Tumor Location of the Lower-Inner Quadrant Is Associated with an Impaired Survival for Women With Early-Stage Breast Cancer

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Background: There is growing evidence that tumors of the inner quadrants (especially the lower-inner quadrant) metastasize more often to the internal mammary chain (IMC). As these metastases are not investigated, patients with lower-inner quadrant tumors have an increased risk of being under-staged and under-treated and may therefore have a higher risk of death from breast cancer.

Methods: We identified all 1522 women operated for stage I breast cancer between 1984 and 2002 recorded at the population-based Geneva Cancer Registry. We compared breast cancer mortality risk by tumor location with multivariate Cox regression analysis that accounted for all factors linked to tumor location and survival.

Results: Ten-year disease-specific survival was 93% (95%CI: 91–94%). Patients with breast cancer of the lower-inner quadrant (n = 118; 7.8%) had an importantly increased risk of dying of breast cancer compared to women with breast cancer of the upper-outer quadrant (multiadjusted Hazard Ratio: 2.3, 95%CI: 1.1–4.5, $P = 0.0206$). The over-mortality associated with this quadrant was particularly evident for tumors > 10 mm (multiadjusted HR: 3.6, 95%CI: 1.6–7.9, $P = 0.0016$). There was no increased breast cancer mortality risk for tumors located in other quadrants.

Conclusions: Tumor location in the lower-inner quadrant is an independent and important prognostic factor of stage I breast cancer. Further research is needed to evaluate if the over-mortality of patients with stage I cancer of the lower-inner quadrant is indeed a result of under-treatment due to undetected IMC metastases. If so, patients with stage I breast cancer of the lower-inner quadrant are good candidates for systematic IMC investigation.

Key Words: Breast cancer—Early-stage—Population-based—Survival—Tumor location.

With the generalization of mammography screening, many breast cancers are detected at an early stage. Women diagnosed with tumors of ≤ 20 mm, without lymph node involvement and distant metastases (T1 N0 M0, stage I), have a five-year disease-specific survival of approximately 98%.[1] Despite this excellent general prognosis, some patients with early stage breast cancer die of their disease. These deaths are often related to poor tumor differentiation,

absence of hormonal receptors, or suboptimal treatment.[2,3] Erroneous staging could also be a reason for some of these breast cancer deaths.

Veronesi and colleagues performed a systematic surgical evaluation of the internal mammary chain (IMC) and found that approximately 10% of breast cancers without axillary lymph node involvement metastasize to the IMC.[4] This risk of IMC involvement increases with tumor size.[4,5] In addition, the presence of IMC metastases depends on tumor location in the breast, with a higher prevalence of IMC metastases in tumors of the inner quadrants, especially the lower-inner quadrant.[6–8]

The IMC is not routinely investigated for the presence of lymph node metastases, and breast cancer is classified as lymph node negative on the basis of axillary lymph node investigations only. Undetected IMC metastases, therefore, lead to under-staging of patients without axillary lymph node involvement and to under-treatment of stage I patients who have no indication of adjuvant chemotherapy. There is growing evidence that tumors occurring in the inner quadrants have a higher breast cancer mortality.[9–12] However, the real impact of tumor location on the risk of IMC node metastases and on prognosis is still controversial, mainly because of the inconclusive findings in older studies.[4,13–15]

We used data from the Geneva Cancer Registry to evaluate the impact of tumor location on breast cancer mortality among women with stage I disease.

PATIENTS AND METHODS

The Geneva Cancer Registry records all incident cancer cases occurring in the population of the canton since 1970. Registration is based on various sources of information and can be considered as accurate, as attested by its low percentage (2%) of cases recorded from death certificates only. Every public hospital, private clinic, pathology laboratory, and physician is requested to report all cancer cases. Individual clinical files from the university public hospitals are systematically consulted and inquiry forms are sent to physicians for patients treated in the private sector. The registry actively assesses survival by an annual, systematic check of vital status in the files of the Cantonal Population Office and passively by routine examination of hospital records and death certificates. The cause of death is systematically recorded and validated. Recorded data include sociodemographic characteristics, method of discovery, tumor characteristics (coded according to the International Classification of Diseases for Oncology [ICD-O]), stage (according to tumor, lymph node, and metastasis classification TNM), treatment during the first six months after diagnosis, healthcare sector, and date and cause of death (coded according to the World Health Organization's classification).

