ISSN: 3029-0910

Research Article

Journal of Gynecological & Obstetrical Research

Breast Cancer in Young Women in Tunisia: Epidemiological, Pathological and Prognostic Profile

Jelloul Rayhane*, Zangar Slim, Somri Bilel, Hannachi Mohamed Amine, Samaali, Khaoula, Malek Monia, Neji Khaled and Ferjaoui Mohamed Aymen

Maternity and Neonatology Center of Tunis, Tunisia

***Corresponding author**
Jelloul Rayhane, Maternity and Neonatology Center of Tunis, Tunisia.

Received: September 19, 2024; **Accepted:** September 30, 2024; **Published:** October 05, 2024

Introduction

Breast cancer was the most common cancer and was the leading cause of cancer mortality among women. According to WHO data from 2018, more than 2 million new cases of breast cancer were diagnosed each year, and approximately 627,000 people died from breast cancer worldwide, especially in underdeveloped countries [1,2].

In Tunisia, breast cancer represented, according to WHO, 33% of female cancers with 1,800 cases diagnosed in 2012 and an incidence of 32 per 100,000 women. It was also the leading cause of cancer death among women [3].

The definition of "young women" in the field of breast oncology was not standardized, but most literature referred to women under the age of 40. Some authors defined a young woman as one who was under 35, 45 years old, or even a premenopausal woman [4-9].

Young women diagnosed with breast cancer had a reserved prognosis compared to older women. However, this remained a controversial topic [6].

Materials and Methods

This was a retrospective, monocentric, descriptive, and analytical study involving 102 patients under the age of 40 who had breast cancer and were treated at the Obstetrics and Gynecology B department of the Maternity and Neonatology Center in Tunis over a period of 15 years, from January 1, 2006, to December 31, 2020.

The objectives of our study were to:

- Study the various epidemiological characteristics of breast cancer in young women recruited to the Obstetrics and Gynecology B department of the Maternity and Neonatology Center in Tunis (CMNT).
- Determine the clinical, histopathological, and prognostic characteristics of breast cancer in this age group.

Statistical analysis was performed using SPSS 28.

Results

Epidemiological Profile

Over a period of 15 years, 764 women were treated in our department for breast cancer. Among them, 102 were under the age of 40, representing a frequency of 13.35%. The average age at diagnosis was 35 years, with ages ranging from 21 to 40 years. The age group 30-35 years was the most frequently observed, with a rate of 52.94%. The most of patients were from northern Tunisia in 73.53% of cases, followed by southern Tunisia in 18.63% of cases, and central Tunisia in 7.84% of cases. Rural origin was found in 52.94% of cases. Pregnant women represented 4.9% of our patients.

Clinical Characteristics

The average delay between the appearance of the first symptom and consultation was 5 months, with extremes ranging from 1 month to 3 years. The most frequent reason for consultation was self-detection of a breast nodule (64.71%). Mastodynia was the second most common reason for consultation (23.53%).

Citation: Jelloul Rayhane, Zangar Slim, Somri Bilel, Hannachi Mohamed Amine, Samaali, Khaoula, et al. Breast Cancer in Young Women in Tunisia: Epidemiological, Pathological and Prognostic Profile. J Gyneco Obstet Res. 2024. 2(4): 1-5. DOI: doi.org/10.61440/JGOR.2024.v2.20

Left-side predominance was observed in 52.94% of cases. Bilateral involvement was present in 4 patients.

Considering bilateral tumors, the most frequent location was the upper outer quadrant (30.19% of cases). It involved the entire breast in 10 patients, representing 9.43% of cases.

Excluding T4 tumors, the average clinical tumor size was 40 mm, with extremes ranging from 5 mm to 100 mm. Additionally, the median clinical tumor size was 30 mm. Clinical tumor size was greater than 5 cm in 11.76% of cases (Table 1).

Table 1: Tumor Size

Nodule Size	Frequency	Percentage
Subclinical tumors	3	3.53%
<3 cm	24	28.24%
[3 cm - 5 cm]	48	56.47%
>5 cm	10	11.76%
Total	85	100.00%

Cutaneous signs included skin retraction in 16.04% of cases, edema in 9.43% of cases, a permeation nodule in one patient, and skin ulceration in one patient. Additionally, inflammatory signs involving the entire breast were found in 5 patients (4.72% of cases).

On examination of the axillary region, ipsilateral suspicious lymphadenopathy was observed in 44.34% of cases. It was fixed in 10.64% of cases. Ipsilateral supraclavicular lymph nodes were found in 2 cases.

