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ORIGINAL ARTICLE – GYNECOLOGIC ONCOLOGY

Does Histologic Type Correlate to Outcome after Pelvic Exenteration for Cervical and Vaginal Cancer?

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ABSTRACT

Background. Adenocarcinoma (AC) of the cervix comprises 15–20 % of all cervical carcinomas, and data regarding the prognostic value of histologic type after pelvic exenteration (PE) are lacking. Our aim was to analyze the prognostic value of histologic type in overall survival (OS) and disease-specific survival (DSS) after PE and correlate it to clinical and pathologic variables.

Methods. We reviewed a series of 77 individuals who underwent PE for cervical or vaginal cancer from January 1980 to December 2010.

Results. Mean age was 54.5 years. Fifty-three patients (68.9 %) had cervical and 24 (31.1 %) vaginal cancer. Fifty-six (72.7 %) were squamous cell carcinoma (SCC) and 21 (27.3 %) ACs. We performed 42 (54.5 %) total, 18 anterior, 8 posterior, and 9 lateral extended PE. Median tumor size was 5 cm. Surgical margins were negative in 91.7 % of cases. Median operative time, length of hospital stay, and blood transfusion volume were, respectively, 420 (range 180–720) mins, 13.5 (range 4–79) days, and 900 (range 300–3900) ml. Median follow-up was 13.7 (range 1.09–114.3) months. SCC statistically correlated with presence of perineural invasion ($p = 0.004$). Five-year OS and DSS were, respectively, 24.4 and 37.1 %. SCC ($p = 0.003$) and grade 3 ($p = 0.001$) negatively affected OS in univariate analysis. SCC ($p = 0.006$), grade 3 ($p = 0.003$), perineural invasion ($p = 0.03$), lymph node metastasis ($p = 0.02$), and positive margins ($p = 0.04$) negatively affected DSS in univariate analysis. SCC and grade 3 retained the higher risk of death (OS and DSS) in multivariate analysis.

Conclusions. AC histology in cervical and vaginal cancer is associated with better outcome after PE compared to SCC.

Cervical cancer is the third most common cancer among women worldwide, causing approximately 500,000 new cases per year and more than 250,000 deaths.[1] In contrast, the incidence and mortality of cervical cancer has progressively decreased over the last 4 decades in developed countries.[2,3] However, an increase in both absolute and relative rates of cervical adenocarcinoma (AC) compared to squamous cell carcinoma (SCC) was found over the same period.[2–10] The current data also suggest that AC and SCC have a distinct behavior in terms of response to treatment, lymph node involvement, and pattern of recurrence. Furthermore, because AC represents only about 10 % of the cases in most of studies of cervical cancer treatment, both histologic types are usually analyzed together.[10–19] Consequently, the current knowledge on the optimal management of AC is still limited.[10]

Patients with locally advanced disease (stage IB2–IVA) currently receive definitive cisplatin-based chemoradiotherapy and can achieve a 5-year overall survival (OS) rate of 66 %.[20] However, 44 % of such patients experience a recurrence, and 35 % of recurrent tumors after radiotherapy occur exclusively in the pelvis.[20]

Pelvic exenteration (PE) refers to radical en bloc resection of multiple pelvic organs, followed by surgical reconstruction to reestablish visceral and parietal function.[21] This

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procedure was first reported by Alexander Brunschwig in 1948, and the most common indication for PE is still persistent or recurrent cervical cancer after radiotherapy.[22] However, only few patients are suitable candidates for PE.

The development of new technologies and appropriate patient selection has affected 5-year survival rates after PE that range from 20 to 73 %.[23,34] Furthermore, it remains a major surgery, with high morbidity and perioperative mortality rates that range, respectively, from 32 to 84 %, and 0–14 %.[24–28,34–40]

The aim of our study was to retrospectively analyze the prognostic role of histologic type in OS and disease-specific survival (DSS) after PE for cervical and vaginal cancer, and to correlate this to clinical and other pathologic variables.

PATIENTS AND METHODS

This retrospective analysis included 77 individuals with cervical and vaginal cancers who underwent PE at AC Camargo Cancer Hospital from August 1982 to September 2010. Our institutional review board approved the study. Sixty-eight patients (88.3 %) had PE from January 2000 to September 2010. All patients were treated with curative intent. Patients with extrapelvic metastatic disease, retroperitoneal lymph node metastasis, or invasion of the pelvic side wall that was unsuitable for resection with free margins were excluded. All histologic slides were reviewed. Perineural invasion was defined as the microscopic extension of malignant cells around the nerves.