We selected all women operated between 1984 and 2002 (n = 1695) for invasive stage I breast cancer, defined as pathological pT1 (≤ 2 cm), pN0 (no lymph node invasion), and without distant metastases. We excluded women with other breast cancers (n = 108) or other invasive cancers (except non-melanoma skin cancer) (n = 65) before or within six months after their breast cancer diagnosis. The study finally included 1522 women.

Variables of interest included age (in continuous), period of diagnosis (1984–1989; 1990–1994; 1995–1999; 2000–2002), method of discovery (symptoms or fortuitous, i.e. diagnosis during the work-up of an unrelated illness, breast self-examination, and screening), civil status (single, married, widowed, and divorced/separated), place of birth (Switzerland, Southern Europe, and other), socioeconomic status based on the woman's last occupation (high, middle, low, unknown), and healthcare sector in charge of breast cancer surgery (private clinics or public university hospitals).

Histologic types were regrouped as ductal (ICD-O codes 8010, 8140, and 8500), lobular (ICD-O codes 8520 and 8522), mucinous (ICD-O codes 8480 and 8481), and other. Tumor differentiation was classified as good (grade I), moderate (grade II), poor (grade III), or unknown. Estrogen receptor status was classified as negative, positive (when ≥ 10% of cells expressed estrogen receptors), or unknown. Tumor size was regrouped as 1–10 mm, 11–20 mm, or unknown. IMC lymph node status was not systematically assessed during the study period in Geneva and the Geneva Cancer Registry has no information on IMC lymph node involvement. Surgery was classified as mastectomy, surgery with positive margins, and breast-conserving surgery. Radiotherapy was considered as yes vs. no. Systemic treatment was categorized as chemotherapy (yes, no) and hormone therapy (yes, no).

We considered the following anatomical breast locations: upper-outer quadrant (ICD-O codes C50.4, C50.6), upper-inner quadrant (ICD-O code C50.2), lower-outer quadrant (ICD-O code C50.5), lower-inner quadrant (ICD-O code 50.3), nipple and central portion of the breast (ICD-O codes C50.0, C50.1), and overlapping quadrant (ICD-O code C50.8), and unknown (ICD-O code C50.9).

Associations between tumor location and socio-demographic, tumor and treatment characteristics were evaluated by chi-square test. With multivariate logistic regression analysis, we identified factors independently and significantly linked to tumor location.[16] Breast cancer-specific survival was calculated using the actuarial method, considering death from breast cancer only. We applied the log-rank test to evaluate differences in survival curves. By means of univariate Cox proportional hazards analysis, we identified all variables significantly associated with breast cancer mortality. With multivariate analysis, adjusting for all variables significantly associated with breast cancer mortality or tumor location, we estimated the effect of tumor location on breast cancer mortality.

Because larger tumors are more prone to metastasize, we tested for the interaction between tumor location and size to investigate if the effect of location was similar for larger (11–20 mm) and smaller tumors (1–10 mm).[16] Moreover, because chemotherapy decreases the higher mortality associated with positive lymph nodes, we also tested for interaction between tumor location and use of adjuvant chemotherapy. Statistical analyses were performed with SPSS software (SPSS 11.5 version Inc., Chicago, IL).

RESULTS

Among the 1522 patients operated for stage I breast cancer, the most common tumor location was the upper-outer quadrant (39%), followed by lesions located in overlapping quadrants (27%), the upper-inner quadrant (14%), the lower-outer quadrant (8%), the lower-inner quadrant (8%), and the central portion of the breast and the nipple (4%). The median follow-up was 7.7 years and 472 patients (31%) had a follow-up of 10 years or more. During the study period, 81 patients (5%) died as a result of breast cancer and 130 patients (8%) were lost to follow-up as they had left Geneva for another canton or country. Ten-year specific survival was 93% (95%CI: 91–94%).

