Minor prognostic factors in squamous cell vulvar carcinoma

J. R. Kouvaris[1], V. E. Kouloulias[1], C. D. Loghis[2], E. J. Balafouta[1], A. C. Miliadou[1], L. J. Vlahos[1]

Department of [1]Radiology-Radiotherapy and [2]2nd Obstetrics-Gynecologic Clinic; Aretaieion Hospital, University of Athens (Greece)

Summary

Purpose of the study: To evaluate minor prognostic factors in a patient population with squamous cell vulvar carcinoma, with particular attention to age, smoking, obesity and parity.

Methods: A total of 50 women with invasive squamous cell vulvar carcinoma were retrospectively analyzed. Factors assessed for prognostic value included age, obesity, diabetes, hypertension, smoking and parity.

Results: The log-rank test and the univariate regression analysis revealed that all factors decreased the overall survival. In the multivariate regression analysis only age, obesity, smoking and parity were independent predictors for survival. The relative risk of death for elderly and patients, obese smokers, and patients with more than three deliveries was 1.008, 1.159, 1.411 and 2.532, respectively. Hypertension and diabetes seemed to be questionable prognostic factors.

Conclusion: Smokers, patients who had more than three children, body mass index >27, and were older than 73 years had a poorer survival rate.

Key words: Vulvar carcinoma; Prognostic factors; Smoking; Obesity; Parity.

Introduction

Vulvar carcinoma is relatively uncommon and its epidemiology is incompletely understood. The impact of major prognostic factors (stage, grade differentiation, node involvement, tumor diameter, depth of invasion and adequate free surgical margins) on overall and disease-free survival is undoubted [1-3]. On the contrary there are few studies on the impact of some minor factors (age, obesity, smoking, diabetes mellitus, hypertension and parity) as prognostic variables [4-6].

The objective of this study was to evaluate some minor prognostic factors in survival.

Material and Methods

From February 1979 to May 1997, 52 patients with invasive squamous cell carcinoma of the vulva were hospitalized in Aretaieion Hospital, Athens University, for staging and treatment. Two patients were excluded from the study for incomplete data and follow-up. The following demographic data were obtained: age, height and weight, smoking history, parity and medical history of diabetes mellitus and hypertension. Blood pressure was regarded high if the systolic was above 140 mmHg and the diastolic above 90 mmHg (140/90). The severity of hypertension was recorded as mild in all hypertensive patients, since diastolic pressure was between 90 and 99 mmHg. The duration of hypertension was a minimum of five years. All diabetic patients were insulin-dependent, but poorly controlled. The staging of disease was performed according to the FIGO criteria (1983 and 1995 revision) [7, 8] in most cases.

Patient distribution according to stage is shown in Table 1. All 17 Stage I patients and two stage II patients were evaluated clinically, as no inguinal lymphadenectomy was performed. The patients were operated on within 20 days after diagnosis. The patient distribution according to stage and surgical procedure is shown in Table 1. All patients received postoperative radiotherapy. The relative accuracy of clinical estimates of lymph node involvement if there are no palpable nodes is 52% [9], and the possibility of lymph node involvement in stage I and II patients without previous treatment is 15.2% and 34.2%, respectively [10]. Nineteen patients (17, stage I; and 2, stage II) had no lymph node biopsy. The remaining patients with stage II were at high risk for recurrence (positive or ≤ 10 mm margins of excision and low differentiation) [11]. Some of them lived in remote areas and a regular clinical examination was impossible. Radiotherapy was given as an adjuvant treatment in stages I and II. Irradiation was directed at the bilateral groin nodes and perineum. Stage III and IV patients were additionally irradiated at the pelvic nodes. Doses ranged from 32.4-54 Gy (median 50 Gy) and the boost dose from 10-20 Gy. The reference depth for inguinal lymph nodes was 3-4 cm. Radiotherapy was given from a 6Mev linear accelerator. Recurrence of the disease was recorded according to the time interval from diagnosis to recurrence. Overall survival was registered according to the time interval from diagnosis to death due to disease. The follow-up was continuous, every six months after treatment until death and ranged from 6 to 155 months (median 61 months).