PE was classified as anterior (APE), posterior (PPE), total (TPE), and total with laterally extended endopelvic resection (LEER). APE refers to the removal of the reproductive tract and bladder; PPE is the removal of the reproductive tract and rectum; and TPE is the removal of reproductive tract, bladder, and rectum. LEER refers to TPE that includes resection of the obturator internus muscle, iliococcygeus muscle, or pubococcygeus muscle.

Postoperative morbidity was considered to be early if it occurred earlier than 30 days after the operation or before hospital discharge. Follow-up time was the interval between the date of surgery and the last date for which information was available. Morbidity was analyzed per the National Cancer Institute (NCI) common toxicity criteria.

The database was generated in SPSS, version 16.0 (IBM, Armonk, NY, USA). The association between parametric variables was assessed by Chi square or Fisher's exact test. Survival curves were constructed by Kaplan–Meier life-table analysis. The multivariate analysis was made by Cox regression. For all tests, an alpha error of up to 5 % ($p < 0.05$) was considered significant.

RESULTS

Clinical and Pathologic Data

The patients' clinical and pathologic data are summarized in Table 1. Median age was 54.5 (range 28–87) years. Of the 77 patients who underwent PE, 69 experienced persistent or recurrent disease, with a median and mean interval from the first treatment and PE of 20.2 and 56.8 months, respectively (range 1–365 months). Eight patients (10.4 %) underwent PE as the primary treatment, all of whom had stage IVA disease that presented with urinary or intestinal fistula. Four had vaginal SCC, and 4 had cervical cancers (1 AC and 3 SCC).

Fifty-six (72.7 %) were SCC and 21 (27.3 %) AC. The primary tumor sites were uterine cervix in 53 patients (68.9 %) and vagina in 24 (31.1 %). Of the 24 patients with vaginal cancer, 8 (33.3 %) had no previous cervical disease, and 16 had undergone previous treatment for cervical cancer. The latter was considered as second primary disease because the cervical treatment interval was more than 5 years, with a median interval of 202.4 (range 91.4–365) months.

Twenty-four patients (31.1 %) were classified as American Association of Anesthesiologists (ASA) grade

TABLE 1 Clinical and pathologic characteristics of 77 patients with cervical and vaginal cancer submitted to PE

Characteristic	Value
Age, years, median (range)	54.5 (28–87)
Primary site	
Cervix	53 (68.9)
Vagina	24 (31.1)
Histologic type	
Squamous cell carcinoma	56 (72.7)
Adenocarcinoma	21 (27.3)
Type of PE	
Total	42 (54.5)
Anterior	18 (23.4)
Posterior	8 (10.4)
Lateral extended resection	9 (11.7)
Perineural invasion	
No	22 (40.7)
Yes	32 (59.3)
Lymph node metastasis	
No	28 (63.1)
Yes	17 (36.9)
Surgical margins	
R0	66 (91.7)
R1	6 (8.3)

PE pelvic exenteration

III. TPE was performed in 42 (54.5 %), APE in 18 (23.4 %), PPE in 8 (10.4 %), and LEER in 9 (11.7 %).

Of the 51 patients who underwent TPE or LEER, 8 (15.7 %) had anal sphincter–sparing surgery and colorectal anastomosis, but no patient was suitable for urinary sphincter–sparing surgery. Of those, 36 (70.6 %) had concomitant diversion with double-barreled wet colostomy, as reported by Guimaraes et al.[41]

The median operation time was 420 (range 180–720) minutes, and 70 patients (91 %) received a blood transfusion (median 900 ml, range 300–3900 ml). The median length of hospital stay was 13.5 (range 4–79) days.

Forty-three patients (55.8 %) and 37 patients (48 %) had early and late complications, respectively. On the basis of NCI common toxicity criteria, 15 (19.5 %) had grade III or IV early complications. Ten patients (13 %) had late complications that required surgical intervention.

There were no intraoperative deaths. Five patients (6.5 %) died postoperatively before 30 days after surgery. Age and ASA were variables that correlated with the risk of postoperative death. ASA III patients had a 25 % mortality rate versus 5.6 % for ASA I and II ($p = 0.021$), and patients aged over 70 years had a 38.5 % mortality rate compared with 6.2 % for younger patients ($p = 0.005$). Further, 69.2 % of patients aged over 70 years were also ASA III.

Twenty-six patients (33.7 %) had grade 3 tumors. Median tumor size was 5 (range 1–15) cm. Forty-six patients had pelvic lymph nodes that were resected; a median of 8.5 lymph nodes were evaluated (range 1–77 nodes). Seventeen patients (36.9 %) had lymph node involvement. Fifty-four patients were evaluated for perineural invasion, and 32 patients (59.3 %) had perineural invasion. Twenty (39.2 %) of 51 patients had lymphovascular space invasion (LVSI). Seventy-two patients had surgical margins described. It was considered microscopically free of disease (R0) in 66 patients (91.7 %) and positive or involved (R1) in 6 cases (8.3 %). There was no statistically significant difference in surgical margin involvement ($p = 1.0$) and presence of lymph node metastasis ($p = 0.17$) between the patients submitted to primary PE compared to PE after recurrence.

