Recurrent cervical carcinoma after radical hysterectomy and pelvic lymph node dissection: a study of 32 cases

B. Piura[1], *M.D., F.R.C.O.G.*; **A. Rabinovich**[1], *M.D.*; **M. Friger**[2], *Ph.D.*

[1]Unit of Gynecologic Oncology, Department of Obstetrics and Gynecology, and [2]Department of Epidemiology, Soroka Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva (Israel)

Summary

Purpose of investigation: To investigate the characteristics of patients with recurrent cervical carcinoma after radical hysterectomy and pelvic lymph node dissection (RHND), and to evaluate the effect of clinical and surgical pathologic factors on the outcome of these patients. *Methods:* Data from the files of 32 patients with recurrent cervical carcinoma after RHND managed at the Soroka Medical Center from 1962 through 2005 were analyzed. *Results:* These 32 patients represent a recurrence rate of 25.4%. The median recurrence-free interval was 19.3 (range, 1-106) months. The prevailing signs and symptoms were obstructive nephropathy, sacral pain and bowel obstruction. Sixteen (50%) patients had loco-regional recurrence alone, 12 (27.5%) loco-regional plus distant recurrence, and four (12.5%) distant recurrence alone. Treatment modalities included radiotherapy, chemotherapy and various surgical procedures. The 5-year survival rate was 35%, with 22 (68.7%) of the patients dead of disease at the end of follow-up. Univariate analysis demonstrated a significant worsening in survival with each of the following factors: loco-regional plus distant recurrence (p = 0.010), positive pelvic lymph nodes (p = 0.010), tumor size ≥ 3 cm (p = 0.013), positive lymph vascular space involvement (p = 0.017) and RHND without bilateral salpingo-oophorectomy (p = 0.042). In a multivariate analysis, extent of recurrent disease (loco-regional alone versus loco-regional plus distant recurrence) and pelvic lymph node status (negative vs positive) at RHND were the only significant predictors of survival. Uremia was the most common cause of death. *Conclusions:* Recurrent cervical carcinoma after RHND is a grave disease with unfavorable prognosis. In both univariate and multivariate analyses, extent of recurrent disease and pelvic lymph node status at RHND were significant predictors of survival.

Key words: Cervical carcinoma; Radical hysterectomy; Recurrence; Prognostic factors; Survival.

Introduction

Recurrent cervical carcinoma after primary treatment with radical hysterectomy and pelvic lymph node dissection (RHND) and/or pelvic radiotherapy poses a grave therapeutic problem. Most patients with recurrent cervical carcinoma after RHND have already exhausted pelvic radiotherapy in a postoperative adjuvant setting and cannot tolerate further pelvic radiotherapy. Although these patients are usually candidates for systemic chemotherapy, and/or irradiation to extra-pelvic sites, and/or various surgical procedures in a palliative setting, the prognosis is most often dismal [1-9]. The Soroka Medical Center (SMC) in Beer-Sheva is the only tertiary care medical facility in the south of Israel that provides hospital care for a population of approximately 500,000 inhabitants. From January 1962 through October 2005, 126 patients with early-stage cervical carcinoma (FIGO clinical Stages IA_2-IIA), were treated by RHND and followed-up at the SMC. Notably, 122 (96.8%) of the 126 patients were treated and followed-up between January 1981 and October 2005. In a study of these 126 patients published previously in this journal, we demonstrated that positive lymph vascular space invasion is the strongest and most significant predictor of positive pelvic

lymph nodes [10]. In another study of these 126 patients published previously in this journal, we showed that pelvic lymph node status is the strongest factor influencing the decision of whether or not to administer adjuvant pelvic radiotherapy after RHND and the most significant predictor of survival [11]. Of these 126 patients, 32 (25.4%) had developed recurrent disease. The aims of this study were (1) to investigate the characteristics, pattern of recurrence and treatment of patients with recurrent cervical carcinoma after RHND and (2) to evaluate the effect of clinical and surgical pathologic factors on the outcome of these patients.