Breast cancer-specific survival curves according to tumor location are presented in Fig. 1. The 10-year specific survival was 94% (95%CI: 91–96%) for patients with cancer of the upper-outer quadrant, 96% (95%CI: 92–99%) for the upper-inner quadrant, 91% (95%C: 85–98%) for the lower-outer quadrant, 94% (95%CI: 87–100%) for the central part of the breast and the nipple, and 93% (95%CI: 89–96%) for overlapping lesions. For patients with tumors of the lower-inner quadrant, however, the 10-year disease specific survival was significantly lower, 88% (95%CI: 81–96%, *P* log-rank test 0.0002).

Table 1 shows that tumors of the lower-inner quadrant were less often detected by screening (*P* = 0.011), were less frequently of lobular histology (*P* = 0.014), were more often poorly differentiated (*P* = 0.031), had less frequently breast conserving surgery and more frequently mastectomy (*P* = 0.003), and received less often hormone therapy (*P* = 0.031). In the multiadjusted logistic regression, only histology, poor differentiation, and type of surgery remained significantly and independently associated with tumor location in the lower-inner quadrant.

Tables 2 and 3 present the effect of patient and tumor characteristics and treatments on breast cancer mortality. In the multivariate model, we included all variables that were significantly associated with mortality in univariate analysis (i.e. age, period, method of discovery, grade, tumor size, surgery, radiotherapy, tumor location), factors significantly associated with tumor location (i.e. method of discovery, histologic type, grade, type of surgery, and hormone therapy), period of diagnosis, and age.

Table 4 presents the impact of tumor location on breast cancer mortality. In multiadjusted Cox proportional hazard analysis, tumor location remains a significant prognostic factor. Women with tumors located in the lower-inner quadrant of the breast had a more than two-fold increased risk of dying as a result of breast cancer compared with women with tumors of the upper-outer quadrant (multi-adjusted HR: 2.3, 95%CI: 1.1–4.5, *P* = 0.021). Tumor location in other quadrants was not associated with a significantly altered mortality risk.

The effect of lower-inner location appeared to be more obvious in patients with tumors larger than 10 mm (n = 1001, multi-adjusted HR: 3.6, 95%CI: 1.6–7.9, *P* = 0.002) than among patients with smaller tumors (n = 491, age adjusted HR: 1.0, 95%CI: 0.2–4.6, *P* = 0.970) and in patients who did not receive adjuvant chemotherapy (n = 1,261, multi-adjusted HR: 2.5, 95%CI: 1.2–5.4, *P* = 0.016) than in patients who underwent chemotherapy (n = 261, age-adjusted HR: 1.6, 95%CI: 0.2–13.2, *P* = 0.662). However, none of the interaction tests between location and size or between location and chemotherapy were statistically significant (*P* = 0.134 and *P* = 0.913, respectively). Since we observed only few deaths (n = 20) among patients with tumors ≤ 10 mm and among patients with chemotherapy (n = 15), we adjusted the hazard ratio's only for age in these subgroup analyses.
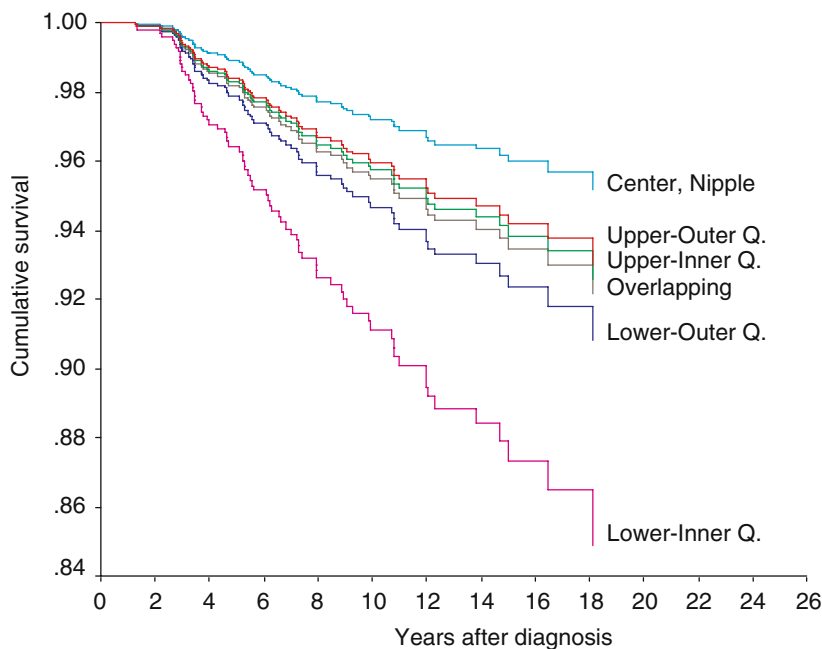
Number of women at risk at the beginning of each period

