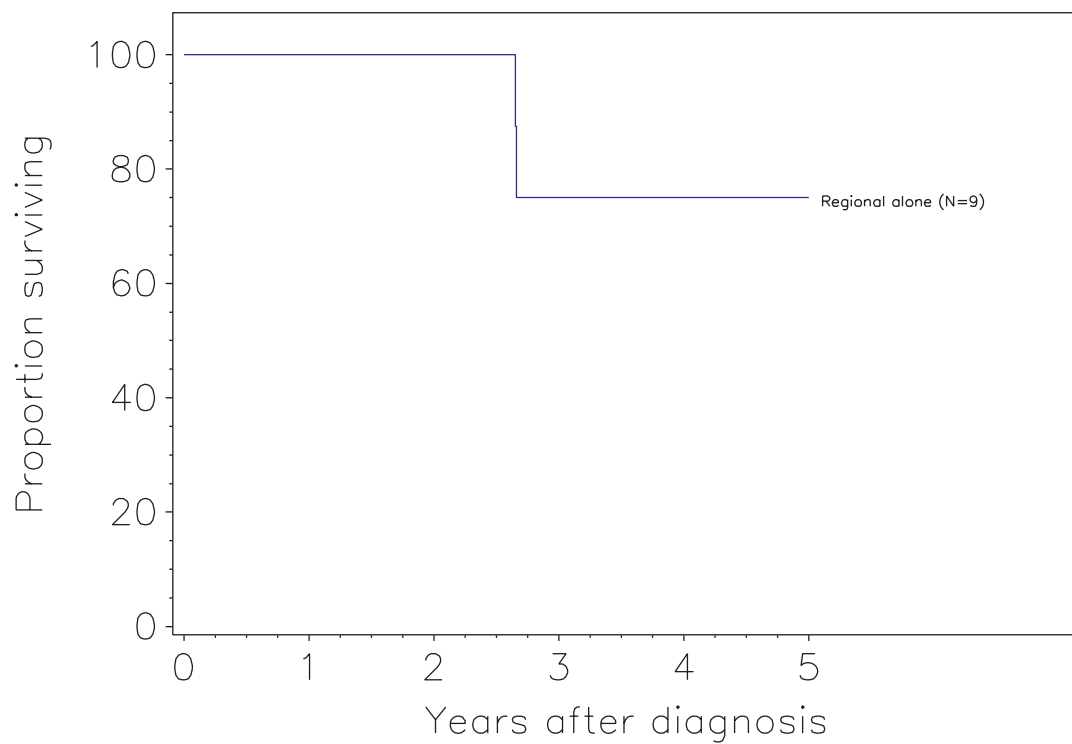
Fig. 45. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Overall survival of Stage IIa patients submitted to surgery + adjuvant RT by number of positive regional lymph nodes (cut-off 3 nodes), $n = 138$.



Lymphnodal involvement	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Regional alone	357	45.8	97.7	91.2	86.6	83.6	79.0	Reference
Regional and paraortic	35	46.7	91.0	78.0	70.8	66.4	53.1	4.0 (1.9–8.2)
Paraortic alone	3	47.3	100.0	–	–	–	–	14.5 (2.9–72.8)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