Patients and Methods

The clinical and pathological records of 32 patients with recurrent cervical carcinoma after RHND treated and followed-up at the SMC between January 1962 and October 2005 were reviewed. The surgical technique performed with RHND was consistent with a Class III extended hysterectomy as described by Piver *et al*. [12]. The pelvic lymph node dissection consisted of removal of all lymphatic tissue around the common, external, and internal iliac vessels and anterior to the obturator nerve. For patients who received postoperative adjuvant pelvic radiotherapy, it consisted of external megavoltage photonic irradiation employing a 10 MeV linear accelerator usually delivering 4,500-5,040 cGy to the whole pelvis in daily fractions of 180 cGy via an AP-PA opposed fields or the four-field box technique. This was usually followed by two vaginal intracavitary

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applications of brachytherapy using cesium-137 (each application, 2,000 cGy) via a vaginal cylinder (Delclos) or ovoids (colpostats). Since January 2000, external pelvic radiotherapy was given as a rule concomitantly with intravenous chemotherapy composed of weekly cisplatin 40 mg/m^2. After a thorough record review, all patients were retrospectively staged according to the revised FIGO staging system for gynecologic cancer [13]. Recurrences were documented with histopathologic examination when possible. Thorough investigations were conducted to delineate the site and extent of recurrent disease including physical examination, chest X-ray, abdominal and pelvic computerized tomography, cystoscopy, rectoscopy, and bone isotopic scan. Sites of tumor recurrence were categorized as vaginal cuff, pelvic, vaginal cuff plus distant recurrence, pelvic plus distant recurrence, and distant alone. Vaginal cuff recurrence was defined as recurrence involving the vaginal cuff only without involvement of other pelvic organs. Pelvic recurrence was defined as recurrence involving at least one of the following pelvic organs: the bladder, rectum, pelvic lymph nodes, and pelvic sidewall. If recurrent disease was found to involve both the vaginal cuff and at least one of the aforementioned pelvic organs, the recurrence was categorized as pelvic recurrence. Vaginal cuff recurrences and pelvic recurrences were grouped under the heading of loco-regional recurrences. Distant recurrence was defined as tumor involving organs outside the pelvis. The following data were retrieved from the files of the patients: age at initial diagnosis, menopausal status, clinical stage at initial diagnosis, handling of ovaries during RHND, pathological findings, administration of adjuvant radiotherapy, length of recurrence-free interval, signs and symptoms of recurrence, sites of recurrence, method of therapy for recurrent disease, results of follow-up and direct cause of death (if applicable).

Differences between patient groups were tested by the chi-square test with Yates' correction for small numbers [14]. Survival was calculated using the Kaplan-Meier method [15] and compared statistically with use of the log-rank test [16]. Multivariate analysis using the Cox proportional hazards regression analysis [17] was employed to evaluate the joint effects of clinical and surgical pathologic variables on survival. Only p values < 0.05 were considered statistically significant.

Results

Patient characteristics are displayed in Table 1. The mean number of pelvic lymph nodes removed per patient during RHND was 25.9 (median, 21.5; range, 1-62). Positive pelvic lymph nodes were found in 14 (43.7%) of the 32 patients. The mean number of positive pelvic lymph nodes per patient in patients with positive pelvic lymph nodes was 4.4 (median, 3; range, 1-15). Lower paraaortic lymph node sampling was performed during RHND in 15 (46.8%) of the 32 patients with a mean of 0.72 (median, 1; range, 0-2) lymph nodes removed per patient. All paraaortic lymph nodes removed were negative for metastases. Eighteen (56.2%) of the 32 patients had adjuvant pelvic radiotherapy after RHND; 11 (34.3%) received external pelvic irradiation (XRT) followed by brachytherapy (BT), six (18.7%) received XRT alone, and one (3.1%) received BT alone. In two of the 11 patients who received XRT followed by BT and in one of the six patients who received XRT alone, the XRT was given concomitantly with intravenous systemic

Table 1. — *Patient characteristics (32 patients).*

	No.	%
Age at initial diagnosis (years)		
Mean	46.8	
Range	24-71	
Menopausal status		
Premenopausal	17	53.1
Postmenopausal	15	46.9
Stage at initial diagnosis		
IA$_2$	1	3.1
IB$_1$	17	53.1
IB$_2$	7	21.9
IIA	7	21.9
Histologic type		
Squamous cell carcinoma	22	68.8
Adenosquamous carcinoma	5	15.6
Adenocarcinoma	3	9.4
Verrucous carcinoma	1	3.1
Clear cell carcinoma	1	3.1
Grade		
1	8	25
2	8	25
3	16	50
Handling of ovaries during RHND		
Both ovaries removed	20	62.5
At least one ovary preserved	12	37.5
Adjuvant radiotherapy		
No	14	43.7
Yes	18	56.2

RHND, radical hysterectomy and pelvic lymph node dissection.

chemotherapy (5 courses of weekly cisplatin 40 mg/m^2). The total dose of XRT per patient ranged from 3,960 cGy to 9,960 cGy (mean, 5,482 cGy; median, 5,040 cGy). The total dose of BT per patient ranged from 1,500 cGy to 6,080 cGy (mean, 3,223 cGy; median, 3,500 cGy).