The median follow-up time was 13.8 (range 1.09–114.3) months. Thirty-six patients (46.7 %) experienced a recurrence (8 AC and 28 SCC). At the end of the follow-up, 21 patients (27.3 %) were alive with no evidence of disease, 31 (40.2 %) had died of cancer, 15 (19.5 %) died of other causes, 5 (6.5 %) died postoperatively, and 5 (6.5 %) were alive with evidence of disease. Seventeen patients (50 %) had local, 12 (35.3 %) distant, and 5 (14.7 %) both local and distant recurrences, and in 1 patient, the site was not reported. The median follow-up time after recurrence was 6.2 (range 1.05–72.8) months. The median OS after recurrence was 19.9 months. The interval of time between PE and recurrence of more than 12 months correlated with better survival (26.2 vs. 11.2 months), but this finding was not statistically significant ($p = 0.07$).

Eighteen patients (50 %) had palliative treatment after recurrence (surgery, chemotherapy, or radiotherapy). The patients who received palliative treatment after recurrence had statistically better OS than patients without treatment (24.2 vs. 9.5 months). Five (62.5 %) of 8 AC patients had palliative treatment (1 surgery R0; 1 surgery R0 + chemotherapy; 3 chemotherapy), compared with 13 (46.4 %) of 28 SCC patients (5 surgery R0; 2 radiotherapy; 4 chemotherapy; 1 surgery R0+ chemotherapy; 1 surgery R1). However, there was no statistically significant difference between histology and type of treatment after recurrence ($p = 0.69$).

Histologic type statistically correlated with primary tumor site, perineural, and LVSI. AC was primary found in cervix in 90.5 % of cases, and SCC in 60.7 % ($p = 0.013$). SCC had a positive correlation to perineural and LVSI. Perineural invasion was found in 69.8 % of SCC and in 18.2 % of AC ($p = 0.004$). LVSI were found in 48.7 % of SCC and 8.3 % of AC ($p = 0.017$). Histologic type did not correlate with the first site of recurrence (local vs. distant), size ($\leq$5 or >5 cm), age ($\leq$70 or >70 years), ASA, histologic grade, presence of lymph node metastasis, and surgical margins status. The patient correlations between histologic type and other clinicopathologic variables data are summarized in Table 2.

Recurrence and Survival

The 2- and 5-year progression-free survival rates were 41.2 and 38.5 %, respectively. The 2- and 5-year OS rates were 45.8 and 24.4 %, respectively. The 2- and 5-year DSS rates were 56.1 and 37.1 %, respectively. Positive surgical margins negatively affected the risk of recurrence ($p = 0.049$), as all patients with positive surgical margins experienced recurrence in 30 months, with median progression-free survival of 7.8 months.

SCC histology (5-year OS: 13.6 % vs. 51.6 %; $p = 0.003$) (Fig. 1), and histologic grade 3 (2-year OS: 22.7 % vs. 54.3 %; $p = 0.001$) negatively affected the risk of death. Moreover, SCC histology (5-year DSS 24.3 % vs. 64.7 %; $p = 0.006$) (Fig. 2), perineural invasion (5-year DSS 17.9 % vs. 62.9 %; $p = 0.031$), histologic grade 3 (2-year DSS 38.1 % vs. 70.3 %; $p = 0.003$), lymph node involvement (2-year DSS 44.9 % vs. 79.7 %; $p = 0.024$), and positive surgical margins (2-year DSS 40 % vs. 64.1 %; $p = 0.046$) negatively affected the risk of death from cancer (Table 3).

Even after excluding from analyses the patients submitted to primary PE, SCC histology persisted as a

TABLE 2 Correlation between histologic type and other clinicopathologic variables for 77 patients with cervical and vaginal cancer submitted to pelvic exenteration

Variable	Histology	*n* (%)	*p*
Cervical primary site	SCC	19/21 (60.7)	0.013
	AC	34/56 (90.5)	
Perineural invasion	SCC	30/43 (69.8)	0.004
	AC	2/11 (18.2)	
LVSI	SCC	19/39 (48.7)	0.017
	AC	1/12 (8.3)	
Tumor size > 5 cm	SCC	21/44 (47.7)	0.58
	AC	7/19 (36.8)	
Age > 70 y	SCC	12/56 (21.4)	0.10
	AC	1/21 (4.8)	
ASA III	SCC	18/56 (32.1)	0.47
	AC	5/21 (23.8)	
Grade 3	SCC	23/50 (46)	0.12
	AC	3/14 (21.4)	
Lymph node metastasis	SCC	3/13 (23.1)	0.31
	AC	14/33 (42.4)	
Surgical margins	SCC	1/21 (4.8)	0.66
	AC	5/51 (9.8)	
Distant first recurrence	SCC	4/8 (50)	1.0
	AC	13/26 (50)	