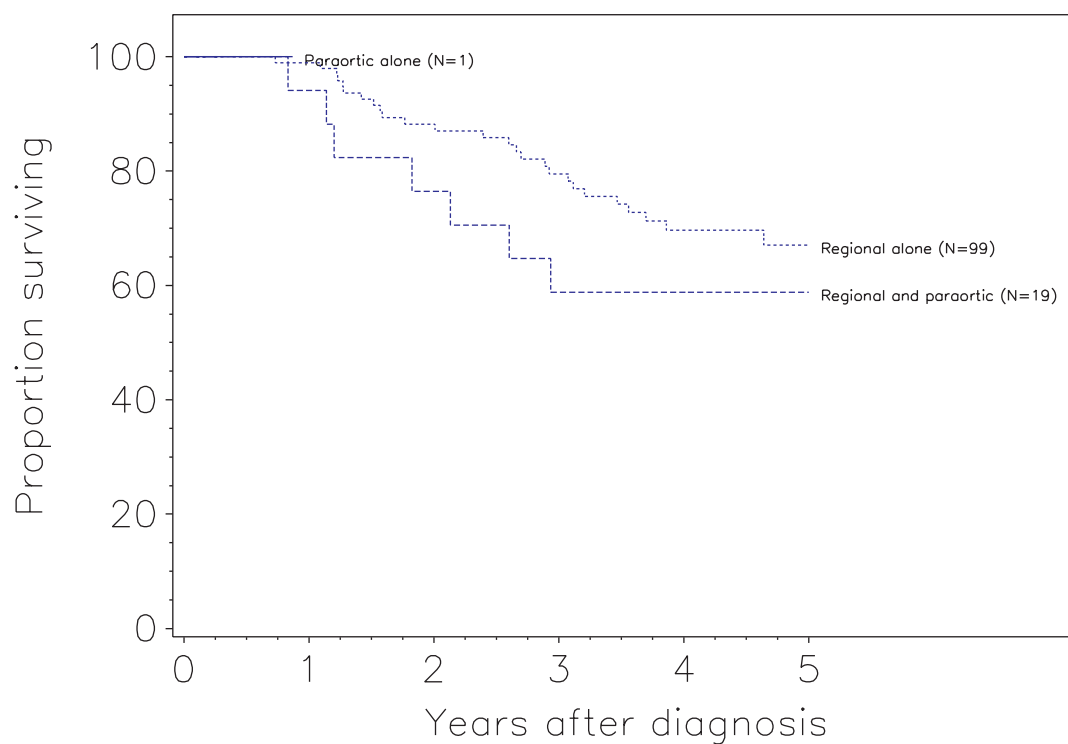
Fig. 46. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Overall survival of Stage Ib1 patients with lymphnodal involvement (stratified as regional alone, regional and paraortic, paraortic alone), $n=395$.



Lymphnodal involvement	Patients (<i>n</i>)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Regional alone	162	42.4	94.3	83.8	72.9	69.1	62.2	Reference
Regional and paraortic	7	48.1	85.7	85.7	57.1	57.1	57.1	2.0 (0.5–9.0)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

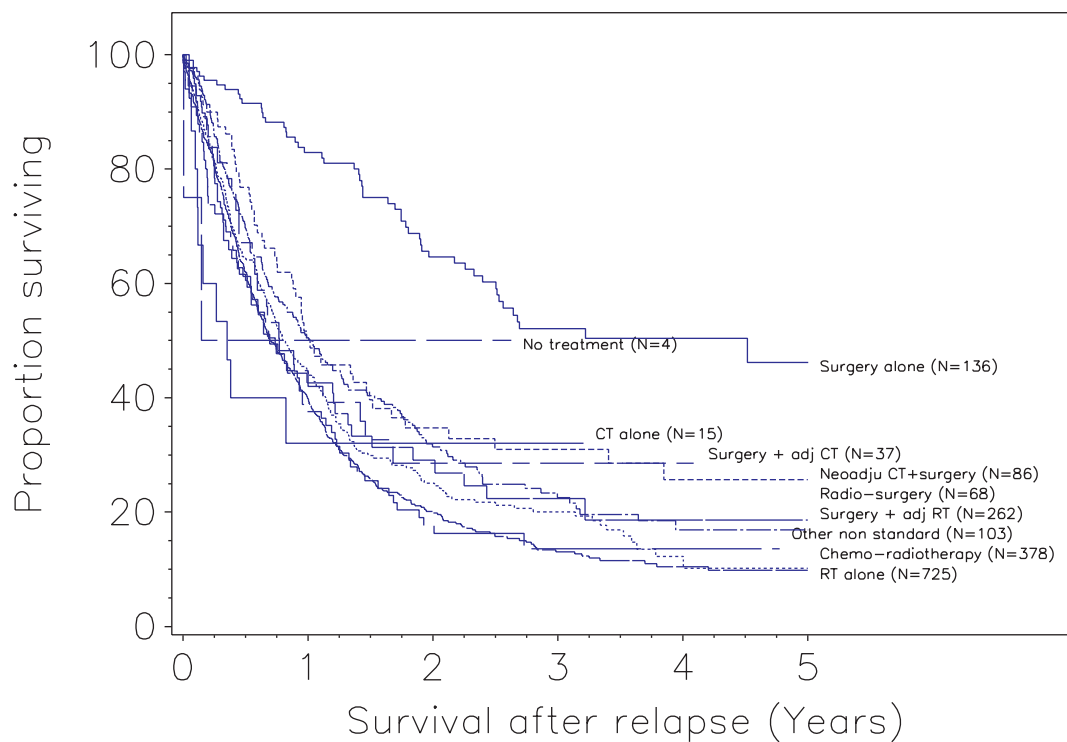
Fig. 47. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Overall survival of Stage Ib2 patients with lymphnodal involvement (stratified as regional alone, regional and paraortic, paraortic alone), *n* = 169.



