CLINICOPATHOLOGICAL CHARACTERISTICS OF SYNCHRONOUS BILATERAL BREAST CARCINOMAS. REPORT OF 30 PATIENTS

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CARACTÉRISTIQUES CLINICOPATHOLOGIQUES DU CARCINOME BILATÉRAL SYNCHRONE DES SEINS : A PROPOS DE 30 PATIENTS

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RÉSUMÉ

Objectif : Le but de cette étude est de déterminer les caractéristiques cliniques, anatomo-pathologiques, incidence et le pronotstic des carcinomes synchrones et bilatérales du sein (CSBS).

Méthodes : C'est une étude rétrospective faite à l'Institut Salah Azaiz de Tunis à propos de 30 patientes traitées sur une période de 21 ans allant de 1997 à 1997. La définition d'un carcinome synchrone est le développement d'un deuxième cancer controlatéral dans un délai de 6 mois.

Résultats : L'âge moyen était de 49 ans. L'incidence de CSBS était de 0,52%. Les antécédents familiaux ont été notés chez 3% de la population. La taille tumorale moyenne était de 40 mm (15-145). Le traitement conservateur était réalisé dans 16% des cas (9 patientes). La survie globale à 5 ans était de 40%. Les taux de survie globale dans les stades II et III étaient respectivement de 72 et 17%. Les principaux facteurs pronostiques pour la survie globale étaient l'envahissement ganglionnaire (P=0.004) et le stade de la maladie (P=0.02).

Conclusion : Le carcinoma synchrone et bilatéral du sein est rare, avec un problème de définition concernant le délai de bilatéralisation. Leur prognostic est similaire à celui d'un carcinome unilatéral du sein à stade égal. Le traitment conservateur peut être réalisé sans problème s'il y a indication.

MOTS-CLÉS

Carcinomes synchrones des seins, épidémiologie, diagnostic traitement, pronostic.

SUMMARY

Aim : The objective of this study is to determine the clinicopathologic characteristics; incidence and prognosis value of synchronous bilateral breast carcinoma (SBBC).

Methods : This is a retrospective study done in Salah Azaiz Institute of Tunis about 30 patients with synchronous bilateral breast carcinomas diagnosed and treated over a 21-years period going from 1977 to 1997. The definition of synchronous breast lesions is the developpement of the contralateral breast cancer within 6 months.

Results : Median age was 49 years. The incidence of SBBC was 0.52%. History family was noted in 3% of our population. Mean tumor size was 40 mm (15-145). Breast conserving therapy was done in 16% of cases (9 patients). Five-year overall survival was 40%. Five year survival rates were 72 and 17% for stage II and III, respectively. Main prognostic factors for survival were lymph node involvement (P=0.004) and disease stage (P=0.02).

Conclusion : Synchronous bilateral breast carcinoma is a rare entity, with a problem of definition concerning the delay of bilaterlisation. Their prognosis is similar to that of unilateral breast carcinoma patients of equal stage. Hence, breast conserving therapy can be used s fely if indicated.

KEY-WORDS

Synchronous breast carcinoma, epidemiology, diagnosis, treatment, prognosis.

الخصائص السريرية المرضية للتواجد المزدوج لسرطان الثدي من الجهتين دراسة ل 30 حالة.

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الهدف من هذه الدراسة التي تشتمل على 21 مريضة هو تحديد الخصائص السريرية و التشريحية المرضية و الإنذارية للسرطان المتزامن المزدوج في الثدي. كان معدل العمر عند المريضات 49 سنة و كان معدل حجم الورم 40 مم. قمنا بجراحة محافظية في 16% من الحالات 9 (مريضات). أما المعدل الجملي للبقاء على قيد الحياة فكان بنسبة % 72 أهم العناصر الإنذارية للبقاء على قيد الحياة هي إجتياح العقد (p : 0.004) و مرحلة تقدم المرض (p : 0.02). نستنتج أن السرطان المزدوج في الثدي نادر و إنذاره مطابق لسرطان الثدي من جهة واحدة و إجراء الجراحة المحافظة ممكن إذا كانت الدواعي تسمح بذلك.

الكلمات الأساسيّة : التواجد المزدوج لسرطان الثدي – و بائيات – تشخيص – علاج – إنذار.