The Body Mass Index (BMI) was used to evaluate obesity. The impact of surgical operation to survival was calculated using the Breslow test pooled over data [12]. The actuarial survival and overall survival for patient groups were calculated using the Kaplan-Meier method. Minor prognostic factors contributing to overall survival were assessed using the log-rank method and Gehan-test. The impact of factors on overall survival was calculated with the Cox-regression model in order to determine their independent contribution to the risk of death. Cox regression analysis was conducted in two steps. In step one univariate regression was estimated individually for each possible prognostic factor. In step two all prognostic factors from the univariate model were entered into a forward stepwise selection routine (likelihood ratio criterion, chi-square model p for entry = 0.05). The analysis was performed using the Statistical Packet for Social Sciences (SPSS, version 6.0, Inc. Chicago, USA).

Revised manuscript accepted for publication April 18, 2001

Table 1. — *Patient distribution according to stage and surgical procedure*

Stage	Patients	%	RWE	RV	TIT
CI I	17	34	17		
CI II	2	32	2		
II	14			7	7
III	12	24			12
IVa	5	10			5
Total	50	100	19	7	24

RWE: Radical Wide Excision; RV: Radical Vulvectomy; TIT: Triple Incision Technique.

Results

Patient age ranged from 38 to 84 years (median 73.5). The BMI ranged from 19.9 kr/m^2 to 33.3 kr/m^2 with a mean value of 25.3 (SD±3.1). Forty-five out of 50 patients (90%) were multiparous. Regarding obstetric history, 54% of patients (27 of 50 women) had no history of abortions, and 90% of patients (45 of 50 women) were multiparas. Eight of 45 multiparas had one or more cesarean deliveries. Of the remaining five patients, two were nulliparas and three were primiparas. One patient had delivered by cesarean section. Thirty-six patients (72%) had more than three deliveries in their obstetric history. Thirty of 50 patients (60%) suffered from diabetes mellitus, 37 patients (74%) had hypertension and 32 (64%) had been smoking more than ten cigarettes per day for over a year. The patient distribution according to stage was Stage I: 17 (34%), Stage II: 16 (32%), Stage III: 12 (24%) and Stage IVa: 5 (10%).

The overall actuarial survival at 2, 3 and 5 years was 62% (SE = Standard Error: 6), 44% (SE: 7.0) and 12% (SE: 4.6), respectively. The 5-year overall actuarial survival according to stage was 60.6% (SE 8.5) for clinical stage I, 64.7% (SE 11.6) for stage II, including the two cases of clinical staging and 17.5% (SE 11.5) for stage III/IVa. The median overall survival in months for stage I/II and III/IVA was 38.9 (SE 7.4) and 13.4 (SE 2.4), respectively (p=0.0004, log-rank test). The Breslow test for comparing the overall survival distributions between different surgical operations showed no statistically significant differences (p=NS).

The population was dichotomized according to median value of age (73.5 years). Patients aged ≥73.5 years had a significant decrease in overall survival (p=0.036, log-rank test). Patients with BMI <27 had a better overall survival (p=0.005). The 2-year actuarial overall survival rates for BMI <27 vs. ≥27 were 78.5% (SE 10.6) and 33.3% (SE 7.8), respectively (p=0.008, Gehan test). The 3-year overall actuarial survival for patients with or without diabetes mellitus was 10% (SE 0.5) and 75% (SE 9.7), respectively (p<0.0001, Gehan test). Patients with or without a medical history of hypertension had a 3-year overall survival of 24.3% (SE 7.0) and 84.8% (SE 10.0), respectively (p<0.0001, Gehan test). Patients with a smoking history had a 5-year overall survival of 3.2% (SE 3.1), in contrast to 27.6% (SE 10.6) for nonsmoking patients (p<0.0001, Gehan test). Patients with >3 versus ≤3 deliveries had a significant decrease in median overall survival (p<0.0001, log-rank test). The Kaplan-Meier survival distribution for all subjects as well as for patients with >3 deliveries versus < deliveries is shown in Figure 1. Table 2 summarizes the results of the log-rank test for overall survival.

