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Mixed Adenosquamous Histology is Associated with Poorer Survival of Cervical Cancer Stage 1b

Research Artcle

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Abstract

Background: Evaluation of histopathological factors for women with radical hysterectomy a.m. Okabayashi for cervical cancer in stage 1bwith similar pre- and postoperative treatment
Methods: Data on 141 women with cervical cancer stage 1b were revised. The local patient registry, data charts, and post mortem sections provided follow-up on survival, relapse, and re-admittance. Histopathological evaluation was performed by the same pathologist.
Results: Histological evaluation showed that adenosquamous cervical cancer in stage 1b was associated with poorer survival than the pure squamous and adenomatous type ($p<0.001$, mixed versus pure type). Five year's survival rate was 40 % (2-78 %) for mixed type and 92 % (87-97 %) for pure type. The mixed type was associated with glandular metastasis ($p<0.02$). The relapse free survival after 5 and 10 years was 88 % (82-94 %) and 83 % (75-91 %), respectively, while survival was found to be 89 % (83-95 %) and 86 % (79-93 %), respectively. The women's age at diagnosis showed no association with histology type or survival.

Keywords: Cervical Cancer; Survival; Histopathology.

Introduction

Cervical cancer is staged preoperatively and the postoperative treatment depends on the combination of staging with histopathological finding. Survival is related to certain histopathological factors, most importantly lymph node status and other findings indicating that tumor may have spread i.e. parametrium and the lymph-vascular space. Other factors like tumor size and depth of stromal invasion indicate aggressive biological behavior. Poorer survival depending on histological type of tumor is reported in adenocarcinoma compared to squamous carcinoma [1-7]. The concurrent increasing incidence of adenocarcinoma associated with use of oral contraceptives in the Western World is a concern to that it may reverse the positive effect of screening [6, 7]. However, the survival relates heavily on different pre-and postoperative treatment regimens and stage of disease [1, 3, 4]. Adverse histopathological factors are often present simultaneously and reviewed heterogeneously.

The aim of our study was to evaluate independent histopathological factors for women with radical hysterectomy with focus on standardized histopathological diagnosis combined with similar pre-and postoperative treatment.

Material and Methods

141 women were diagnosed with cervical cancer stage 1b and operated with radical hysterectomy during 24 years at Holstebro Hospital. The hospital served as centre for the county with a population of approximately 275.000. The stage, pre- and postoperative treatment was registered as the data charts were reviewed. The local patient registry provided information of survival, relapse, and re-admittance. None of the women was lost to follow-up. Data charts or post mortem sections confirmed the cause of death.

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The type and differentiation of tumor as well as its size and depth were uniformly evaluated and the specimens photographed by the same pathologist (M.V.) and reviewed by another pathologist. The procedure consisted of routinely staining with hemotoxylin/eosin, alsacian blue, mucicarmin, and mucin in 5-7 μm thin sections. Adenomatous carcinoma is defined as a mucin positive (at least 10 %) carcinoma with glandular differentiation, squamous is epithelial carcinoma negative for mucin production and no glandular differentiation. Some epithelial cancers were slight mucin positive but had no glandular differentiation and were thus classified as squamous. Adenosquamous carcinoma is a combination of cylindrical cell carcinoma that is mucin positive and squamous epithelium cancer with no atypical glandular structure that could be identified in invasive areas. The depth of invasion of the uterus was measured with micrometer in mm and evaluated in thirds of wall thickness, too. Lymph vessels were identified by absence of muscle tissue in the vessel's wall by means of a negative staining by elastin.

The operator preoperatively performed the staging according to the FIGO classification. No re-staging was performed by the authors, so the women kept their initial staging. After 1997, the gynecological examination was performed under anesthesia. At the same session cystoscopy was performed. The absence of hydronephrosis and ureteral passage was assured with urography, CT scan or ultrasound. All women were operated with a modification of Okabayashi's operation with systematic pelvic lymphadenectomy. All operations were performed by the same three gynecologists in the whole study time.

Statistical analysis was performed on the difference between two means with Student's *t*-test, if Gaussian distribution could be assured. Otherwise, Mann-Whitney's test was used for unpaired analysis. Cox regression analysis was performed with BMI, age, vessels emboli presence, parametrial involvement, lymph node metastasis, histopathology grouping, and adjuvant treatment as covariates. Survival analysis was performed with Kaplan-Meier and survival compared using the Log-Rank test. Results are given with cumulative proportion of survival with 95% confidence intervals in parenthesis. Fischer's Exact Test was applied to test independence between groups. Odds ratio (OR) with 95 % confidence intervals were calculated using Woolf's approximation. Values are given as median with 95 % confidence intervals within parenthesis, unless otherwise stated. A two-sided p-value < 0.05 was the level of significance. The statistical software was SPSS, version 13.0.