SCC squamous cell carcinoma, *AC* adenocarcinoma, *LVSI* lymphovascular space invasion, *ASA* American Society of Anesthesiology

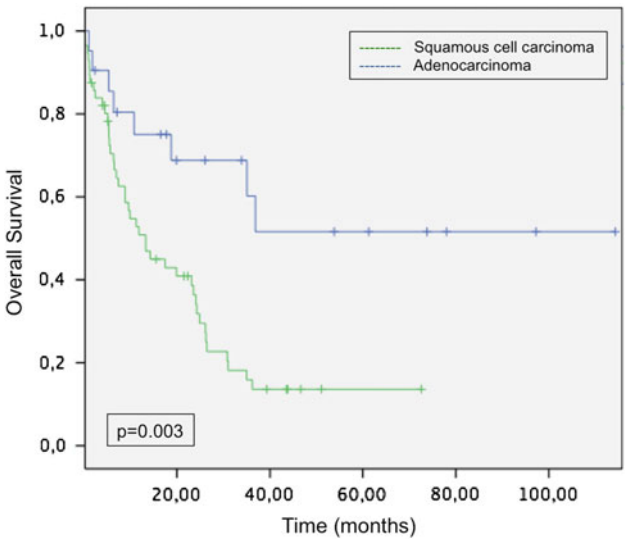

FIG. 1 Overall survival curves for patients with adenocarcinoma and squamous cell carcinoma after pelvic exenteration ($p = 0.003$)

negative prognostic factor for DSS ($p = 0.011$) and OS ($p = 0.008$). Furthermore, there was no statistically difference in OS ($p = 0.10$) and DSS ($p = 0.17$) for patients submitted to primary PE compared to PE after recurrence.

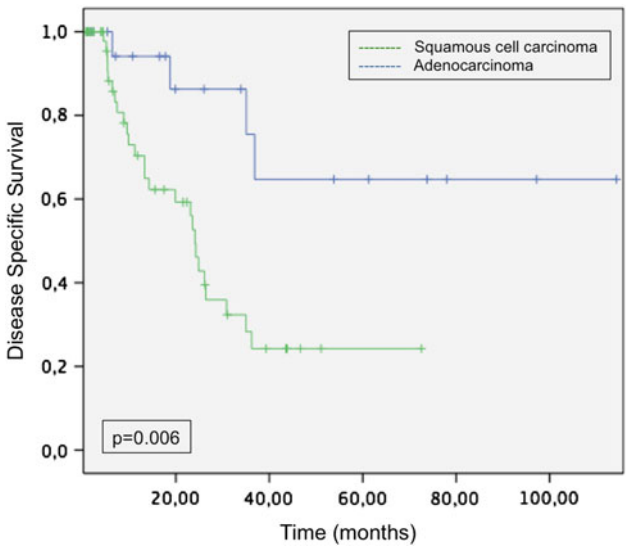

FIG. 2 Disease-specific survival curves for patients with adenocarcinoma and squamous cell carcinoma after pelvic exenteration ($p = 0.006$)

Tumor size >5 cm, primary tumor site (cervix vs. vagina), and interval from the first treatment to PE of <24 months did not correlate with outcome.

Histologic grade 3 and SCC were the only variables that retained the risk of death and death due to cancer in the multivariate analysis (Table 4).

DISCUSSION

The prognostic value of histologic type in cervical cancer is still controversial. Some studies have suggested that there is no difference in outcome between AC and SCC.[42–47] However, most demonstrated the opposite. They have shown that AC carries a worse prognosis with 10 to 20 % differences in 5-year OS rates.[11,48–56]

After comparing stage for stage, AC histology significantly correlates to worse outcomes compared to SCC.[5,48,49,52] Furthermore, as clinical stage progresses, the difference in survival between AC and SCC also increases. Recently, Galic et al. reported the largest series of AC in the literature using the Surveillance, Epidemiology, and End Results database.[57] They identified 4103 patients with AC and 1480 with adenosquamous carcinoma among 24,562 patients. They found that patients with early and advanced stage AC were, respectively, 39 and 21 % more likely to die from their disease than SCC patients. PE is a major surgical procedure; however, it might be the only approach that affects long-term survival in select patients with persistent or recurrent gynecological malignancies.