Year	1st	5th	10th	15th	18th
Center, nipple	54	36	25	10	4
Upper-outer	588	424	217	74	30
Upper-inner	212	137	70	27	11
Overlapping	413	283	137	55	24
Lower-outer	118	82	43	24	9
Lower-inner	118	84	45	18	6

[a] Survival curves derived from Cox model adjusted for age (variable in continuous), period of diagnosis, method of discovery, grade, tumor size, surgery, radiotherapy, tumor location, histologic type and hormone therapy; Only deaths from breast cancer are considered.

FIG. 1. Specific survival curves[a] according to tumor location among women operated for stage 1 breast cancer, Geneva Cancer Registry, 1984–2002.

DISCUSSION

This study shows that tumor location within the breast is an important and independent prognostic factor of early-stage breast cancer. After adjustment for all factors linked to tumor location or prognosis, patients with tumors of the lower-inner quadrant have a more than two-fold increased risk of dying as a result of breast cancer compared to patients with tumors of the upper-outer quadrant. No difference in mortality from breast cancer was observed for the other tumor locations. Differences in tumor characteristics or treatment did not explain the over-mortality associated with the lower-inner quadrant. The results of this study also suggest that the impact of tumor location is more pronounced for women with larger tumors and for women who are not treated with adjuvant chemotherapy.

We acknowledge that we had information on various prognostic factors for breast cancer. However, for a relatively high proportion of patients (49%), we had no information on estrogen receptor status as this information became available only after 1995. When considering only patients diagnosed after this date (n = 798, proportion of patients with unknown receptor status: 3%), we observed similar results (multiadjusted HR for tumors of the lower-inner quadrant compared to the upper-outer quadrant: 3.7, 95% CI: 0.7–18.7, $P = 0.110$). We also acknowledge that our study has limited power for subgroup analyses due to the relatively low number of breast cancer deaths occurring in patients with stage I breast cancer.

TABLE 1. *Patient and tumor characteristics according to tumor location among patients operated for stage I breast cancer, Geneva Cancer Registry, 1984–2002*

	Tumor location		
	Lower-inner quadrant	Other	*P* value for X^2 of heterogeneity
Total	n = 118 (%)	N = 1404 (%)	
Age group			
< 40	8 (6.8)	73 (5.2)	0.673
40–49	21 (17.8)	268 (19.1)	
50–59	31 (26.3)	450 (32.1)	
60–69	38 (32.2)	373 (26.6)	
70–79	17 (14.4)	196 (14.0)	
≥ 80	3 (2.5)	44 (3.1)	
Period of diagnosis			
1984–1989	38 (32.2)	313 (22.3)	0.100
1990–1994	26 (22.0)	347 (24.7)	
1995–1999	32 (27.1)	416 (29.6)	
2000–2002	22 (18.6)	328 (23.4)	
Method of discovery			
Symptoms/fortuitous	60 (50.8)	528 (37.6)	0.011
Self-examination	22 (18.6)	274 (19.5)	
Screening	36 (30.5)	602 (42.9)	
Histologic type			
Ductal	99 (83.9)	1174 (83.6)	0.014
Lobular	3 (2.5)	119 (8.5)	
Mucinous	3 (2.5)	35 (2.5)	
Other	13 (11.0)	76 (5.4)	
Grade			
I	30 (25.4)	529 (37.7)	0.031
II	47 (39.8)	526 (37.5)	
III	21 (17.8)	186 (13.2)	
Unknown	20 (16.9)	163 (11.6)	
Tumor size			
1–10 mm	37 (31.4)	454 (32.3)	0.947
11–20 mm	79 (66.9)	922 (65.7)	
Unknown	2 (1.7)	28 (2.0)	
Estrogen receptor status			
Negative	8 (6.8)	95 (6.8)	0.254
Positive	44 (37.3)	631 (44.9)	
Unknown	66 (55.9)	678 (48.3)	
Surgery			
Mastectomy	38 (32.2)	361 (25.7)	0.003
Positive margins	6 (5.1)	20 (1.4)	
Breast-conserving surgery	74 (62.7)	1023 (72.9)	
Radiotherapy			
Yes	85 (72.0)	1066 (75.9)	0.344
No	33 (28.0)	338 (24.1)	
Chemotherapy			
Yes	17 (14.4)	244 (17.4)	0.411
No	101 (85.6)	1160 (82.6)	
Hormone therapy			
Yes	46 (39.0)	692 (49.3)	0.031
No	72 (61.0)	712 (50.7)	