Pre-Therapeutic TNM Classification

Tumor T

A predominance of tumors classified as T2 was noted in 49 patients (46.23% of cases). Early forms ≤ 2 cm represented only 22.64% of cases (Table 2). Tumors classified as T4 were found in 16.98% of cases, with a predominance of T4b forms in 11.32% of cases.

The 5-year overall survival (OS) and disease-free survival (DFS) for tumors classified as TX, T0, and T1-T2 were 82.5% and 82.7%, respectively, which were better than for tumors classified as T3 and T4 (41.7% and 40.4%, respectively). The T stage significantly influenced overall survival and disease-free survival ($p<0.001$).

Table 2: stage T

Stage	Frequency	Percentage
TX	3	2.83%
T0	3	2.83%
TIS	2	1.89%
T1	21	19.81%
T2	49	46.23%
T3	10	9.43%
T4a	1	0.94%
T4b	12	11.32%
T4c	0	0.00%
T4d	5	4.72%

Lymph Node N

The clinical study of lymph node involvement revealed that N0 forms were by far the most common, with a rate of nearly 52.83%. The tumor was classified as N1 in 38.68% of cases.

The 5-year overall survival (OS) was 81.8% for N0 tumors, 67.7% for N1 tumors, and 25% for N2a tumors. The lymph node status (N) was a significant prognostic factor for overall survival ($p<0.001$) and disease-free survival (DFS) ($p=0.013$).

Metastases M

The initial staging revealed metastases in 12.75% of cases. Bone metastases were the most frequent, occurring in 50% of cases (Table 3).

The 5-year overall survival (OS) was 81.7% for patients with M0 status, while it was zero for metastatic patients. This difference was significant ($p<0.001$).

Histopathological Study

The tumor was bilateral in 4 patients (106 cases).

Invasive non-specific carcinoma, also known as invasive ductal carcinoma (IDC), was the predominant histopathological type found in 75.47% of cases (Table 3).

Table 3: Histopathological Type

Histopathological Type	Frequency	Percentage (%)
IDC (Invasive Ductal Carcinoma)	80	75.47
IDC + DCIS (Ductal Carcinoma In Situ)	13	12.26
IDC + LCIS (Lobular Carcinoma In Situ)	3	2.83
Mucinous Carcinoma	2	1.89
Apocrine Carcinoma	2	1.89
Phyllodes Tumor	1	0.94
LCIS	2	1.89
DCIS	2	1.89
Angiosarcoma	1	0.94
Total	**106**	**100**

Histopathological Findings

The average histopathological tumor size was 4 cm, with extremes ranging from 1 to 16 cm. Tumors larger than 5 cm significantly influenced both overall survival (OS) and disease-free survival (DFS).

SBR grade III was the most common, with a rate of 54.29%, followed by SBR grade II at 38.10%. The 5-year overall survival was 80% for SBR grade I tumors, 75% for SBR grade II tumors, and 68.2% for SBR grade III tumors. This difference was statistically significant ($p<0.001$).

The tumor was unifocal in 53.77% of cases, bifocal in 24.53% of cases, and multifocal in 21.70% of cases. Tumor emboli were investigated in 67 patients, with a positive result in 19 of them, representing 28.36% of cases. These were associated with lymph node involvement in 100% of cases.

Molecular classification (Table 4) was established for 87 patients based on hormonal receptor data and HER2 status.

Immunohistochemistry revealed HER2 overexpression in 26.43% of cases. The Ki-67 proliferation index was not commonly practiced but was investigated by immunohistochemistry in 48 patients, of whom 18 (37.5%) had a high rate, while the others had a low rate.

Thus, the Luminal subtype was the most frequent, with a rate of 64.37%.

Table 4: Molecular Subtypes

Molecular Subtype	Frequency	Percentage
Luminal	56	64.37%
HER2-positive	4	4.60%
Triple-negative	27	31.03%

The average number of lymph nodes removed was 14, with extremes ranging from 8 to 32 lymph nodes.

Patients with positive lymph nodes (N+) represented 58 cases, or 58.86%, with an average of 12 lymph nodes and extremes ranging from 1 to 30 invaded lymph nodes.

The 5-year overall survival (OS) was 86.1% for tumors without axillary lymph node invasion, compared to 60% for tumors with lymph node invasion (N+). This difference was statistically significant (p=0.007).

Additionally, the presence of lymph node invasion significantly influenced disease-free survival (DFS) (p=0.041).

Capsular rupture was observed in more than half of the cases, specifically in 29 patients, or 56.86% of the cases with lymph node invasion. Capsular rupture was a prognostic factor in terms of overall survival and disease-free survival, with a significant difference (p=0.014 and p=0.003, respectively).