The median time to recurrence was 19.3 (mean, 24.9; range, 1-106) months; 20 (62.5%) patients recurred within two years after RHND (12 during the first year and 8 during the second year), whereas 12 (37.5%) recurred from two to 8.83 years after RHND. Signs and symptoms of recurrent disease are listed in Table 2. The prevailing signs and symptoms were obstructive nephropathy (14 patients, 43.7%), sacral pain (9 patients, 28.1%) and bowel obstruction (5 patients, 15.6%). Specific sites of recurrence were the vaginal cuff alone in five (15.6%) patients, pelvic – 11 (34.4%), vaginal cuff + distant recurrence – two (6.2%), pelvic + distant – ten (31.2%), and distant recurrence alone – four (12.5%). Overall, 16 (50%) patients had loco-regional recurrence alone (vaginal cuff and/or pelvis), 12 (27.5%) loco-regional plus distant recurrence, and four (12.5%) distant recurrence alone. Thus, loco-regional recurrence occurred in 28 (87.5%) patients and distant recurrence in 16 (50%). Distant sites of recurrence are listed in Table 3. The most common sites of distant recurrence were the lungs (8 patients, 25%) and bones (7 patients, 21.8%). Treatment modalities for recurrent disease are listed in Table 4. Twenty-four (75%) of the 32 patients had radiotherapy and/or chemotherapy for recurrent disease; nine had radiotherapy, six radiotherapy followed by

Table 2. — *Signs and symptoms of recurrent cervical carcinoma (32 patients).*

Signs and symptoms	Number of patients	%
Obstructive nephropathy	14	43.7
Sacral pain	9	28.1
Bowel obstruction	5	15.6
Vaginal bleeding	4	12.5
Leg deep vein thrombosis	2	6.2
Inguinal lymphadenopathy	2	6.2
Leg lymphedema	1	3.1
Back pain,	1	3.1
Leg pain	1	3.1
Perineal lesion	1	3.1
Hematuria	1	3.1
Pleural effusion	1	3.1
Abdominal swelling	1	3.1
Mediastinal lymphadenopathy	1	3.1

Note: Some patients had more than one sign or symptom; therefore, the number of patients adds up to more than 32.

Table 3. — *Distant sites of recurrent disease (16 patients).*

Site	Number of patients	%
Lung	8	25
Bone	7	21.8
Liver	4	12.5
Inguinal lymph node	2	6.2
Paraaortic lymph node	2	6.2
Perineum	1	3.1
Abdominal wall	1	3.1
Omentum	1	3.1
Mediastinum	1	3.1
Brain	1	3.1

Note: Some patients had more than one distant recurrent site; therefore, the number of patients adds up to more than 16.

Table 4. — *Treatment modalities for recurrent disease (32 patients).*

Treatment	Number of patients	%
Radiotherapy	22	
Chemotherapy	15	
Surgery	5	
Nephrostomy	10	
Ureteric stent	1	
Colostomy	2	
Ileostomy	1	
Pleurodesis	1	

Note: Some patients had more than one treatment modality; therefore, the number of patients adds up to more than 32.

chemotherapy, seven chemotherapy followed by radiotherapy, and two chemotherapy. Overall, 22 (68.7%) of the 32 patients had radiotherapy and 15 (46.9%) chemotherapy. Of the 22 patients who had radiotherapy for recurrent disease, 13 had not received adjuvant pelvic radiotherapy after RHND and nine had received adjuvant pelvic radiotherapy after RHND. All 13 radiotherapy-naïve patients had pelvic radiotherapy for loco-regional recurrent disease, whereas the nine patients who had already exhausted pelvic radiotherapy for their primary disease received radiotherapy for recurrent disease to sites other than the pelvis. Of the 15 patients who had chemotherapy for recurrent disease, six patients had cis-