Results

The median follow-up was 83 months for all women, for the survivors it was median 93 months. Preoperative data and perioperative findings are given in Table 1. In three women who initial were staged to 1b the histopathologic evaluation showed metastasis beyond the cervix apart from lymph glandular involvement; one had several pelvic metastases, the second ovarian hilus metastasis and pelvic metastasis, and the third woman parametrial involvement of tumor. In 95 women the tumor was localized in the cervix only, i.e. absence of vessel emboli, lymph gland metastasis, parametrial and vaginal involvement.

All women with lymph node metastasis were discussed with the oncologist (Table 1). Only half of the women with lymph node metastasis received adjuvant treatment; nine had radiotherapy, one chemotherapy, and thirteen chemotherapy as well as radiotherapy.

Table 1. Clinical data of women in stage 1b operated with radical hysterectomy.

FIGO stage1b	All	Dead of cancer	Survived cancer	Dead vs. survivors, p-value
No.	141	15	126	
Age (yrs)[a]	43 (23,80)	43 (28,70)	43 (23,80)	0.63
BMI (kg/m^2)[a]	23 (17,41)	23 (17,41)	23 (17,39)	0.33
Duration of symptoms (months)[a]	2 (0,12)	3 (1,6)	2 (0,12)	0.70
Days between initial visit and operation[a]	19 (6,110)	8 (7,10)	20 (6,110)	0.001
Operation time (minutes)[a]	158 (105,275)	150 (145,180)	160 (105,275)	0.37
Histology: Squamous c. /adenomatous c. / adenosquamous carcinoma	102/29/10	10/1/4	92/28/6	0.01[b]
Lymph node metastasis (No.)	24	7	17	0.004
Adjuvant treatment (No.)	22	3[c]	19d	0.71
(radiation/radiation+chemotherapy)	(9/13)	(2/1)	(7/12)	
Follow-up time (years)[a]	7 (0.2-20)	2.5 (0.5,10)	7.8 (0.2,20)	0.001
No. of relapses (%)	23 (16)	15	8 (6)	
Dead of cancer: No. (%)	15 (11)	15	0	

a: median (range),
b: mixed vs.pure type, OR=7.2 (95% CI: 1.8,29.7),
c: all 3 had glandular metastasis, d: nine had glandular metastasis.

Survival was associated with presence of lymph node metastasis (χ^2 = 13, p<0.001) with a 5 years survival of 70 % (50-90 %, n = 24) and 93 % (89.4-96.5 %, n = 117) for lymph node positive and negative cervical cancer, respectively.

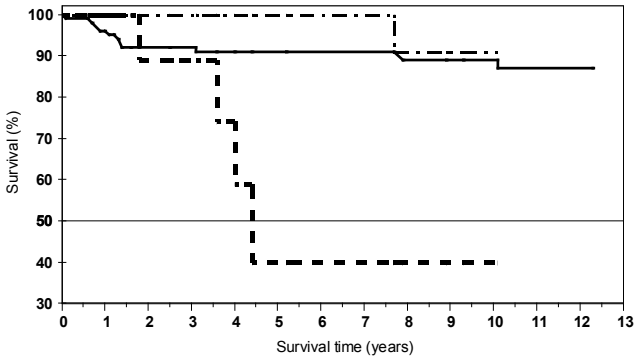
Histological evaluation showed that adenosquamous cervical cancer was associated with poorer survival than the pure squamous and adenocarcinoma type (Figure 1). Five years survival rate was 40 % (2-78 %, n = 7) for mixed type and 92 % (87-97 %, n = 90) for pure type. The adenosquamous type was associated with lymph node metastasis (OR = 5.6 (1.8, 17.4), Fischer's Exact test, p<0.02) but not with size of tumor, involvement of vagina, parametrium, and lymph vessels. Similarly, adjuvant treatment was associated with presence of lymph node metastasis (OR = 10.7 (3.8, 30), p<0.001) and the survival with adjuvant treatment tended to be lower (p<0.09, Log-rank test) which was associated with lymph node involvement.