Follow-Up

A mean follow-up of 60 months (5 years) was established for 82 patients; 21 patients were in complete remission, 24 patients had died, and 37 patients had relapsed or continued to progress with the disease. The overall survival was 84.1% at 2 years and 70.7% at 5 years. The average survival was 50 months after diagnosis. Excluding patients with metastatic tumors from the start, the overall survival was 81.7% at 5 years. The relapse-free survival was 88.4% at 2 years and 74.6% at 5 years. The average relapse-free survival was 53 months. The metastasis-free survival was 95.6% at 2 years and 88.4% at 5 years. The average metastasis-free survival was 57 months.

Discussion

The mean age of onset of breast cancer in young women varied in the literature. It was 31 years in Portugal according to Eiriz et al. 36 years in Brittany according to Copson et al. 35 years in the United States according to Langman et al. 30 years in Morocco 32 years in Casablanca and 31.3 years according to Bouzid [7,10-14]. It was 35 years in our study. The time between the appearance of the first clinical symptoms and the first consultation varied according to the studies. It was 6 months according to Boufettal et al. and 8.8 months according to Boudaoud et al. [15,16].

In our series, as in the literature, the breast nodule was the most common reason for consultation [11,13,15,17,18]. Breast cancer most often localized to the supero-external quadrant, which is richer in fibroglandular tissue [19]. According to many authors, breast cancer was more common in the left breast [20]. The average tumor size was larger in younger patients [1]. For classification, we used the 7th edition of the T.N.M. system. T2 stage cancers predominated among young women in several studies, with a rate varying from 40% to 50% [14,21-23]. Several studies reported a higher proportion of advanced tumors (T3 and T4) compared to older women [24].

The infiltrating carcinoma of the non-specific type was the most common histopathological type in young women, according to the literature, with a rate varying between 73% and 100% [13,22,25]. Several authors significantly noted a higher number of grade III tumors in young women [11,26,27]. Lymph node involvement was the main prognostic factor, independent of other factors, for overall survival and progression-free survival. The rate of lymph node invasion in the literature varied between 51% and 75% [12,21,22,28]. Young women had a higher frequency of vascular emboli compared to older women [29].

In our series, the rate of vascular emboli was 28.36%. This low rate compared to the literature could be explained by the fact that the search for vascular emboli was not routinely performed before 2010. Hormonal receptors are both prognostic and predictive factors for treatment response. Thus, tumors presenting with ER and/or PR are likely to respond to antihormonal treatment (castration, selective ER modulators, aromatase inhibitors). Most series agree that hormonal receptors were more often negative in young patients [30,31]. A higher incidence of Her-2 overexpression, conferring a more aggressive phenotype, was reported in breast tumors occurring at a young age [32]. However, these tumors were amenable to targeted therapy: Herceptin®.

The Ki-67 index was one of the most important prognostic parameters in breast cancers. In Tunisia, in the series by Mahjoub, a high Ki-67 rate was 51.8%, while it was 37.5% in our series [3]. This low rate could be explained by the fact that the search for Ki-67 was not routinely practiced. We classified tumors as luminal subtype in 56 patients, triple-negative in 27 patients, and Her2 in 4 patients. Despite a small sample size, our results were consistent with the literature, showing a higher rate of the luminal subtype followed by triple-negative tumors [11, 27,33,34].

The different molecular subtypes could indicate the presence of BRCA gene mutations. Indeed, several studies showed that triple-negative tumors included most of the mutations related to the BRCA1 gene [35]. Breast cancer in young women presents

specific prognostic characteristics. The prognosis of breast cancers diagnosed in young women has long been a subject of controversy. It is more often correlated with lower survival and higher recurrence rates [12].

In our study, the overall survival at 5 years was 70.7% with an average survival of 50 months after diagnosis. This rate was close to the data in the literature (Table 5).

Table 5: Overall Survival Rates in Different Series

Series	Overall Survival at 5 Years
Villarreal, et al, Latin America [36]	64.7%
Liukkonen, et al, Finland [21]	80%
Bakkali, et al, France [37]	78%
Chan, et al, Canada [38]	67%
Assi, et al, Great Britain [39]	82%
Francis, et al, Korea [40]	81.5%
Eiriz, et al, Portugal [7]	86.5%
Bouzid, et al, Tunisia [14]	67.7%
Our series	70.7%

In the literature, the relapse-free survival rate is relatively low (Table 6). This can be explained by a higher rate of locoregional and distant recurrence in young women [41].