Table 2. — *Synoptic table of log-rank test for overall survival of vulvar carcinoma (months)*

Factors		Median overall survival (SE)	p
Stage	I/II	38.9 (7.4)	0.0004
	III/IVa	13.4 (2.4)	
Age	<73.5	38.4 (7.5)	0.036
	≥73.5	29.7 (2.5)	
BMI	<27	40.7 (3.2)	0.005
	≥27	25.8 (4.2)	
Diabetes	Yes	18.6 (2.6)	<0.0001
	No	44.1 (1.5)	
Hypertension	Yes	24.3 (2.9)	<0.0001
	No	49.3 (4.1)	
Smoking	Yes	20.6 (3.7)	0.0001
	No	44.2 (3.7)	
Deliveries	≤3	49.3 (7.6)	<0.0001
	>3	27.3 (2.2)	

BMI = Body Mass Index. N.S. = non significant (p>0.05).

Table 3. — *Risk factors for decreased overall survival due to vulvar carcinoma: Univariate and stepwise multivariate Cox regression analysis. Significance of log likehood-ratio for stage, age, BMI, smoking and deliveries >3 in multivariate analysis was 0.0013, 0.039, 0.0068, 0.015 and 0.0118, respectively. The multivariate model chi-square with five degrees of freedom was 13.554 (p=0.0187)*

Covariates	Univariate analysis		Multivariate analysis	
	p	Relative risk (CI)	p	Relative risk (CI)
Stage III/IVa	0.0026	4.611 (1.705, 12.469)	0.008	3.025 (1.586, 5.770)
Age	0.0385	1.031 (1.010, 1.059)	0.043	1.008 (1.002, 1.041)
BMI	0.014	1.149 (1.005, 1.394)	0.0089	1.159 (1.038, 1.294)
Diabetes	0.0122	1.038 (1.006, 1.099)	N.S.	—
Hypertension	0.044	1.024 (1.001, 1.075)	N.S.	—
Smoking	0.0177	2.091 (1.172, 3.077)	0.023	1.411 (1.172, 2.007)
Deliveries >3	0.0190	2.381 (1.153, 4.925)	0.021	2.532 (1.165, 5.503)

N.S. = non significant (p-value >0.05). CI = 95% confidence interval.

Results of univariate and multivariate Cox-regression analysis regarding the impact of the above factors to overall survival are entered in the model described in Table 3. According to the univariate analysis all factors significantly influenced overall survival. The relative risk of death for stage, age, obesity, more than three deliveries, smoking, hypertension and diabetes was 4.611 (p=0.0026), 1.031 (p=0.0385), 1.149 (p=0.014), 2.581 (p=0.0190), 2.091 (p=0.0177), 1.024 (p=0.044) and 1.038 (p=0.0122), respectively. These factors were subsequently tested on a multivariate model in terms of stepwise Cox-regression analysis. Thus the only significant effect on overall survival was due to stage (p=0.008), age (p=0.043), obesity (p=0.0089), smoking (p=0.023) and more than three deliveries (p=0.021) as independent factors, while the medical history of diabetes and hypertension lost its prognostic value (p>0.05). The Cox-pro-

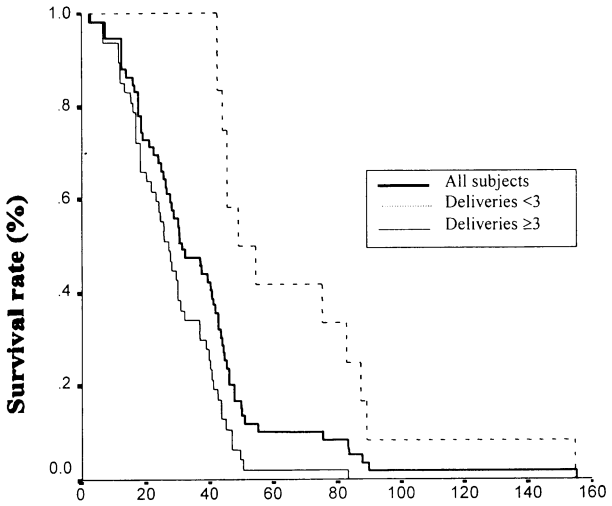

Figure 1. — Kaplan-Meier survival distribution for all subjects as well as for patients with more than three deliveries versus less than three deliveries ($p<0.001$, log-rank test).