platin + 5-fluorouracil (5-FU), three - single-agent cisplatin, one - cisplatin + 5-FU followed by carboplatin + ifosfamide, one - cisplatin + 5-FU followed by doxorubicin, one - BIP (bleomycin + ifosfamide + cisplatin), one - cisplatin + 5-FU followed by BIP, one - BIP followed by paclitaxel (taxol), and one - BIP followed by BIC (bleomycin + ifosfamide + carboplatin) followed by vinorelbine. Five (15.6%) of the 32 patients had various surgical procedures for recurrent disease; these included inguinal lymphadenectomy for inguinal lymph node metastases in two patients, anterior exenteration for central pelvic recurrence involving the bladder in one, amputation of the leg below the knee for tibial metastases in one, resection of the ischial bone in one, and resection of an abdominal mass in one. Obstructive nephropathy was managed by unilateral percutaneous nephrostomy (PCN) in ten (31.2%) patients, and insertion of ureteric stent in one patient. Bowel obstruction was handled by colostomy in two patients and ileostomy in one patient. Pleural effusion was managed by pleurodesis in one patient.

Follow-up after detection of recurrent disease ranged from 1-241 months, with eight (25%) of the 32 patients followed for at least five years or until the time of death. No patients were lost to follow-up; 22 (68.7%) patients had died of disease, one (3.1%) had died of intercurrent disease, eight (25%) were alive free of disease, and one (3.1%) was alive with disease. The cumulative 1-, 2-, 3-, 4-, and 5-year survival rates after detection of recurrence were 66%, 46%, 39%, 35% and 35%, respectively. Notably, none of the five patients with vaginal cuff recurrence alone were dead of recurrent disease at the end of follow-up. Two (50%) of the four patients with distant recurrence alone were dead of disease at the end of follow-up. Outcome, pelvic lymph node status at RHND and length of recurrence-free interval ($\leq$ 2 years vs > 2 years) in relation to recurrence site in the 28 patients with loco-regional ± distant recurrence are displayed in Table 5. Eight (50%) of 16 patients with loco-regional recurrence alone were dead of disease at the end of follow-up, whereas all 12 patients (100%) with loco-regional + distant recurrence were dead of disease at the end of

Table 5. — *Recurrence site (loco-regional vs loco-regional + distant) in relation to pelvic lymph node status at RHND, recurrence-free interval, and number of patients dead of disease at the end of follow-up (28 patients).*

Site of recurrence	No. of patients	Pelvic lymph node status at RHND		Recurrence-free interval		Dead of disease
		Negative	Positive	$\leq$ 2 years	> 2 years	
Loco-regional	16	12	4	8	8	8
Loco-regional + Distant	12	4	8	8	4	12
Total	28	16	12	16	12	20

Note: The difference in the proportion of patients dead of disease between loco-regional recurrence alone and loco-regional + distant recurrence is significant ($X^2Y = 11.02$; $p < 0.001$). The difference in the proportion of patients with positive pelvic lymph node at RHND between loco-regional recurrence alone and loco-regional + distant recurrence is of borderline significance ($X^2Y = 3.3$; $0.1 > p > 0.05$). The difference in the proportion of patients with recurrence-free interval $\leq$ 2 years between loco-regional recurrence alone and loco-regional + distant recurrence was not significant ($X^2Y = 1.6$; $p > 0.1$).

follow-up; this difference was statistically significant ($X^2Y = 11.02$; $p < 0.001$) (Table 5). The difference with respect to pelvic lymph node status at RHND between patients with loco-regional recurrence alone and patients with loco-regional + distant recurrence was of borderline significance ($X^2Y = 3.3$; $0.1 > p > 0.05$) (Table 5). The difference with respect to length of recurrence-free interval (≤ 2 years vs > 2 years) between patients with loco-regional recurrence alone and patients with loco-regional + distant recurrence was not significant ($X^2Y = 1.6$; $p > 0.1$) (Table 5). Univariate analysis with use of the log-rank test demonstrated a significant worsening in survival from recurrent cervical carcinoma with each of the following factors: loco-regional recurrence in conjunction with distant recurrence ($p = 0.010$), positive pelvic lymph nodes at RHND ($p = 0.010$), tumor size ≥ 3 cm at RHND

Table 6. — *Univariate analysis with use of the log-rank test of clinical and surgical pathologic factors in relation to 5-year survival in patients with recurrent cervical carcinoma after radical hysterectomy and pelvic lymph node dissection.*