Adding the individual risk factors as covariates in a stepwise forward conditional Cox regression analysis showed that total numbers of positive nodes (χ^2=31), adenosquamous histology (χ^2=10, n=10), and lymph node involvement (χ^2=13, n = 24) was significantly associated with survival. The full covariate analysis included only histopathology and numbers of positive nodes as the mere presence of lymph nodes was cancelled out and added no more to the regression analysis (χ^2= 38, p<0.001).

Major complications amongst the 141 hysterectomies were vesicovaginal fistula (n=1), intestinal perforation (n=1), and ureteral lesion (n=2). None of the women had permanent impairment of their lesion after operative correction. Two women experienced unilateral lesion of nervus obturatorius.

Relapse was seen in 16 % women and no difference in survival was seen associated with relapse treatment. For all women in stage 1b the five and ten years survival was found to be 89 % (83-95 %, n = 95) and 86 % (79-93 %, n = 69), respectively. The relapse free survival after 5 and 10 years (95 % CI) was 88 % (82-94 %, n = 80 at 5 years observation) and 83 % (75-91 %, n = 51 at 10 years observation), respectively. The women's age and BMI at diagnosis showed no association with histology type or survival at regression analysis.

Figure 1. Survival of 141 women operated a.m. Okabayashi for cervical cancer stage 1b by histopathology.



Squamous cancer: Continuous line. Adenomatous cancer: Interrupted line with dots. Mixed type: Long, interrupted line Mixed vs. pure type: p<0.001, Log-rank test

Discussion

The finding of poorer survival of the mixed type cervical cancer independent of age is controversial, confirmed by some [8-10], however, disputed by other studies [11, 12]. The latter had a high degree of non-surgical, radiation treatment only (>20%) for stage 1a-2a, non-reviewed histopathology, and different treatment regimens for similar stages. For women with similar tumor grades the finding of an association with advanced stage and poorer survival rate indicate an aggressive behavior of the tumor type [9, 12, 13]. Not all studies with uniform operative treatment and reviewed histopathology find different survival rates [14]. The high percentage of mixed type (25%) and relatively few pure adenocarcinomas (8%) suggests that selection or diagnostic criteria may play a role.

The incidence of relapse in this study does not differ from other studies, which states 5 years survival rate of stage 1b between 79 % [2] and 88 % [15-17]. Most have relative short median follow-up time of five years and less and give information on relapse-free interval and survival rate in stage 1b in variable ways. The survival depends on a number of factors like tumor size, invasion depth, lymph vessel involvement, histology, and metastasis [1, 4]. The lymph node involvement is still the single most common and, thus, important find. The mortality of cervical cancer in Denmark is associated with age at diagnosis and the time when the screening for cancer was introduced locally. Since central registration was introduced in 1943 survival of younger women improved steadily while women above 60 have poorer survival after 1970 [18]. After operation the relapse-free interval is the best prognostic factor for survival in as much as women more commonly return for check-up of suspected relapse outside the regular intervals [16, 19].

The age of the women may influence the results in several ways a retrospective cannot detect. Primarily, the time of diagnosis may be influenced by changing incidences as adenocarcinoma is increasing over time, presumably due to increased use of hormonal anticonception [6, 7, 20]. Secondly, lead-time bias will increase age in early stages and decrease age in advanced stages if advancing stages are expected due to aggressive behaviour of the tumor [13]. Thirdly, if survival depends on age it may do so differentially according to tumor type [20]. Due to design and the

limited number of women we cannot exclude these effects. In comparison, the larger studies, which should be able to find a trend in age, are contradictory to each other [9-14]; the Achilles' heel being the exact histopathology diagnosis, which for practical reasons cannot be uniformly verified. Those who do undertake the tremendous task confirm the poorer survival of adenosquamous histology [9, 10].

The poorer survival found in multivariate analysis with the known factors of lymph space invasion, parametrial involvement, lymph node metastasis, and tumor growth will apply for all tumor types. However, the mixed type, usually reported rarer than the pure types, will increase in significance as screening will decrease the general detection limit and find more stage 1 tumors. The future question is whether the mixed type is associated with certain HPV types of infection or is of similar background as the adenocarcinomas so appropriate preventive care can be taken.

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References

[1]. Lin HH, Cheng WF, Chan KW, Chang DY, Chen CK, Huang SC (1996) Risk factors for recurrence in patients with stage IB, IIA, and IIB cervical carcinoma after radical hysterectomy and postoperative pelvic irradiation. Obstet Gynecol. 88(2): 274-9.