We have noted 5-year OS and DSS rates of 24.4 and 37.1 %, respectively, a finding consistent with other series of PE for gynecologic malignancies, in which median 5-year survival has ranged from 20 to 73 %.[23–34] Our data

TABLE 3 Correlation between clinicopathologic variables and DSS for 77 patients with cervical and vaginal cancer submitted to PE

Variable	2-year DSS, %	5-year DSS, %	*p*
Cervical primary site			
Cervix	62.1	44.4	0.11
Vagina	66.3	12.6	
Histologic type			
SCC	52.7	24.3	0.006
AC	86.3	64.7	
Perineural invasion			
Present	53.7	17.9	0.031
Absent	75.5	62.9	
Lymphatic invasion			
Absent	73.7	36.8	0.21
Present	45.4	27.2	
Tumor size > 5 cm			
Yes	60.6	43.3	0.65
No	58.2	31	
Primary PE			
Yes	41.7	20.8	0.17
No	65.5	39.8	
Histologic grade 3			
Yes	38.1	0[a]	0.003
No	70.3	41.3	
Lymph node metastasis			
Present	44.9	0[b]	0.024
Absent	79.7	50.7	
Surgical margins			
Positive	40	0[c]	0.046
Negative	64.1	39.6	

DSS disease-specific survival, *PE* pelvic exenteration, *SCC* squamous cell carcinoma, *AC* adenocarcinoma

[a] Median DSS of 9.8 months

[b] Median DSS of 23 months

[c] Median DSS of 13.3 months

TABLE 4 Multivariate analysis showing association between clinicopathologic variables and risk of death from cancer [a]

Variable	HR	95 % CI	*p*
Squamous cell carcinoma	3.74	1.09–12.8	0.036
Grade 3	2.59	1.13–5.95	0.025
Presence of perineural invasion	1.13	0.37–3.43	0.82
Lymph node involvement	1.89	0.73–4.9	0.18
Positive surgical margins	1.83	0.61–5.48	0.27
Primary site: vagina	1.07	0.48–2.35	0.86
Primary pelvic exenteration	1.89	0.69–5.21	0.21

HR hazard ratio, *CI* confidence interval

[a] Estimated risk from Cox regression model

reflect a heterogeneous population with associated illnesses, in which 30.8 % of subjects were ASA III. We also included extremely locally advanced tumors; the median tumor size in our series was 5 cm, and 11.7 % underwent PE that extended to the pelvic side wall.

Literature is lacking on the prognostic value of histologic type after PE. Only one study addressed AC histology as a prognostic factor after PE. From 1955 to 1989, Crozier et al. evaluated 35 patients with AC and 70 controls (SCC) and noted no difference for size, margin status, and time elapsed from initial treatment and PE.[58] They noted a better, but not statistically significant, median survival of 38 months for AC and 25 months for SCC. Moreover, the 5-year OS was nearly identical (37 % AC and 39 % SCC). They also found 23 of 35 relapses for AC and 32 of 70 for SCC, and the likelihood of distant recurrence was not statistically different.

Schmidt et al. published a large series of PE for cervical cancer that included 282 patients.[59] They did not describe the number of patients with AC, but they found a 5-year OS of 41 % for SCC and 31 % for AC, although this finding was not statistically significant.

In our series, SCC histology correlated with worse OS and DSS. Because SCC correlated with perineural and LVSI, one might ask whether this finding was influenced by these well-known prognostic factors after PE. However, the increased risk of death for SCC remained in the multivariate analysis.

The incidence of lymph node involvement has been reported to be higher for AC compared to SCC; not only the incidence but also the survival rate was shown to be worse with the presence of lymph node metastasis.[55] Among patients with positive lymph nodes, AC negatively affects survival compared to SCC.[42,54,55]

The suggested higher prevalence of lymph node involvement for cervical cancer during the primary treatment was not corroborated by our data. We did not find differences in lymph node involvement for SCC or AC after PE. Nevertheless, our data confirm that of several groups that have described lymph node metastasis as an important negative prognostic factor after PE.[30,35,60–62]

Current data also note that AC differs from SCC regarding patterns of disease dissemination and recurrence. Several studies suggest higher rates of distant metastasis and recurrence for AC.[6,45,48,50,63] In the Eifel et al. series, which included 367 patients with AC, the prevalence of distant metastasis for stage II and III AC was, respectively, 46 and 38 %, whereas for stage II and III SCC, it was 13 and 21 %.[5]

In contrast to previous data where higher distant recurrence rates were reported for AC after the primary treatment, we did not find a difference regarding histologic type and relapse site after PE. We also found no difference

in size, age, histologic grade, and margins status for AC compared to SCC.

Higher chemotherapy response rates are expected for AC compared to SCC.[64] We analyzed whether there was any difference between treatments for patients whose disease recurred after PE, and we found no difference between histologic type and palliative treatment after recurrence. However, in a retrospective setting, it is difficult to analyze the real benefit of palliative treatment; patients suitable for any palliative approach may also have a better performance status.