Lymphnodal involvement	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Regional alone	99	48.6	99.0	88.0	79.4	69.1	66.9	Reference
Regional and paraortic	19	51.3	94.4	76.7	59.0	59.0	59.0	2.4 (0.9–6.3)
Paraortic alone	1	52.0	–	–	–	–	–	–

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

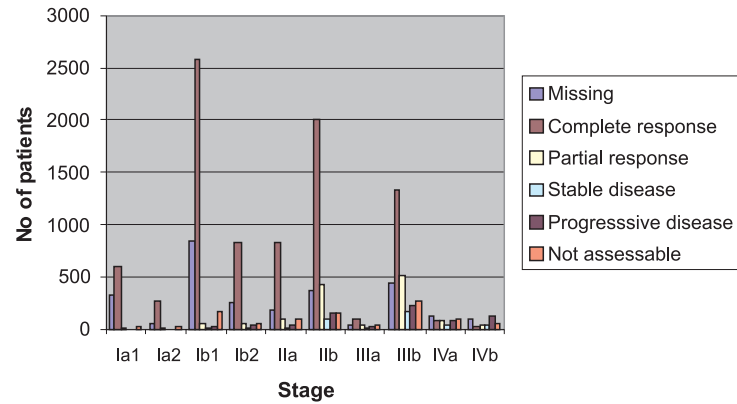
Fig. 48. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Overall survival of Stage IIa patients with lymphnodal involvement (stratified as regional alone, regional and paraortic, paraortic alone), $n = 119$.



Treatment	Patients (n)	Mean age (yrs)	Overall survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
No treatment	4	63.0	42.9	42.9	—	—	—	2.5 (0.6–10.7)
Surgery alone	136	46.9	83.0	65.2	51.5	49.6	45.7	Reference
Radiotherapy alone	725	56.0	43.8	21.5	14.4	11.6	10.7	3.4 (2.4–4.7)
Radio-surgery	68	49.4	44.2	30.4	22.5	17.5	17.5	2.7 (1.7–4.2)
Neoadjuvant CT + surgery	86	45.8	52.3	35.7	31.6	26.3	26.3	2.3 (1.5–3.5)
Surgery + adjuvant RT	262	47.2	51.5	32.4	23.1	17.4	17.4	2.5 (1.8–3.4)
Surgery + adjuvant CT	37	50.4	45.2	27.8	27.8	27.8	—	3.4 (2.1–5.7)
Chemo-radiotherapy	378	51.3	48.0	26.7	21.0	13.2	10.2	3.0 (2.1–4.2)
Chemotherapy alone	15	55.3	31.0	31.0	31.0	—	—	4.8 (2.3–10.1)
Other non-standard treatment	103	47.0	39.6	18.5	14.8	14.8	—	3.1 (2.1–4.5)