portional hazard model revealed that the relative risk of death for advanced stage, elderly and obese patients, smokers and patients with >3 deliveries was 3.025, 1.008, 1.159, 1.411 and 2.532, respectively.

Discussion

Since vulvar carcinoma yields early symptoms, its prognosis should be very favorable. Unfortunately this is not always true because there are factors and circumstances related to age and life style that may modify the prognosis.

According to our results there was a poor five-year overall survival for both stage I and II. The five-year survival for the FIGO 1 cases was 60.6%, which is about 10% less than FIGO data, but the FIGO 2 patients had a better five-year survival of 64.7%. The reason is associated with the fact that 38% of our patients were staged clinically concerning the presence of regional lymph node metastases, and as a matter of fact, the risk for substaging was exceptionally high. Among the 19 patients with clinical stage I/II, six patients with stage I (35.3%) and one with stage II presented inguinal lymph node recurrence within two years after treatment. This reflects inappropriate staging and therefore inadequate treatment. In our opinion radiation doses of 45Gy given in 3-cm depth are insufficient to prevent lymph node recurrences in patients with clinical stage I/II without lymph-node dissection.

Most authors agree that advanced age, smoking and a compromised immune system are risk factors for developing vulvar carcinoma [5, 13-16], while there are many controversies on the role of obesity, diabetes mellitus, hypertension and parity [4-6, 13-15, 17]. The impact of the above factors on the prognosis of vulvar carcinoma has not been well established. Andreasson *et al.* [17] concluded that age belongs among the clinical variables with a significant prognostic value. Moreover, Frankman *et al.* [18] and Kosary [19] reported a negative impact of age on survival. Andreasson *et al.* [13] concluded that obesity had a negative impact on survival. On the contrary Kirschner *et al.* [4] reported no significant impact of obesity on overall survival.

In vulvar carcinoma it has been reported that smokers have a 6.3 times greater risk of death than nonsmokers due to the deleterious effects of smoking on the immune system [4]. A decrease of survival in smokers was observed, despite younger age and fewer positive nodes at diagnosis, compared to nonsmokers. Kirschner *et al.* reported that diabetes and hypertension showed no negative impact on survival [4]. According to Busch *et al.* [6] parity is a significant independent factor affecting survival. Patients with 0-3 children had significantly better results (32% at 5 years) than patients with 4-7 children (11%).

Conclusion

Despite the small number of patients and the inhomogeneity of staging, the examined minor factors affected prognosis as follows: Age seemed to have a negative, although critical, impact on survival ($p=0.043$). Obese patients had a relative risk of death up to 1.159. Smokers versus nonsmokers had 1.411 greater risk of death. Diabetes and hypertension had a questionable impact on survival since there was disagreement between univariate and multivariate analyses. Women with more than three children had 2.532 times greater risk of death than patients with 0-3 children. Finally it is important to state that radical surgery is the treatment of choice for patients with vulvar carcinoma, and radiation therapy doses of ≤45Gy given in 3 cm depth are insufficient to prevent recurrences.

References

[1] Heaps J. M., Fu Y. S., Montz F. J., Hacker N. F., Berek J. S.: "Surgical-pathological variables predictive of local recurrence in squamous cell carcinoma of the vulva". *Gynecol. Oncol.*, 1990, *38*(3), 309.

[2] Homesley H. D., Bundy B. N., Sedlis A., Yordan E., Berek J. S., Jahshan A., Mortel R.: "Assessment of current International Federation of Gynecology and Obstetrics staging of vulvar carcinoma relative to prognostic factors of survival (A Gynecologic Oncology Group Study)". *Am. J. Obstet. Gynecol.*, 1991, *164*(4), 997.