Our series has intriguing new data. Notably, we found that AC had a better outcome compared to SCC after PE. We tested whether histologic type was an independent variable after adjusting it with other well-known prognostic factors after PE, such as grade, lymph node status, margin status, and presence of perineural invasion.[27,30,35,60–62,65] The only prognostic factors that retained the risk of death in multivariate analyses were grade 3 disease and SCC histology. It still remains elusive whether this finding is due to differences in tumor biology that favored a subset of patients with AC or a result of other factors. Overall, our series sample size can be compared to the most important studies of this kind and may add important information to the literature. Our data suggest that AC histology in patients with cervical and vaginal cancer correlates to a better outcome after PE.

CONFLICT OF INTEREST The authors declare that there is no conflict of interest

REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin.* 2011;61:69–90.
2. Sasieni P, Adams J. Changing rates of adenocarcinoma and adenosquamous carcinoma of the cervix in England. *Lancet.* 2001;357:1490–3.
3. Bray F, Carstensen B, Møller H, et al. Incidence trends of adenocarcinoma of the cervix in 13 European countries. *Cancer Epidemiol Biomark Prev.* 2005;14:2191–9.
4. Lai CH, Hsueh S, Hong JH, et al. Are adenocarcinomas and adenosquamous carcinomas different from squamous carcinomas in stage IB and II cervical cancer patients undergoing primary radical surgery? *Int J Gynecol Cancer.* 1999;9:28–36.
5. Eifel PJ, Morris M, Oswald MJ, Wharton JT, Delclos L. Adenocarcinoma of the uterine cervix: prognosis and patterns of failure in 367 cases. *Cancer.* 1990;65:2507–14.
6. Sherman ME, Wang SS, Carreon J, Devesa SS. Mortality trends for cervical squamous and adenocarcinoma in the United States. *Cancer.* 2005;103:1258–64.
7. Smith HO, Tiffany MF, Qualls CR, Key CR. The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States: a 24-year population-based study. *Gynecol Oncol.* 2000;78:97–105.
8. Castellsagué X, Díaz M, De Sanjosé S, et al. Worldwide human papillomavirus etiology of cervical adenocarcinoma and its cofactors: implications for screening and prevention. *J Natl Cancer Inst.* 2006;98:303–15.
9. Wang SS, Sherman ME, Hildesheim A, Lacey JV Jr, Devesa S. Cervical adenocarcinoma and squamous cell carcinoma incidence trends among white women and black women in the United States for 1976–2000. *Cancer.* 2004;100:1035–44.
10. Gien LT, Beauchemin MC, Thomas G. Adenocarcinoma: a unique cervical cancer. *Gynecol Oncol.* 2010;116:140–6.
11. Landoni F, Maneo A, Colombo A, et al. Randomized study of radical surgery versus radiotherapy for stage Ib–IIa cervical cancer. *Lancet.* 1997;350:535–40.
12. Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and paraaortic radiation for high-risk cervical cancer. *N Engl J Med.* 1999;340:1137–43.
13. Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage 1b carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a gynecologic oncology group study. *Gynecol Oncol.* 1999;73:177–83.
14. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med.* 1999;340:1154–61.
15. Rose PG, Bundy BN, Watkins J, et al. Concurrent cisplatin-based chemotherapy and radiotherapy for locally advanced cervical cancer. *N Engl J Med.* 1999;340:1144–53.
16. Landoni F, Maneo A, Cormio G, et al. Class II versus class III radical hysterectomy in stage IB-IIA cervical cancer: a prospective randomized study. *Gynecol Oncol.* 2001;80:3–12.
17. Peters WA, Liu PY, Barrett RJ, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early stage cancer of the cervix. *J Clin Oncol.* 2000;18:1606–13.
18. Eifel PJ, Winter K, Morris M, et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01. *J Clin Oncol.* 2004;22:872–80.
19. Monk BJ, Wang J, Im S, et al. Rethinking the use of radiation and chemotherapy after radical hysterectomy: a clinical–pathologic analysis of a Gynecologic Oncology Group/Southwest Oncology Group/Radiation Therapy Oncology Group trial. *Gynecol Oncol.* 2005;96:721–8.
20. Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. *J Clin Oncol.* 2008;26:5802–12.
21. Höckel M, Dornhöfer N. Pelvic exenteration for gynaecological tumours: achievements and unanswered questions. *Lancet Oncol.* 2006;7:837–47.
22. Brunschwig A. Complete excision of pelvic viscera for advanced carcinoma. *Cancer.* 1948;1:177–83.
23. Lawhead RA, Clark DG, Smith DH, Pierce VK, Lewis JL Jr. Pelvic exenteration for recurrent or persistent gynaecologic malignancies: a 10- year review of the Memorial-Sloan-Kettering Cancer Center experience (1972–1981). *Gynecol Oncol.* 1989;33:279–82.
24. Magrina JF, Stanhope CR, Waever AL. Pelvic exenterations: supralevator, infralevator, and with vulvectomy. *Gynecol Oncol.* 1997;64:130–5.
25. Morley GW, Hopkins MP, Lindenauer SM, Roberts JA. Pelvic exenteration, university of Michigan: 100 patients at 5 years. *Obstet Gynecol.* 1989;74:934–43.
26. Shingleton HM, Soong SJ, Gelder MS, Hatch KD, Baker VV, Austin JM Jr. Clinical and histopathologic factors predicting recurrence and survival after pelvic exenteration for cancer of the cervix. *Obstet Gynecol.* 1989;73:1027–34.