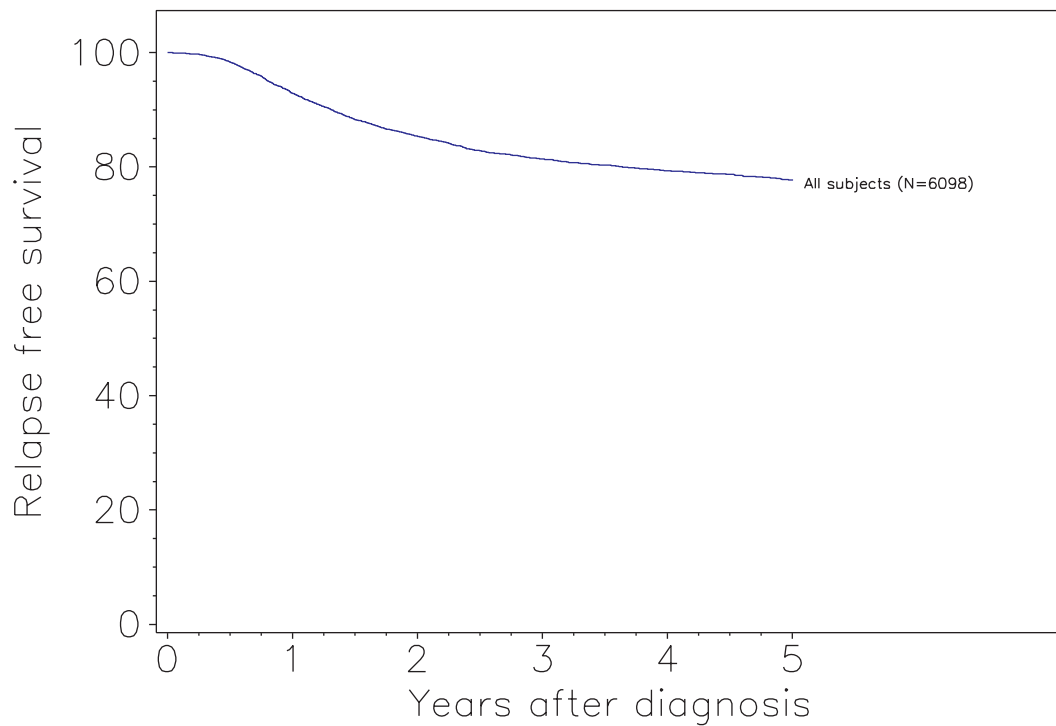
^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

Fig. 49. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Overall survival from recurrence in relapsed patients by mode of primary treatment, $n = 1814$.



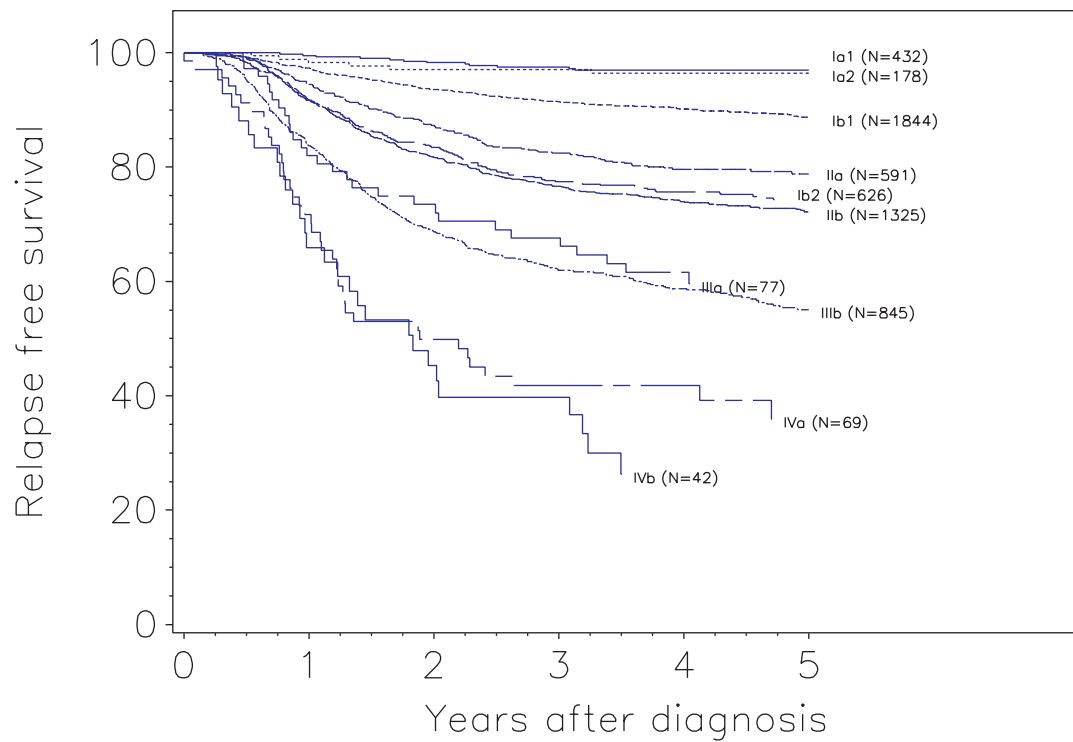
Response	Ia1	Ia2	Ib1	Ib2	IIa	IIb	IIIa	IIIb	IVa	IVb
Missing	323	62	847	257	179	368	47	438	117	94
Complete response	599	279	2594	827	822	2005	97	1325	71	27
Partial response	8	8	65	66	96	426	51	519	69	47
Stable disease	4	4	18	19	19	99	16	166	40	49
Progressive disease	1	5	38	43	47	154	23	222	80	125
Not assessable	33	26	164	63	86	157	40	276	95	56