Table 6: Relapse-Free Survival in the Literature

Series	RFS Rate
Villarreal et al, Latin America (36)	58.4%
Eiriz et al, Portugal (7)	79.7%
Bouzid et al, Tunisia (14)	58.2%
Znati et al, Morocco (12)	60.8%
Mahjoub et al, Tunisia (3)	79.2%
Our series	74.6%

Conclusion

Over the past few decades, this cancer has increasingly affected young women under 40 years old. It is often more aggressive, with a poorer prognosis and lower survival rates compared to older women. Despite significant progress, breast cancer remains a major health issue and a top priority in biomedical research.

References

1. Wu Y, Wang M, Sun W, Li S, Wang W, et al. Age at last birth and risk of developing breast cancer: a meta-analysis, Eur J Cancer Prev. 2020. 29: 424-432.
2. Fazel A, Hasanpour-Heidari S, Salamat F, Rajaie S, Kazeminezhad V, et al. Marked increase in breast cancer incidence in young women: A 10-year study from Northern Iran, 2004–2013, Cancer Epidemiology. 2019. 62: 101573.
3. Mahjoub N, Kamel BS, Mokrani A, Mansouri H, Achour L, et al. Profil épidémiologique et anatomopathologique du cancer du sein dans la région du Nord-Ouest de la Tunisie, Tunis Med. 2021. 99: 441-448.
4. Rossi L, Mazzara C, Pagani O. Diagnosis and Treatment of Breast Cancer in Young Women, Curr Treat Options Oncol. 2019. 20: 86.
5. Arshi A, Sharifi FS, Ghahfarokhi MK, Faghih Z, Doosti A, et al. Expression Analysis of MALAT1, GAS5, SRA, and NEAT1 lncRNAs in Breast Cancer Tissues from Young Women and Women over 45 Years of Age, Mol Ther Nucleic Acids. 2018. 12: 751-757.
6. Anastasiadi Z, Lianos GD, Ignatiadou E, Harissis HV, Mitsis M. Breast cancer in young women: an overview, Updates Surg. 2017. 69: 313-317.
7. Eiriz IF, Vaz Batista M, Cruz Tomás T, Neves MT, Guerra-Pereira N, et al. Breast cancer in very young women—a multicenter 10-year experience, ESMO Open. 2021. 6: 100029.
8. Shoemaker ML, White MC, Wu M, Weir HK, Romieu I. Differences in breast cancer incidence among young women aged 20-49 years by stage and tumor characteristics, age, race, and ethnicity, 2004-2013, Breast Cancer Res Treat. 2018. 169: 595-606.
9. Erić I, Petek Erić A, Kristek J, Koprivčić I, Babić M. Breast cancer in young women: pathologic and immunohistochemical features, Acta Clin Croat. 2018. 57: 497-502.
10. Copson E, Eccles B, Maishman T, Gerty S, Stanton L, et al. Prospective observational study of breast cancer treatment outcomes for UK women aged 18-40 years at diagnosis: the POSH study, J Natl Cancer Inst. 2013. 105: 978-988.
11. Langman EL, Kuzmiak CM, Brader R, Thomas SM, Alexander SL, et al. Breast cancer in young women: Imaging and clinical course, Breast J. 2021. 27: 657-663.
12. Znati K, Bennis S, Abbass F, Akasbi Y, Chbani L, et al. Cancer du sein chez la femme jeune dans le Nord-Est du Maroc, Gynécologie Obstétrique & Fertilité. 2014. 42: 149-154.
13. Bouamama I, Bourhaleb Z, Moukhlissi M, Benchakroun N, Jouhadi H, et al. Le cancer du sein chez la femme jeune : particularités épidémiologiques, génétiques, pathologiques, biologiques et thérapeutiques, Cancer/Radiothérapie. 2009. 13: 691.
14. Bouzid N, Lahmar R, Tebra S, Bouaouina N. Cancer du sein chez la femme jeune de moins de 35 ans en Tunisie: étude rétrospective à propos de 124 cas, Gynécologie Obstétrique & Fertilité. 2013. 41: 356-360.
15. Boufettal H, Noun M, Samouh N. Breast cancer in young patient in Morrocco, Cancer Radiother. 2010. 14: 698-703.
16. Boudaoud K, Benahcene A, Sahli M, Djemaa A. Prise en charge du cancer du sein chez la femme jeune dans le service d'oncologie radiothérapie du centre hospitalier universitaire de Constantine, Cancer/Radiothérapie. 2011. 15: 578-579.
17. Sabiani L, Houvenaeghel G, Heinemann M, Reyal F, Classe JM, et al, Breast cancer in young women: Pathologic features and molecular phenotype, Breast. 2016. 29: 109-116.
18. Ben Abdelkrim S, Fathallah K, Rouatbi R, Ayachi M, Hmissa S, et al. Om.breast cancer in very young women aged 25 year-old or below in the center of Tunisia and review of the literature, Pathol Oncol Res. 2015. 21: 553-561.
19. Chen L, Zhou WB, Zhao Y, Liu XA, Ding Q, et al. Bloody nipple discharge is a predictor of breast cancer risk: a meta-analysis, Breast Cancer Res Treat. 2012. 132: 9-14.
20. Mathelin C. L'examen clinique des seins, Médecine thérapeutique. 2016. 22: 374-381.