27. Symmonds RE, Pratt JH, Webb MJ. Exenterative operations: experience with 198 patients. *Am J Obstet Gynecol.* 1975;121: 907–18.
28. Rutledge F, Smith J, Wharton J, O'Quinn AG. Pelvic exenteration; analysis of 296 patients. *Am J Obstet Gynecol.* 1977;129: 881–92.
29. Roberts W, Cavanagh D, Bryson P, Lyman GH, Hewitt S. Major morbidity after pelvic exenteration: a seven year experience. *Obstet Gynecol.* 1987;69:617–21.
30. Hatch KD, Gelder MS, Soong SJ, Baker VV, Shingleton HM. Pelvic exenteration with low rectal anastomosis: survival, complications, and prognostic factors. *Gynecol Oncol.* 1990;38:462–7.
31. Matthews C, Morris M, Burke T, Gershenson DM, Wharton JT, Rutledge FN. Pelvic exenteration in the elderly patient. *Obstet Gynecol.* 1992;79:773–7.
32. Morris M, Alvarez RD, Kinney WK, Wilson TO. Treatment of recurrent adenocarcinoma of the endometrium with pelvic exenteration. *Gynecol Oncol.* 1996;60:288–91.
33. Miller B, Morris M, Rutledge F, et al. Aborted exenterative procedures in recurrent cervical cancer. *Gynecol Oncol.* 1993;50:94–9.
34. Maggioni A, Roviglione G, Landoni F, et al. Pelvic exenteration: ten-year experience at the European Institute of Oncology in Milan. *Gynecol Oncol.* 2009;114:64–8.
35. Sharma S, Odunsi K, Driscoll D, Lele S. Pelvic exenteration for gynecological malignancies: twenty-year experience at Rosewell Park Cancer Institute. *Int J Gynecol Cancer.* 2005;15:475–82.
36. Pawlik TM, Skibber JM, Miguel AR. Pelvic exenteration for advanced pelvic malignancies. *Ann Surg Oncol.* 2005;13:612–23.
37. Houvenaeghel G, Moutardier V, Karsenty G, et al. Major complications of urinary diversion after pelvic exenteration for gynecologic malignancies: a 23-year mono-institutional experience in 124 patients. *Gynecol Oncol.* 2004;92:680–3.
38. Ketcham AS, Deckers PJ, Sugarbaker EV, Hoye RC, Thomas LB, Smith RR. Pelvic exenteration for carcinoma of the uterine cervix—a 15-year experience. *Cancer.* 1970;26:513–21.
39. Saunders N. Pelvic exenteration: by whom and for whom? *Lancet.* 1995;345:5–6.
40. Stanhope CR, Symmonds RE. Palliative exenteration—what, when, and why? *Am J Obstet Gynecol.* 1985;152:12–6.
41. Guimaraes GC, Ferreira FO, Rossi BM, et al. Double-barreled wet colostomy is a safe option for simultaneous urinary and fecal diversion. Analysis of 56 procedures from a single institution. *J Surg Oncol.* 2006;93:206–11.
42. Shingleton HM, Bell MC, Fremgen A, et al. Is there really a difference in survival of women with squamous cell carcinoma, adenocarcinoma, and adenosquamous cell carcinoma of the cervix? *Cancer.* 1995;76:1948–55.
43. Grigsby PW, Perez CA, Kuske RR, et al. Adenocarcinoma of the uterine cervix: lack of evidence for a poor prognosis. *Radiother Oncol.* 1988;12:289–96.
44. Look KY, Brunetto VL, Clarke-Pearson DL, et al. An analysis of cell type in patients with surgically staged stage IB carcinoma of the cervix: a gynecologic oncology group study. *Gynecol Oncol.* 1996;63:304–11.
45. Lee KBM, Lee JM, Park CY, Lee KB, Cho HY, Ha SY. What is the difference between squamous cell carcinoma and adenocarcinoma of the cervix? A matched case–control study. *Int J Gynecol Cancer.* 2006;16:1569–73.
46. Kilgore LC, Soong SJ, Gore H, Shingleton HM, Hatch KD, Partridge EE. Analysis of prognostic features in adenocarcinoma of the cervix. *Gynecol Oncol.* 1998;31:137–48.