Today, staging for breast cancer is mainly based on axillary lymph node status. Systematic IMC investigation stopped at the beginning of the 1980s after the publication of two important trials reporting no survival benefit for patients with negative axillary lymph nodes who underwent IMC dissection.[5,17] However, none of these patients received adjuvant therapy, even if they had axillary or IMC lymph node metastases. This could explain the lack of efficacy of IMC staging, as lymph node dissection is only a staging and not a curative procedure.[5]

Lymph node status, either axillary or internal mammary, is an important prognostic factor for patients with operable disease.[17,18] Patients with IMC metastases have an impaired prognosis compared to patients with no mammary or axillary lymph node metastases (10-year survival of 53 vs. 80%, respectively) and they have a similar survival as

TABLE 2. *Distribution and effect of sociodemographic characteristics, period of diagnosis and sector of care on breast cancer mortality among women operated for stage I breast cancer, Geneva Cancer Registry, 1984–2002*

Patient characteristics	N	%	N of death	%	10-year survival (95%CI)	Age-adjusted HR (95%CI)	Multiadjusted HR[a] (95%CI)
Age group							
< 40	81	5.3	8	9.9	0.82 (0.70–0.94)	2.1[b] (0.9–4.8)	1.4[b] (0.6–3.2)
40–49	289	19.0	19	23.5	0.93 (0.89–0.96)	1.2[b] (0.6–2.2)	0.8[b] (0.4–1.6)
50–59	481	31.6	21	25.9	0.93 (0.89–0.96)	1 (reference)	1 (reference)
60–69	411	27.0	17	21.0	0.94 (0.90–0.97)	1.0[b] (0.5–1.8)	0.8[b] (0.4–1.6)
70–79	213	14.0	14	17.3	0.95 (0.92–0.98)	1.3[b] (0.7–2.6)	1.2[b] (0.6–2.5)
≥ 80	47	3.1	2	2.5	0.95 (0.86–1.00)	1.0[b] (0.2–4.4)	0.6[b] (0.1–2.9)
Period of diagnosis							
1984–1989	351	23.1	44	54.3	0.89 (0.85–0.92)	1 (reference)	1 (reference)
1990–1994	373	24.5	22	27.2	0.95 (0.92–0.97)	0.6 (0.3–1.0)	0.9 (0.5–1.6)
1995–1999	448	29.4	14	17.3	0.95[c] (0.92–0.98)	0.5 (0.3–1.0)	1.2 (0.5–3.0)
2000–2002	350	23.0	1	1.2	0.99[d] (0.98–1.00)	0.3 (0.0–1.9)	0.6 (0.1–5.6)
Method of discovery							
Symptoms/fortuitous	588	38.6	56	69.1	0.90 (0.88–0.93)	1 (reference)	1 (reference)
Breast self-examination	296	19.4	6	7.4	0.95[c] (0.90–1.00)	0.5 (0.2–1.2)	0.6 (0.2–1.8)
Screening	638	41.9	19	23.5	0.95 (0.93–0.98)	0.5* (0.3–0.9)	0.8 (0.4–1.3)
Civil status							
Single	186	12.2	12	14.8	0.91 (0.85–0.97)	1 (reference)	1 (reference)
Married	916	60.2	51	63.0	0.92 (0.90–0.94)	0.8 (0.4–1.5)	1.0 (0.5–1.9)
Widowed	211	13.9	8	9.9	0.97 (0.94–1.00)	0.6 (0.2–1.4)	0.7 (0.2–1.7)
Divorced, separated	209	13.7	10	12.3	0.92 (0.86–0.97)	0.7 (0.3–1.6)	0.8 (0.3–1.8)
Place of birth							
Switzerland	816	53.6	45	55.6	0.93 (0.91–0.95)	1 (reference)	1 (reference)
Southern Europe	386	25.4	21	25.9	0.93 (0.89–0.96)	1.0 (0.6–1.7)	0.9 (0.5–1.6)
Other	320	21.0	15	18.5	0.92 (0.87–0.96)	1.1 (0.6–1.9)	1.1 (0.6–2.0)
Socioeconomic status							
High	204	13.4	10	12.3	0.94 (0.90–0.98)	1 (reference)	1 (reference)
Middle	686	45.1	39	48.1	0.92 (0.90–0.95)	1.1 (0.6–2.3)	1.1 (0.5–2.2)
Low	267	17.5	13	16.0	0.93 (0.89–0.97)	1.0 (0.4–2.3)	0.9 (0.4–2.3)
Unknown	365	24.0	19	23.5	0.92 (0.89–0.96)	1.0 (0.4–2.1)	1.0 (0.4–2.2)
Sector of care							
Private	917	60.2	45	55.6	0.93 (0.91–0.95)	1 (reference)	1 (reference)
Public	605	39.8	36	44.4	0.92 (0.89–0.95)	1.3 (0.8–2.0)	1.2 (0.8–2.0)