Factor	Number of patients	5-year survival	p value
Recurrence site			
Loco-regional	16	48.1%	
Loco-regional + distant	12	0.0%	0.010
Positive pelvic lymph nodes at RHND			
No	18	51.8%	
Yes	14	14.3%	0.010
Tumor size at RHND			
< 3 cm	13	56.4%	
≥ 3 cm	12	16.7%	0.013
Lymph vascular space invasion at RHND			
No	16	54.1%	
Yes	13	7.7%	0.017
RHND			
Without BSO	12	22.2%	
With BSO	18	50.0%	0.042
Parametrial/paracervical involvement at RHND			
No	21	40.4%	
Yes	7	0.0%	0.069
Vaginal margin involvement at RHND			
No	22	25.3%	
Yes	7	45.7%	0.089
Penetration of cervical wall at RHND			
< 50%	9	53.3%	
≥ 50%	18	26.7%	0.219
Adjuvant radiotherapy after RHND			
No	14	48.2%	
Yes	18	25.9%	0.310
Stage at RHND			
IA2+IB1	18	41.9%	
IB2+IIA	14	25.7%	0.398
Recurrence-free interval			
≤ 2 years	20	30.0%	
> 2 years	12	45.7%	0.448
Lower uterine segment involvement at RHND			
No	19	34.1%	
Yes	10	25.0%	0.998

Note: Information regarding survival was available for 32 patients. Some factors were not available for all patients; therefore, the number of patients in some of the patient groups adds up to less than 32.
RHND, radical hysterectomy and pelvic lymph node dissection; BSO, bilateral salpingo-oophorectomy.

($p = 0.013$), positive lymph vascular space involvement at RHND ($p = 0.017$) and RHND without bilateral salpingo-oophorectomy ($p = 0.042$), whereas positive parametrial and/or paracervical involvement at RHND ($p = 0.069$) and positive or close vaginal margin involvement at RHND ($p = 0.089$) were of borderline significance (Table 6). Univariate analysis failed to demonstrate a significant worsening in survival with each of the following clinical and surgical pathologic factors: penetration $\geq 50\%$ of the thickness of the cervical wall at RHND ($p = 0.219$), administration of adjuvant radiotherapy after RHND ($p = 0.310$), Stage IB2 + IIA at RHND ($p = 0.398$), recurrence-free interval ≤ 2 years ($p = 0.448$) and positive lower uterine segment involvement at RHND ($p = 0.998$) (Table 6). Multivariate analysis with use of the Cox proportional hazards regression analysis of clinical and surgical pathologic variables with endpoint death demonstrated after sequential elimination by backward stepwise logistic regression of non-significant factors ("better fit" model) that recurrence site (loco-regional alone vs loco-regional + distant recurrence) and pelvic lymph node status at RHND were the only significant predictors of survival from recurrent cervical carcinoma (Table 7). Uremia was recorded as the direct cause of death in 12 (54.5%) of the 22 patients who were dead of disease at the end of follow-up; other direct causes of death included sepsis, pulmonary embolism and brain metastases.

Table 7. — *Multivariate analysis (Cox proportional hazards regression analysis) of clinical and surgical pathologic variables with endpoint death in patients with recurrent cervical carcinoma after RHND. This "better fit" model was achieved after sequential removal of non-significant factors by backward stepwise logistic regression.*

Factor	Odds Ratio	95% confidence interval	p value
Recurrence site			
Loco-regional	1.000	Reference	
Loco-regional + distant	2.785	1.055-7.352	0.039
Positive pelvic lymph nodes at RHND			
No	1.000	Reference	
Yes	2.738	1.040-7.208	0.041

RHND, radical hysterectomy and pelvic lymph node dissection.