Fig. 50. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Response to treatment by stage.



	Patients (n)	Mean age (yrs)	Relapse-free survival (%) at				
			1 year	2 years	3 years	4 years	5 years
All subjects	6098	51.1	92.9	85.4	81.4	79.3	77.7

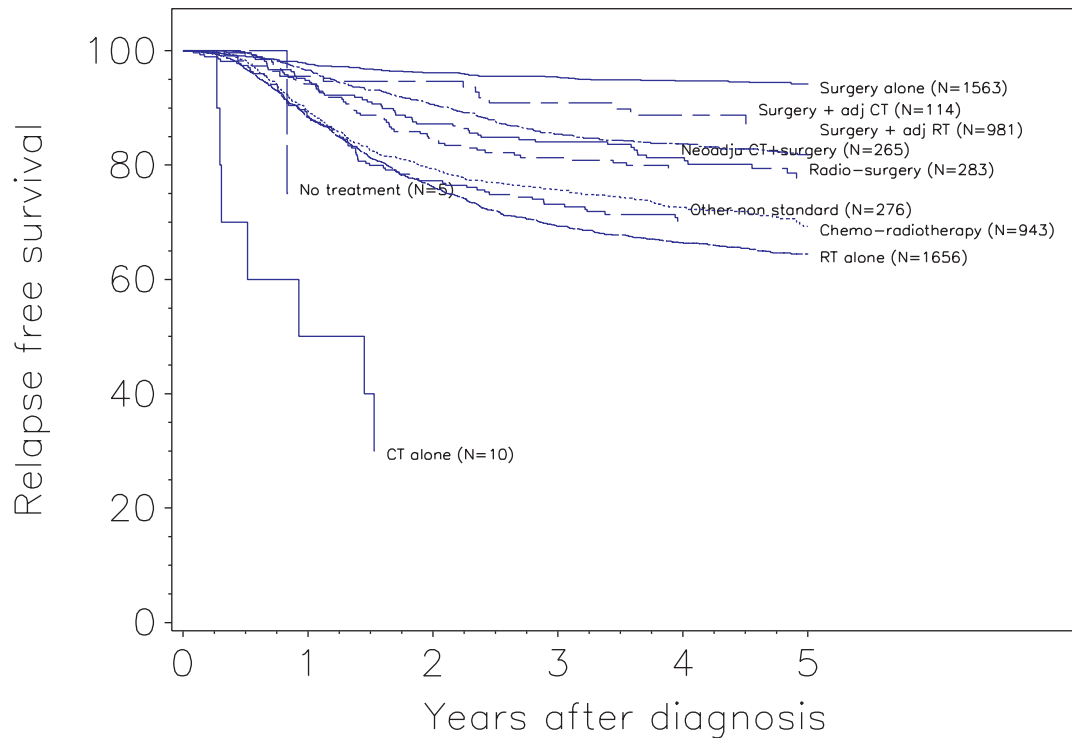
Fig. 51. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Relapse-free survival, $n = 6098$.