[a] Hazard ratio adjusted for age (variable in continuous), period of diagnosis, method of discovery, grade, tumor size, surgery, radiotherapy, tumor location, histologic type, and hormone therapy; [b] not adjusted for age, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$; [c] 9-year specific survival; [d] 4-year specific survival.

patients with axillary lymph node metastases.[15] The efficacy of adjuvant chemotherapy to reduce mortality in patients with lymph node positive disease has been well established.[19] Adjuvant radiotherapy of the IMC is still controversial and under investigation.[20,21] Misclassification of patients as having lymph node negative disease has minor consequences if adjuvant chemotherapy is already indicated. For patients who have no indication for adjuvant chemotherapy, such under-staging results in under-treatment and probably in a higher risk of death from breast cancer.

IMC investigation is a rather invasive procedure, even with minimally invasive techniques. Are the available data sufficient to propose systematic IMC investigations for women who have no indication for adjuvant chemotherapy and present stage I breast cancer located in the lower-inner quadrant? In fact, there is growing evidence that the lower-inner quad-rant drains more often to the IMC than the other quadrants.[8,22,23] In particular, Shahar and colleagues recently reported that 43% of the tumors of the lower-inner quadrant drains to the IMC compared to about 30% to the lower-outer quadrant or central portion, and approximately 15% of the other quadrants.[8] Some authors, though, concluded that the risk of IMC metastases does not depend on the quadrant. In particular, the large study on extended radical mastectomy performed by Veronesi and colleagues[4] showed an equal rate of IMC metastases for the inner and central quadrants (20%) and the outer quadrants (16%). Unfortunately, the 90 patients with tumors of the inner-lower were considered jointly with the 634 patients with tumors of the other inner and central quadrants. A reanalysis of this important series could therefore be particularly important to confirm whether IMC metastases are more frequent for cancers of the lower-inner quadrant or not.