The bilateralisation of breast cancer is not rare, that's why the surveillance of the contralateral breast is mandotoray. The bilateralisation is underestimated in the literature and the Synchronous bilateral breast carcinoma (SBBC) is very rare with a reported incidence ranging between 0.3 to 3% [1-4]. This disagreement in incidences is accounted for by the different criteria used to define SBBC. For some [5] it is based on pathologic findings defining SBBC as a new primary when it is histologically different from the cancer in the first breast. Others [6, 7], similar to us, define SBBC as two independent primary lesions appearing in the absence of distant metastases within six months of the first diagnosed lesion. It is controversial whether SBBC has a poorer prognosis or not and whether the treatment modalities are similar or not to that of unilateral breast carcinoma (UBC). We report this series of 30 patients with SBBC to provide answers to these questions.

PATIENTS AND METHODS

Between January 1977 and December 1997, thirty patients were treated at the Salah Azaiz Institute of Tunis for a synchronous bilateral breast carcinoma (SBBC), accounting for 0,6% of all breast cancer treated in the same period. All tumors are classified according to the UICC classification for breast carcinoma (1988). SBBC are defined as tumors being diagnosed in both breasts within a 6 months period in the absence of distant metastases. At the last patients news, we found: 10 deaths, six patients are alive and 14 are lost to follow up of whom 10 with disease progression.

For each patient, the largest tumor at diagnosis was defined as STMAX. Survivals were calculated using Kaplan-Meier methods. Comparison between survival curves was assessed by the Log rank test. A P values < 5% were considered as significant. The date of first surgery was considered the t0 from which overall and disease free survival were calculated.

RESULTS

The incidence in our institute of SBBC was 0,6% of all breast cancers treated in the same period.Median age at diagnosis was 49 years (23-76) with a peak between 30 and 39 (Fig 1). Five patients were nulliparous while 12 women were postmenopausal.One patient had a family history of breast cancer (her mother died because of it). The association between SBBC and pregnancy was recorded in one patient, while simultaneous SBBC, vaginal spinocellular carcinoma and rectal adenocarcinoma are noted in another. Mean delay of consultation was eight months (1-120). Fifty nine per cent of women consult within six months following first symptoms. Unilateral breast anomalies were revealing in 24 patients while contralateral breast cancers were diagnosed in 71% of cases at the methodical bilateral breast examination. Upper outer and inner quadrants were mostly affected in 43% and 33% respectively. Mirror localizations are noted in the inferior quadrants after correlations between bilateral tumors. Clinicopathologic characteristics of 60 tumors were summerized in Table 1.Mean clinical tumor size was 39 mm ranging from 15 to 145 mm. Clinical Multifocal disease was noted in six patients.Out of total of 60 tumors, 12% were T0 (10% are discovered on mammography and 2% on histology), 38% were T2 and 29% were T4 of which 75% were T4b. Correlating N and T stages of bilateral tumors, we note that T and N status on both side were similar in 17% and 60% of cases, respectively.Early stages (0, I) represented only 15% of cases while stage II and III were noted in 47% and 38%, respectively. Similar stages were recorded in 47% of cases. With regard to histological findings, invasive ductal carcinomas were predominant in 81% while invasive lobular carcinomas were found in 13% of cases (Table 1). Extensive in situ component (EIC) was associated in 40% of tumors. The concordance between the histological types revealed 47% of patients having a contra lateral tumor with double component (in situ and invasive). Paget's disease was found in 5% of cases. Multifocality and multicentricity were recorded in 40% and 10% of cases, respectively. Correlation between ductal carcinoma and tumor localization revealed that ductal carcinomas were found mostly in the upper outer qudrants. Mirror localization was observed in two cases.Mean pathologic tumor size was 44 mm with 28% of tumors were larger than 60 mm. Bilateral tumor grade was available in 43 tumors. Of these, Grade II and III were found in 56 and 16%.Axillary lymph node dissection was performed in 54 cases. Mean number of lymph nodes removed was 13, while the mean number of involved nodes was 7 reaching up to 21 nodes. Fifteen (50%) patients had lymph node invasion at diagnosis. Capsular rupture of lymph node metastases and lymph vascular space invasion were recorded in 14% and 3% of cases, respectively. The concordance of the lymph nodes removed status between the two tumors revealed an identical lymph nodes invasion in 46% of cases. The dosage of hormonal receptor was performed either in left or right sided tumor in 80% of patients. Twelve patients had positive hormonal receptors.Radical surgery was performed in 84% of tumors; it was bilateral in 70% of cases. Surgical treatment modalities are shown in Table 2. Breast conserving therapy was done in 16% of tumors (9 cases). Radiotherapy was done in 26 patients (86%), unilateral in 9 and bilateral in 17. Radiation to the breast and tumor bed was done in case of breast conserving therapy. After radical surgery radiation was administered to chest wall, axilla and supraclavicalar nodes in case of axillar lymph node involvement. Internal mammary nodes were irradiated in case of central or internal tumor. The whole breast was treated to a mean total dose of 55 Gy (50-65), with initially 2 Gy/fraction, five times a week. Anthracyclin-based combination chemotherapy was indicated in 17 patients (57%) and only 16 of them received it. Neoadjuvant and adjuvant chemotherapy was administered in three patients with inflammatory carcinomas. Post operative chemotherapy was indicated in 14 patients, while hormonotherapy was done in 19 patients (63%) as follows: 11 castrations (2 surgical, 9 radiotherapeutic), Tamoxifene was administered in seven women. Local recurrences were recorded in five cases of which four unilateral and one bilateral. They were associated to distant metastases (DM) in four cases. The mean disease free interval (DFI) was 24 months ranging from 9 to 57 months. The LR tumor was treated by combination of radiotherapy and hormontherapy while patients with concomitant LR and DM received exclusive chemotherapy associated in one case to hormontherapy. Distant metastases were observed in 50% of