[2]. Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ (1999) A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: Gynecologic Oncology Group Study. Gynecol Oncol. 73(2): 177-83.

[3]. Delgado G, Bundy B, Zaino R, Sevin BU, Creasman WT, Major F (1990) Prospective surgical-pathological study of disease-free interval in patients with stage IB squamous cell carcinoma of the cervix: Gynecologic Oncology Group study. Gynecol Oncol. 38(3): 352-7.

[4]. Takeda N, Sakuragi N, Takeda M, Okamoto K, Kuwabara M, Negishi H, et al., (2002) Multivariate analysis of histopathologic prognostic factors for invasive cervical cancer treated with radical hysterectomy and systematic retroperitoneal lymphadenectomy. Acta Obstet Gynecol Scand. 81(12): 1144-51.

[5]. Hoyer M, Ljungstroem B, Nyland M, Jakobsen A (1990) Radical hysterectomy in cervical carcinoma stage Ib. Eur J Gynaecol Oncol. 11(1): 13-17.

[6]. Larsen LG, Rank F (1988) Adenocarcinoma of the uterine cervix.[in Danish] Ugeskr Laeger. 150:469-71.

[7]. Eide TJ (1987) Cancer of the uterine cervix in Norway by histologic type, 1970-84. J Natl Cancer Inst. 79(2): 199-205.

[8]. Pekin T, Kavak Z, Yildizhan B, Kaya H (2001) Prognosis and treatment of primary adenocarcinoma and adenosquamous cell carcinoma of the uterine cervix. Eur J Gynaecol Oncol. 22(2): 160-3.

[9]. Grisaru D, Covens A, Chapman B, Shaw P, Colgan T, Murphy J, et al., (2001) Does histology influence prognosis in patients with early-stage cervical carcinoma? Cancer. 92(12): 2999-3004.

[10]. Lea JS, Coleman RL, Garner EO, Duska LR, Miller DS, Schorge JO (2003) Adenosquamous histology predicts poor outcome in low-risk stage IB1 cervical adenocarcinoma. Gynecol Oncol. 91(3): 558-62.

[11]. Shingleton HM, Bell MC, Fremgen A, Chmiel JS, Russell AH, Jones WB et al., (1995) Is there really a difference in survival of women with squamous cell carcinoma, adenocarcinoma, and adenosquamous cell carcinoma of the cervix? Cancer. 76(10): 1948-55.

[12]. Farley JH, Hickey KW, Carlson JW, Rose GS, Kost ER, Harrison TA (2003) Adenosquamous histology predicts a poor outcome for patients with advanced-stage, but not early-stage, cervical carcinoma. Cancer. 97(9): 2196-202.

[13]. Look KY, Brunetto VL, Clarke-Pearson DL, Averette HE, Major FJ, Alvarez RD, et al., (1996) An analysis of cell type in patients with surgically staged stage IB carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol. 63(3): 304-11.

[14]. Harrison TA, Sevin BU, Koechli O, Nguyen HN, Averette HE, Penalver M, et al., (1993) Adenosquamous carcinoma of the cervix: prognosis in early stage disease treated by radical hysterectomy. Gynecol Oncol. 50(3): 310-5.

[15]. Knudsen HJ, Rasmussen KL, Ledertoug S, Mamsen A, Nyland M, Jakobsen A (1995) A comparison of survival and side effects in two periods with a different approach to radical hysterectomy as treatment of cervical cancer stages 1b and 2a. Zentralbl Gynakol. 117(9): 476-480.

[16]. Tay EH, Yeap ML, Ho TH (1997) A 5-year review of FIGO stage IB cervical cancer in an Asian population. Singapore Med J. 38(12): 520-4.

[17]. Peters WA, Liu PY, Barrett RJ 2nd , Stock RJ, Monk BJ, Berek JS, et al., (2000) 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. 18(8): 1606-13.

[18]. Kjær SK, Storm HH (1993) Survival of Danish cancer patients 1943-1987. Female genital organs. APMIS. 33:107-21.

[19]. Duyn A, Van Eijkeren M, Kenter G, Zwinderman K, Ansink A (2002) Recurrent cervical cancer: detection and prognosis. Acta Obstet Gynecol Scand. 81(8): 759-63.

[20]. Chen RJ, Lin YH, Chen CA, Huang SC, Chow SN, Hsieh CY (1999) Influence of histologic type and age on survival rates for invasive cervical carcinoma in Taiwan. Gynecol Oncol. 73(2): 184-90.