Stage	Patients (n)	Mean age (yrs)	Relapse-free survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Ia1	432	45.3	99.5	98.3	97.5	96.9	96.9	0.2 (0.1–0.4)
Ia2	178	46.8	98.3	97.1	97.1	96.4	96.4	0.3 (0.2–0.7)
Ib1	1844	48.7	97.3	93.5	91.4	90.2	88.7	} Reference
Ib2	626	46.9	91.7	83.5	77.4	75.7	74.3	
IIa	591	54.6	94.5	87.3	82.4	79.4	78.8	1.6 (1.3–2.0)
IIb	1325	53.2	91.7	81.7	76.6	73.9	72.2	2.1 (1.8–2.5)
IIIa	77	61.3	82.6	73.9	68.0	61.5	59.1	3.7 (2.5–5.4)
IIIb	845	56.1	83.8	68.7	62.0	58.8	55.3	3.7 (3.2–4.4)
IVa	69	58.7	71.6	49.8	41.4	41.4	35.7	6.4 (4.6–9.0)
IVb	42	57.1	65.9	45.2	39.5	26.4	26.4	10.6 (7.1–15.8)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age and country

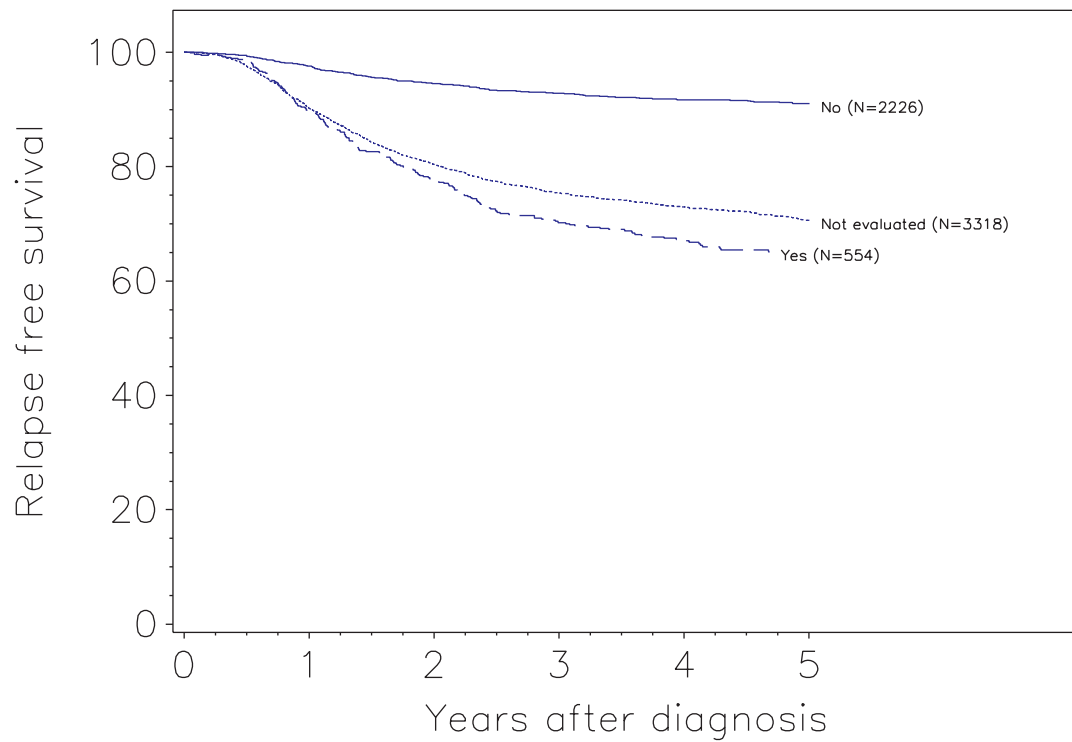
Fig. 52. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Relapse-free survival by FIGO stage, $n=6029$.



Treatment	Patients (n)	Mean age (yrs)	Relapse-free survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
No treatment	5	56.8	77.8	77.8	77.8	77.8	—	4.4 (0.6–33.4)
Surgery	1563	45.9	97.6	96.2	95.4	94.7	94.2	Reference
Radiotherapy	1656	59.1	88.4	76.3	69.4	66.5	64.5	4.4 (3.2–5.9)
Radio-surgery	283	47.4	94.9	87.3	84.1	81.2	77.8	2.6 (1.7–3.8)
Neoadjuvant CT + surgery	265	45.8	94.2	84.7	81.3	79.4	79.4	2.6 (1.8–3.8)
Surgery + Adjuvant RT	981	49.2	96.6	90.6	85.4	83.6	81.8	2.4 (1.8–3.1)
Surgery + Adjuvant CT	114	45.6	95.5	94.6	90.8	88.6	86.9	1.7 (0.9–3.0)
chemo-radiotherapy	943	52.4	89.3	79.3	75.7	72.5	69.7	3.4 (2.5–4.6)
Chemotherapy	10	62.6	50.0	27.8	27.8	27.8	27.8	16.2 (6.8–38.4)
Other non-standard treatment	276	44.8	88.6	77.2	73.2	70.1	70.1	3.7 (2.6–5.3)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age, FIGO stage and country

Fig. 53. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Relapse-free survival by treatment age, $n = 6096$.