patients. The metastasis free interval was 28 months. Median follow up was 50 months. Five year- overall and disease free survival were 40 and 38%, respectively. Univariate analysis of overall survival showed N-stage, tumor stage as significant prognostic factors.

Table n°1 : Clinicopathologic characteristics of 60 tumors (30 patients)

Factor	All tumors No. (%)	Left tumors No.	Right tumors No.
T-Stage			
T0	7 (11.6)	4	3
T1	5 (12)	2	3
T2	23 (38)	12	11
T3	8 (13.3)	2	6
T4b	13 (21.6)	7	6
T4d	4 (6.6)	3	1
Clinical node status			
N0	18 (30)		
N1	36 (60)		
N2	6 (10)		
Histologic subtypes			
Ivasive ductal carcinoma	49 (81)		
Invasive lobular carcinoma	8 (13)		
Ductal carcinoma in situ	1 (2)		
Lobular carcinoma in situ	1 (2)		
Mucinous carcinoma	1 (2)		
Mean pathologic tumor size	44 mm		
Grade			
I	12 (28		
II	24 (6)		
III	7 (6)		
Axillary lmph node status			
pN -		12	13
pN+		12	11
1-3		2	2
> 3		3	3
Receptor status			
ER++ PR+	10 (76)		
ER++PR-	1 (8)		
ER-+PR+	1 (8)		
ER-+PR-	1 (8)		
Multifocality	36 (40)		
Multicentricity	6 (10)		
Extensive in situ component	36 (40)		

ER : Estrogen receptor; PR : Progestron receptor

Table n°2 : Surgical treatment modalities

Surgical act	No. of patients	%
Patey type mastectomy	13	46
Bilateral Patey type mastectomy	5	18
BCT + Patey type mastectomy	2	7
Patey mastectomy + BCT	2	7
BCT followed by mammectomy + Patey type mastectomy	2	7
Patey + B.L followed by Patey post-chemotherapy	1	3
Lumpectomy + Lumpectomy followed by Patey type mastectomy	1	3
BCT + (BL+castration) followed by Patey post chemotherapy	1	3
Halsted type mastectomy + Patey type mastectomy	1	3
Patey + (BL + castration) followed by Patey type mastectomy	1	3
	29	100