TABLE 3. *Distribution and effect of tumor characteristics and treatment on breast cancer mortality among women operated for stage I breast cancer, Geneva Cancer Registry, 1984–2002*

Tumor characteristics and treatment	N	%	N of death	%	10-year survival (95%CI)	Age-adjusted HR (95%CI)	Multiadjusted HR^a (95%CI)
Histologic type							
Ductal	1273	83.6	71	87.7	0.92 (0.90–0.94)	1 (reference)	1 (reference)
Lobular	122	8.0	3	3.7	0.94 (0.88–1.00)	0.5 (0.2–1.7)	0.6 (0.2–2.0)
Mucinous	38	2.5	2	2.5	0.96 (0.87–1.00)	0.8 (0.2–3.4)	1.0 (0.2–4.5)
Other	89	5.8	5	6.2	0.94 (0.88–1.00)	0.8 (0.3–2.0)	0.7 (0.2–1.8)
Grade							
I	559	36.7	12	14.8	0.97 (0.94–0.99)	1 (reference)	1 (reference)
II	573	37.6	31	38.3	0.93 (0.90–0.95)	2.2* (1.1–4.2)	1.9 (1.0–3.8)
III	207	13.6	19	23.5	0.86 (0.80–0.92)	3.9*** (1.9–8.0)	3.5*** (1.7–7.4)
Unknown	183	12.0	19	23.5	0.91 (0.86–0.95)	2.6* (1.2–5.4)	1.6 (0.7–3.7)
Tumor size							
1–10 mm	491	32.3	20	24.7	0.94 (0.91–0.97)	0.7 (0.4–1.1)	0.7 (0.4–1.2)
11–20 mm	1001	65.8	54	66.7	0.93 (0.91–0.95)	1 (reference)	1 (reference)
Unknown	30	2.0	7	8.6	0.75 (0.57–0.93)	2.6* (1.2–5.8)	2.8* (1.1–7.1)
Estrogen receptors status							
Negative	103	6.8	5	6.2	0.92^b (0.86–0.99)	1 (reference)	1 (reference)
Positive	675	44.3	9	11.1	0.96^b (0.92–0.99)	0.3 (0.1–1.0)	0.6 (0.2–2.0)
Unknown	744	48.9	67	82.7	0.92 (0.90–0.94)	0.7 (0.3–1.9)	0.8 (0.1–7.8)
Surgery							
Mastectomy	399	26.2	37	45.7	0.90 (0.87–0.94)	1 (reference)	1 (reference)
Breast-conserving surgery	1097	72.1	42	51.9	0.94 (0.92–0.96)	0.6* (0.4–0.9)	0.8 (0.4–1.7)
Positive margins	26	1.7	2	2.5	0.94 (0.83–1.00)	3.4 (0.8–14.4)	4.0 (0.8–19.4)
Radiotherapy							
Yes	1151	75.6	48	59.3	0.93 (0.91–0.95)	1 (reference)	1 (reference)
No	371	24.4	33	40.7	0.92 (0.88–0.95)	1.6* (1.0–2.5)	1.1 (0.5–2.3)
Chemotherapy							
Yes	261	17.1	15	18.5	0.90 (0.84–0.95)	1 (reference)	1 (reference)
No	1261	82.9	66	81.5	0.93 (0.91–0.95)	0.8 (0.4–1.4)	1.0 (0.5–1.8)
Hormone therapy							
Yes	738	48.5	16	19.8	0.94 (0.90–0.97)	1 (reference)	1 (reference)
No	784	51.5	65	80.2	0.92 (0.89–0.94)	1.7 (1.0–3.1)	1.4 (0.7–2.8)

^{a} Hazard ratio adjusted for age (variable in continuous), period of diagnosis, method of discovery, grade, tumor size, surgery, radiotherapy, tumor location, histologic type, and hormone therapy; * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$; ^{b} 9-year specific survival as information on estrogen receptors was available only from 1995.