[3] Piura B., Masotina A., Murdoch J., Lopes A., Morgan P., Monaghan J.: "Recurrent squamous cell carcinoma of the vulva: A study of 73 cases". *Gynecol. Oncol.*, 1993, *48*(2), 189.

[4] Kirschner C. V., Yordan E. L., De Geest K., Wilbanks G. D.: "Smoking, obesity, and survival in squamous cell carcinoma of the vulva". *Gynecol. Oncol.*, 1995, *56*(1), 79,

[5] Brinton L. A., Nasca P. C., Mallin K., Baptiste M. S., Wilbanks G. D., Richart R. M.: "Case control study of cancer of the vulva". *Obstet. Gynecol.*, 1990, *75*(5), 859.

[6] Busch M., Wagener B., Duhmke E.: "Long-term results of radiotherapy alone for carcinoma of the vulva". *Adv. Ther.*, 1999, *16*(2), 89.

[7] Shepherd J. H.: "Revised FIGO staging for gynecological cancer". *Br. J. Obstet. Gynecol.*, 1989, *96*(8), 889.

[8] Creasman W. T.: "New gynecologic cancer staging". *Gynecol. Oncol.*, 1995, *58*(2), 157.

[9] Green T. H Jr., Ulfelder H., Meigs J. V.: "Epidermal carcinoma: An analysis of 238 cases. I. Etiology and diagnosis". *Am. J. Obstet. Gynecol.*, 1958, *75*, 834.
[10] McKelvey J. L., Adcock L. L.: "Cancer of the vulva". *J. Obstet. Gynecol.*, 1965, *26*(4), 455.
[11] Perez C. A., Grigsby P. W., Clifford Chao K. S., Garipagaoglu M.: "Vulva". In: Perez C. A., Brady L. W. eds. "Principles and Practice of Radiation Oncology". Philadelphia, Lippincott 3rd edition 1998, 1915.
[12] Abraham B., Ledolter J.: "Statistical Methods for Forecasting". New York, Wiley & Sons, 1983.
[13] Andreasson B., Nyboe J.: "Value of prognostic parameters in squamous cell carcinoma of the vulva". *Gynecol. Oncol.*, 1985, *22*(3), 341.
[14] Ansink A. C., Heintz A. P.: "Epidemiology and etiology of squamous cell carcinoma of the vulva". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 1993, *48*, 11.
[15] Carter J., Carlson J., Fowler J., Hartenbach E., Adcock L., Carson L. *et al.*: "Invasive vulvar tumors in young women. A disease of the immunosuppressed?". *Gynecol. Oncol.*, 1993, *51*(3), 307.
[16] Daling J. R., Sherman K. J., Hislop T. G., Maden C., Mandelson M. T., Beckmann A. M. *et al.*: "Cigarette smoking and the risk of anogenital cancer". *Am. J. Epidemiol.*, 1992, *135*(2), 180.
[17] O'Mara B. A., Byers T., Schoenfeld E.: "Diabetes mellitus and cancer risk: A multisite case-control study". *J. Chronic. Dis.*, 1985, *38*(5), 435.
[18] Frankman O., Kabulski Z., Nilsson B., Silfversward C.: "Prognostic factors in invasive squamous cell carcinoma of the vulva". *Int. J. Gynaecol. Obstet.*, 1991, *36*(3), 219.
[19] Kosary C. L.: "FIGO stage, histology, histologic grade, age and race as prognostic factors in determining survival for cancers of the female gynecological system: An analysis of 1973-87 SEER cases of cancers of the endometrium, cervix, ovary, vulva, and vagina". *Semin. Surg. Oncol.*, 1994, *10*(1), 31.

Address reprint requests to:
JOHN R. KOUVARIS, M.D.,
Asso. Professor of Radiotherapy
Aretaieion Hospital
76, Vas. Sophias Ave
Athens 115 28 (Greece)