DISCUSSION

The frequency of synchronous bilateral breast carcinomas (SBBC) ranges from 0.3 to 3% [8, 9]. In our study, SBBC represented 0.52% of all breast tumors. The frequency of SBBC detected clinically or by mammography within the six months following the diagnosis of the primary breast carcinomas are ranging from 0.4 to 3% [10, 11]. It represented 0.5% in our cohort. The reported incidence of occult SBBC revealed by random contralateral biopsy or contralateral mastectomy ranges from 4.5 to 50% [12, 13]. Mirror biopsy showed occult SBBC in 0.02% of our population. In our series, the median age was 50 years while in literature; it is higher ranging from 53 to 63.7 years [14, 15]. We didn't observe a trend toward a young age in the SBBC since the median age was similar to that of unilateral breast cancers diagnosed in our country. History family is known to be associated with bilateral breast carcinomas with an incidence ranging from to 18 to 39% [11, 16]. In contrast, only 3% of our patients were found with positive family history. However, as showed in our study, bilaterality does not necessarily reflect a genetic predisposition unless it is associated with a young age of onset. Multicentricity is identified by many studies as a risk factor for SBBC with a reported incidence ranging from 5 to 63% [17, 18]. In our series, it was registered in 10% of cases. These large variations are accounted for by the various methods used for the examination of the operating specimen as well as the different histological criteria.The treatment of SBBC is subject to controverse. Indeed, some authors believe that SBBC is related with a dismal prognosis and recommend, in consequence, more aggressive surgical treatment. Conversely, some others find that surgical treatment is similar to that of unilateral breast cancer with a frequency of bilateral conserving therapy (BCT) reaching up to 82% (22-82%) in some study [18-21]. In our institution, 16% of our patients underwent BCT. This much lower frequency is explained by the fact that 80% of patients had a tumor size greater than 2 cm and our study covered a long period span during which the use of BCT increased and become the treatment of choice for early stage breast carcinomas since the 1980s.For some clinicians, SBBC are related with a higher metastatic outcome when compared with unilateral or bilateral asynchronous breast carcinomas with a reported incidence ranging between 22 and 46% [6, 20, 22]. In our series, 50% of our patients had distant metastases following the initial treatment. The local recurrence rate ranges from 4 to 17% according to literature [6, 23, 24]; this is consistent with our results since the local recurrence rate registered was 10%. Maculotti [25] consider that local recurrences are more frequently associated with bilateral asynchronous breast carcinomas than with SBBC while some others find that local and distant failure rates are higher in patients with bilateral carcinomas.Overall survival rates are varied. Indeed, the moment from what survivals are calculated is not well defined. Some authors consider the date of first surgery while Bdian and Hangensen recommend that of the second surgery of the contralateral carcinoma. Five and ten years-overall survivals rates vary from 38 to 100% and from 20 to 78.7%, respectively according to the series [14, 26]. For some authors, SBBCs are related with a good prognosis. This is accounted for by a large proportion of old women and the frequency of early stages diagnosed by mammographic screening and the presence of hormonal receptors within tumors. As for some studies, in our series, SBBCs are related with a poorer diagnosis with a five and ten OS of 40 and 36%. This can be explained by the higher proportion of advanced stages.

In literature, survival rates are divergent; some report an OS rates lower, closer, similar or finally higher than those of unilateral breast carcinoma. Schell [27] find a better OS rate of asynchronous bilateral breast carcinoma in comparison with SBBC and unilateral breast carcinoma.

Haagensen [28] find a five OS of 52% for UBC and 33% for SBBC but when correlated to stage these differences disappear. Considering the date of first surgery as the moment from what survival is estimated, Burns report a better outcome for synchronous and unilateral breast carcinomas when compared to UBC, but survivals remain similar when considering the second surgery for the estimation of survival.

Systematic biopsy of any radiological abnormality is admitted by the majority of authors. In contrast, the blind contralateral biopsy in absence of any clinical or radiological abnormality is controversial. However, some authors recommend the practice of contralateral biopsy in case of hereditary cancer, previous exposition to ionizing radiations and lobular carcinoma. Yeatman [24] do not support the routine use of blind contralateral biopsy or prophylactic mastectomy in case of infiltrating lobular carcinoma because their incidence of bilaterality is only slightly higher than invasive ductal carcinoma associated or not to infiltrating lobular carcinoma (8.1% vs. 7.8%) and their risk to the opposite breast also appears to be low. Certainly the genetic progress would help to identify the patients at high risk to develop a bilateral breast cancer, and would allow envisaging a preventive treatment.

CONCLUSION

Synchronous bilateral breast carcinoma is a rare disease. Their prognosis is similar to that of unilateral breast carcinoma patients of equal stage. In recent years, the use of high quality mammography allows detection of early stage contralateral carcinoma. Hence, breast conserving therapy can be used safely if indicated.

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