Discussion

The presently reported 32 patients represent a recurrence rate of 25.4%. Other authors have reported a recurrence rate after RHND ranging from 7.5% to 19.8% [5,6,8,18]. In this study, the median time from RHND to recurrence was 19.3 (mean, 24.9; range, 1-106) months; approximately one-third (37.5%) of the patients developed recurrent disease within one year after RHND and nearly two-thirds (62.5%) within two years. Samlal *et al.* [6] observed a median recurrence-free interval of 14 (range, 3-64) months, with 77% of the recurrences occurring within three years after RHND. Grisaru *et al.* [18] noted that the median time from initial surgery to recurrence was 14 months, with 67% of the patients having

recurrent disease within two years after initial surgery. Wang *et al*. [5] demonstrated that the median time from RHND to recurrent disease was 18.9 (range, 1.3-95.3) months, with 34.5% of patients recurring within the first 12 months after surgery, 75.5% within the first three years, and 90.4% within five years. We have observed that of the 32 patients, 16 (50%) had loco-regional recurrence alone (vaginal cuff and/or pelvis), 12 (27.5%) had loco-regional plus distant recurrence, and 4 (12.5%) had distant recurrence alone. Thus, loco-regional recurrence occurred overall in 28 (87.5%) of the 32 patients and distant recurrence occurred overall in 16 (50%). The most common sites of distant recurrence were the lungs and bones. Of the 27 patients with recurrent cervical carcinoma after RHND reported by Samlal *et al*. [6], 11 (40.7%) developed pelvic recurrence, three (11.1%) pelvic plus distant recurrence, and 13 (48.1%) distant recurrence. Of the 66 patients with recurrent cervical carcinoma after RHND documented by Grisaru *et al*. [18], 40 (60.6%) had recurrence in the pelvis, 13 (19.7%) in the pelvis plus distant sites, and 13 (19.7%) in distant sites. Wang *et al*. [5] categorized loco-regional recurrences differently from us. Central recurrence was defined as recurrence in the vaginal cuff, bladder, or rectum without involvement of the pelvic sidewall, and pelvic recurrence was defined as recurrent tumor limited to the pelvis. In a series of 177 patients with recurrent cervical carcinoma after RHND, they observed central recurrence in 36 (20.3%), pelvic in 50 (28.2%), pelvic plus distant recurrence in 23 (13%), distant recurrence in 45 (25.4%), and unknown site in 23 (13%) [5]. Like us, Wang *et al*. [5] noted that the most common sites of distant recurrence were the lungs and bones. Of the 23 patients with recurrent disease after RHND reported by Tinga *et al*. [8], seven (30.4%) had pelvic recurrence alone, one (4.3%) pelvic plus distant recurrence, and 15 (65.2%) distant recurrence.

Of the 32 patients reported in this study, 18 (56.2%) had adjuvant pelvic radiotherapy after RHND and 14 (43.7%) did not. Samlal *et al*. [6] observed that 52% (14/27) of patients with recurrent cervical carcinoma had received adjuvant pelvic radiotherapy after RHND. Wang *et al*. [5] obtained information about adjuvant treatment after RHND for 154 patients with recurrent disease; 79 (51.3%) had adjuvant pelvic radiotherapy after RHND and 75 (48.7%) did not. In this series, treatment modalities employed for recurrent cervical carcinoma after RHND included radiotherapy (22 patients), chemotherapy (15 patients) and various surgical procedures (5 patients). Various cytotoxic drugs and chemotherapy regimens have been used as salvage chemotherapy for relapsed cervical carcinoma, but the results have usually been poor and the ideal chemotherapy regimen has yet not been established [2,4,5,9]. In this study, nevertheless, cisplatin-based chemotherapy had most often been employed as salvage chemotherapy for recurrent cervical carcinoma.

Attention has traditionally been called to the development of ominous signs and symptoms of the so-called "terrible triad" (obstructive nephropathy, leg lymphedema and intractable sacral pain) in patients with cervical carcinoma. The emergence of at least one of these signs and symptoms indicates advancing loco-regional disease and predicts a dismal prognosis. In this series, obstructive nephropathy had developed in 14 (43.7%) patients and sacral pain in nine (28.1%) patients. Percutaneous nephrostomy for temporary amelioration of obstructive nephropathy had been performed in ten (31.2%) patients. The most common direct causes of death from cervical carcinoma have traditionally been uremia due to bilateral obstructive nephropathy, sepsis due to infection of ulcerated and necrotic tumor, and massive hemorrhage due to rupture of blood vessels by penetrating tumor. In this study, uremia was the most common direct cause of death.