47. Alfsen GC, Kristensen GB, Skovlund E, Pettersen EO, Abeler VM. Histologic subtype has minor importance for overall survival in patients with adenocarcinoma of the uterine cervix: a population-based study of prognostic factors in 505 patients with nonsquamous cell carcinomas of the cervix. *Cancer.* 2001;92:2471–83.
48. Eifel PJ, Burke TW, Morris M, Smith TL. Adenocarcinoma as an independent risk factor for disease recurrence in patients with stage 1B cervical carcinoma. *Gynecol Oncol.* 1995;59:38–44.
49. Hopkins MP, Morley GW. A comparison of adenocarcinoma and squamous cell carcinoma of the cervix. *Obstet Gynecol.* 1991; 77:912–7.
50. Berek JS, Hacker NS, Fu YS, Sokale JR, Leuchter RC, Lagasse LD. Adenocarcinoma of the uterine cervix: histologic variables associated with lymph node metastasis and survival. *Obstet Gynecol.* 1985;65:46–52.
51. Kleine W, Rau K, Schwoerer D, Pfleiderer A. Prognosis of adenocarcinoma of the cervix uteri: a comparative study. *Gynecol Oncol.* 1989;35:145–59.
52. Chen RJ, Lin YH, Chen CA, Huang SC, Chow SN, Hsieh CY. Influence of histologic type and age on survival rates for invasive cervical carcinoma in Taiwan. *Gynecol Oncol.* 1999;73:184–90.
53. Davy MLJ, Dodd TJ, Luke CJ, Roder DM. Cervical cancer: effect of glandular cell type on prognosis, treatment, and survival. *Obstet Gynecol.* 2003;101:38–45.
54. Nakanishi T, Ishikawa H, Suzuki Y, Inoue T, Nakamura S, Kuzuya K. A comparison of prognoses of pathologic stage IB adenocarcinoma and squamous cell carcinoma of the uterine cervix. *Gynecol Oncol.* 2000;79:289–93.
55. Irie T, Kigawa J, Minagawa Y, et al. Prognosis and clinicopathological characteristics of Ib-IIb adenocarcinoma of the uterine cervix in patients who have had radical hysterectomy. *Eur J Surg Oncol.* 2000;26:464–7.
56. Takeda N, Sakuragi N, Takeda M, et al. Multivariate analysis of histopathologic prognostic factors for invasive cervical cancer treated with radical hysterectomy and systematic retroperitoneal lymphadenectomy. *Acta Obstet Gynecol Scand.* 2002;81:1144–51.
57. Galic V, Herzog TJ, Lewin SN, et al. Prognostic significance of adenocarcinoma histology in women with cervical cancer. *Gynecol Oncol.* 2012;125:287–91.
58. Crozier M, Morris M, Levenback C, Lucas KR, Atkinson EN, Wharton JT. Pelvic exenteration for adenocarcinoma of the uterine cervix. *Gynecol Oncol.* 1995;58:74–8.
59. Schmidt AM, Imesch P, Fink D, Egger H. Indications and long-term clinical outcomes in 282 patients with pelvic exenteration for advanced or recurrent cervical cancer. *Gynecol Oncol.* 2012;125:604–9.
60. Barakat RR, Goldman NA, Patel DA, Venkatraman ES, Curtin JP. Pelvic exenteration for recurrent endometrial cancer. *Gynecol Oncol.* 1999;75:99–102.
61. Marnitz S, Köhler C, Müller M, Behrens K, Hasenbein K, Schneider A. Indications for primary and secondary exenterations in patients with cervical cancer. *Gynecol Oncol.* 2006;103:1023–30.
62. Rutledge FN, McGuffee VB. Pelvic exenteration: prognostic significance of regional lymph node metastasis. *Gynecol Oncol.* 1987;26:347–80.
63. Drescher CW, Hopkins MP, Roberts JA. Comparison of the pattern of metastatic spread of squamous cell cancer and adenocarcioma of the uterine cervix. *Gynecol Oncol.* 1989;33:340–3.
64. Rose PG. Are the differences in treatment outcome for adenocarcinoma of the cervix different enough to change the treatment paradigm? *Gynecol Oncol.* 2012;125:285–6.
65. Fotopoulou C, Neumann U, Kraetschell R, et al. Long-term clinical outcome of pelvic exenteration in patients with advanced gynecological malignancies. *J Surg Oncol.* 2010;101:507–12.