TABLE 4. *Distribution and effect of tumor location on breast cancer mortality among women operated for stage I breast cancer, Geneva Cancer Registry, 1984–2002*

Patient distribution	N	%	N of death	%	10-year survival (95%CI)	Age-adjusted HR (95%CI)	Multiadjusted HR^a (95%CI)
Location							
Upper-outer quadrant	588	38.6	25	30.9	0.94 (0.91–0.96)	1 (reference)	1 (reference)
Upper-inner quadrant	212	13.9	9	11.1	0.96 (0.92–0.99)	1.0 (0.5–2.2)	1.0 (0.5–2.2)
Lower-outer quadrant	118	7.8	7	8.6	0.91 (0.85–0.98)	1.3 (0.6–3.0)	1.3 (0.6–3.1)
Lower-inner quadrant	118	7.8	13	16.0	0.88 (0.81–0.96)	2.6** (1.3–5.0)	2.3* (1.1–4.5)
Centre, nipple	54	3.5	2	2.5	0.94 (0.87–1.00)	0.8 (0.2–3.6)	0.6 (0.1–2.8)
Overlapping quadrants	413	27.1	19	23.5	0.93 (0.89–0.96)	1.1 (0.6–2.1)	1.1 (0.6–2.0)
Unknown	19	1.2	6	7.4	0.69 (0.47–0.92)	–	–

^{a} Hazard ratio adjusted for age (variable in continuous), period of diagnosis, method of discovery, grade, tumor size, surgery, radiotherapy, tumor location, histologic type, and hormone therapy; * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Studies on the effect of tumor location on prognosis report inconsistent results. Some studies showed higher risks of death from breast cancer in patients with tumors of the inner quadrants,[9,10,12] or inner quadrants plus central portion of the breast,[11] or lower quadrants,[24] or all quadrants except the upper-outer quadrant,[25] whereas other studies showed no association whatsoever between tumor location and breast cancer prognosis.[13–15,26]

These inconsistencies could be explained by the fact that some studies that reported no association date from an era when women did not receive

adjuvant chemotherapy in case of axillary or IMC lymph node metastases.[4,14,15] It is impossible to evaluate an effect of undertreatment linked to understaging if node positive patients do not receive adjuvant treatment. One study did not observe increased breast cancer mortality but reported a significant increased risk of distant metastases in patients with inner quadrant tumors who did not receive chemotherapy.[13] Longer follow-up will probably show an increased mortality risk among these patients.

Another explanation for the discrepancies between the studies is that most previous studies included patients with positive axillary lymph nodes.[9–12,24,25,27,28] As these patients were already candidates for adjuvant therapy, the potential impact of undetected IMC metastases on survival was low. Among the few studies providing powerful subgroup analyses for lymph node negative patients,[9,12,25,29] the majority reported a stronger effect of tumor location on breast cancer mortality among lymph node negative patients.[9,25,29] Like our study, the recent study of Colleoni and colleagues reported that the effect of tumor location was greater for larger than for smaller tumours.[9]

As discussed above for the study of Veronesi and colleagues, the discrepancies between previous studies could also be explained by the dilution of the effect of the lower-inner quadrant, by regrouping this quadrant with other quadrants.[4] Unfortunately, most studies reporting an association between breast location and survival did not distinguish between the two inner quadrants or the two lower quadrants, making it impossible to draw any conclusion for just the lower-inner quadrant. When we regrouped patients with tumors of the inner quadrants and compared them to patients with tumors of all other quadrants, as performed in previous studies,[9,10,12] we found a similar mortality risk (HR: 1.3, 95%CI: 0.8–2.2, $P = 0.241$). Also, when we regrouped patients with tumors of the lower quadrants and compared them to patients with tumors of all other quadrants, as performed in one other study,[24] again we observed very comparable results (HR: 1.7, 95%CI: 1.0–2.8, $P = 0.058$).

With the generalization of sentinel lymph node biopsy for early breast cancer,[21,22,30] studies on the importance and consequences of IMC involvement among patients without axillary lymph node metastases become increasingly important. Systematic investigation of sentinel nodes of the IMC is feasible with an experienced team of professionals, even if difficulties exist in distinguishing between the radioactivity of the primary tumor located in the internal site of the breast and the radioactivity of the involved sentinel nodes in the IMC.

In conclusion, tumor location in the lower-inner quadrant is an independent and important prognostic factor for patients with node negative breast cancer. If further research demonstrates that this over-mortality is indeed due to a higher frequency of undetected IMC metastases, patients with stage I breast cancer of the lower-inner quadrant should become candidates for systematic evaluation of the IMC.

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