Lymphnodal status	Patients (n)	Mean age (yrs)	Relapse-free survival (%) at					Hazards ratio ^a (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Negative	3318	54.7	90.2	80.5	75.4	72.9	70.7	Reference
Positive	554	45.6	89.8	77.7	70.2	67.0	64.8	3.3 (2.6–4.0)
Unknown	2226	47.0	97.6	94.5	92.9	91.7	91.1	2.7 (2.2–3.3)

^a Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age, FIGO stage and country

Fig. 54. Carcinoma of the cervix uteri: Patients treated in 1999–2001. Relapse-free survival by lymphnodal status, $n=6098$.

Table 12
Carcinoma of the cervix uteri: Patients treated in 1999–2001. Multivariate analysis

Strata	Hazards ratio (95% CI) ^a			
	Stage I	Stage II	Stage III	Stage IV
Age				
Aged <50	Reference	Reference	Reference	Reference
Aged ≥50	1.45 (1.22–1.71)	1.01 (0.89–1.14)	1.01 (0.89–1.15)	1.05 (0.87–1.27)
Histological type				
No/biopsy negative	2.00 (1.15–3.50)	1.24 (0.72–2.13)	1.36 (0.78–2.39)	0.40 (0.17–0.90)
Epidermoid	Reference	Reference	Reference	Reference
Adenocarcinoma	1.94 (1.56–2.41)	1.39 (1.14–1.69)	1.51 (1.22–1.88)	1.46 (1.06–1.99)
Adenosquamous carcinoma	1.20 (0.87–1.67)	1.16 (0.84–1.61)	1.24 (0.92–1.65)	1.76 (1.19–2.60)
Clear cell carcinoma	2.55 (1.33–4.89)	0.81 (0.26–2.57)	3.23 (1.20–8.73)	1.31 (0.47–3.65)
Other	2.09 (1.38–3.14)	1.37 (0.93–2.02)	1.60 (1.13–2.27)	2.41 (1.62–3.58)
Grade				
Grade 1	Reference	Reference	Reference	Reference
Grade 2	1.82 (1.32–2.49)	1.00 (0.78–1.29)	0.97 (0.77–1.23)	0.85 (0.52–1.37)
Grade 3	2.52 (1.82–3.48)	1.20 (0.92–1.56)	1.15 (0.90–1.46)	0.99 (0.61–1.61)
Grade unknown	1.41 (1.02–1.97)	1.02 (0.79–1.32)	1.06 (0.84–1.35)	1.09 (0.67–1.76)
Lymphovascular space involvement				
Absent	Reference	Reference	Reference	Reference
Present	2.17 (1.56–3.03)	1.61 (1.12–2.31)	1.27 (0.90–1.78)	1.41 (0.82–2.44)
Unknown	1.78 (1.32–2.41)	1.38 (1.02–1.86)	0.92 (0.69–1.23)	1.48 (0.90–2.42)
Tumor size				
>4 cm	2.03 (1.49–2.76)	1.58 (1.36–1.85)	1.39 (1.16–1.67)	1.18 (0.87–1.60)
≤4 cm	Reference	Reference	Reference	Reference
Tumor size unknown	1.00 (0.75–1.34)	1.29 (1.02–1.62)	1.41 (1.14–1.76)	1.09 (0.77–1.54)
Lymphnodal status				
Negative	Reference	Reference	Reference	Reference
Positive	3.83 (3.01–4.86)	2.37 (1.75–3.22)	1.52 (0.85–2.72)	1.36 (0.53–3.50)
Unknown	3.13 (2.52–3.88)	2.12 (1.63–2.75)	1.87 (1.16–3.03)	1.82 (0.78–4.27)

^a From Cox proportional hazard regression model, also adjusted for country