Recurrence of cervical carcinoma after primary treatment carries a poor prognosis, which is reflected in this series by a 5-year survival of only 35%. This survival, however, is better than the 5-year survival rate of 10.1% reported by Wang *et al*. [5] in their series of 177 patients with recurrent cervical carcinoma after RHND. In this series, 22 (68.7%) of the 32 patients were dead of disease at the end of follow-up. Notably, all five patients with vaginal cuff recurrence alone were successfully treated with pelvic radiotherapy for recurrent disease and were alive with no evidence of disease at the end of follow-up. These patients could undergo pelvic radiotherapy for recurrent disease because they had not already previously exhausted pelvic radiotherapy in an adjuvant setting after RHND. Nevertheless, eight (72.7%) of the remaining 11 patients with recurrence in the pelvis beyond the vaginal cuff were dead of disease at the end of follow-up. Overall, we have observed that eight (50%) of 16 patients with loco-regional recurrence alone (vaginal cuff ± recurrence in the pelvis beyond the vaginal cuff) were dead of disease at the end of follow-up, whereas all 12 (100%) patients with loco-regional plus distant recurrence were dead of disease at the end of follow-up. Thus, we have shown that recurrence site is a significant predictor of survival. Samlal *et al*. [6] observed that 22 (81.5%) of 27 patients with recurrent disease after RHND had died of disease. Of the 11 patients who had pelvic recurrence alone, only one of the four patients with an isolated pelvic central recurrence died of disease compared with all seven patients with an isolated pelvic sidewall recurrence (p = 0.02) [6]. All three patients with pelvic plus distant recurrence died of disease, whereas 11 (84.6%) of 13 patients with distant disease alone died of disease [6]. Wang *et al*. [5] demonstrated a significantly better 5-year survival rate for patients with vaginal vault recurrence alone as compared to patients with extra-vaginal recurrence (23.9% vs 7.8%, respectively, p = 0.0007). They demonstrated by means of univariate analysis that each of the following factors: positive pelvic lymph nodes at RHND, recurrence beyond the vaginal cuff, and avoidance of any therapy for recurrent disease was significantly associated with a worse survival. In a multivariate analysis, they confirmed that positive pelvic lymph nodes

at RHND and avoidance of any therapy for recurrent disease were significantly associated with a worse survival [5]. Wang *et al*. [5] also demonstrated that the 5-year survival rate of patients who had not exhausted pelvic radiotherapy in an adjuvant setting after RHND was significantly better than that of patients who had already received pelvic radiotherapy in an adjuvant setting after RHND (19.6% vs 3.6%, respectively, p = 0.0054). This can be explained by the fact that patients who do not need adjuvant treatment after RHND represent a low-risk group (i.e., absence or minimal presence of high-risk factors) with an a priori better prognosis. Moreover, since these patients had not already exhausted pelvic radiotherapy in an adjuvant setting after RHND, pelvic radiotherapy can be given for loco-regional recurrent disease. We have demonstrated by means of univariate analysis a significant worsening in survival from recurrent cervical carcinoma after RHND with each of the following factors: loco-regional recurrence in conjunction with distant recurrence, positive pelvic lymph nodes at RHND, tumor size ≥ 3 cm at RHND, positive lymph vascular space involvement at RHND, and RHND without bilateral salpingo-oophorectomy. In a multivariate analysis, however, extent of recurrent disease (loco-regional alone vs loco-regional plus distant recurrence) and pelvic lymph node status (negative vs positive) at RHND were the only significant predictors of survival from recurrent disease.

Conclusion

One-quarter of patients with cervical carcinoma treated primarily by RHND at the SMC developed recurrent disease. Obstructive nephropathy and sacral pain were the most common signs and symptoms. Overall, loco-regional recurrence occurred in nearly 90% of the patients with recurrent disease and distant recurrence in 50%. Treatment modalities employed for recurrent cervical carcinoma included radiotherapy, chemotherapy and various surgical procedures. The prognosis was unfavorable with a 5-year survival rate of 35%. Uremia was the most common direct cause of death. Extent of recurrent disease (loco-regional alone vs loco-regional plus distant) and pelvic lymph node status (negative versus positive) at RHND were significant predictors of survival from recurrent cervical carcinoma on both univariate and multivariate analysis.

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Address reprint requests to:
B. PIURA, M.D., F.R.C.O.G.
Unit of Gynecologic Oncology
Department of Obstetrics and Gynecology
Soroka Medical Center
and Faculty of Health Sciences
Ben-Gurion University of the Negev
P.O. Box 151
84101 Beer-Sheva (Israel)
e-mail: piura@bgu.ac.il