21. Liukkonen S, Leidenius M, Saarto T, Sjöström-Mattson. Breast cancer in very young women, Eur J Surg Oncol, 2011. 37: 1030-1037.
22. Kallel F, Meziou M, Trabelsi K, Boudawara T, Mnif J, et al. Le cancer du sein de la femme jeune dans le sud tunisien, Cancer/Radiothérapie. 2006. 10: 565-571.
23. Thangjam S, Laishram RS, Debnath K. Breast carcinoma in young females below the age of 40 years: A histopathological perspective, South Asian J Cancer. 2014. 3: 97-100.
24. Espié M, Cottu PH. Breast cancer in young women: problem and questions, Pathol Biol (Paris). 2003. 51: 391-392.
25. Foxcroft LM, Evans EB, Porter AJ. The diagnosis of breast cancer in women younger than 40, Breast. 2004. 13: 297-306.
26. Arnould L, Penault-Llorca F, Dohollou N, Caron O, Levy C. Cancer du sein de la femme jeune. Spécificités histologiques, pronostiques: en quoi sont-elles différentes des femmes plus âgées? Bulletin du Cancer. 2019. 106: S10-S18.
27. Cancello G, Maisonneuve P, Rotmensz N, Viale G, Mastropasqua MG, et al. Prognosis and adjuvant treatment effects in selected breast cancer subtypes of very young women (<35 years) with operable breast cancer, Ann Oncol. 2010. 21: 1974-1981.
28. Dodelzon K, Starikov A, Reichman M, Cheng E, Lu CM, et al. Breast cancer in women under age 40: A decade of trend analysis at a single institution, Clin Imaging. 2021. 78: 165-170.
29. Bollet MA, Sigal-Zafrani B, Mazeau V, Savignoni A, de la Rochefordière A, et al. Age remains the first prognostic factor for loco-regional breast cancer recurrence in young (<40 years) women treated with breast conserving surgery first, Radiother Oncol. 2007. 82: 272-280.
30. Desiris K, Dragoumis D, Assimaki A, Tsiftsoglou A. 51 Very Young Women (< 35 Years) with Primary Breast Cancer. a Single Institution Retrospective Analysis (2005-2009). European Journal of Cancer. 2012.
31. Kroman N, Jensen MB, Wohlfahrt J, Mouridsen HT, Andersen PK, et al. Factors influencing the effect of age on prognosis in breast cancer: population-based study, BMJ. 2000. 320: 474-478.
32. Anders CK, Hsu DS, Broadwater G, Acharya CR, Foekens JA, et al. Young age at diagnosis correlates with worse prognosis and defines a subset of breast cancers with shared patterns of gene expression, J Clin Oncol. 2008. 26: 3324-3330.
33. Ihemelandu CU, Leffall Jr LD, Dewitty RL, Naab TJ, Mezghebe HM, et al. Molecular breast cancer subtypes in premenopausal and postmenopausal African-American women: age-specific prevalence and survival, The Journal of surgical research. 2007. 143.
34. Azim HA, Partridge AH. Biology of breast cancer in young women, Breast Cancer Res. 2014. 16: 427.
35. Molyneux G, Geyer FC, Magnay FA, McCarthy A, Kendrick H, et al. BRCA1 basal-like breast cancers originate from luminal epithelial progenitors and not from basal stem cells, Cell Stem Cell. 2010. 7: 403-417.
36. Villarreal-Garza C, Aguila C, Magallanes-Hoyos MC, Mohar A, Bargalló E, et al. Breast cancer in young women in Latin America: an unmet, growing burden Oncologist. 2013. 18: 1298-1306.
37. Bakkali H, Marchal C, Lesur-Schwander A, Verhaeghe JL. Le cancer du sein chez la femme de 30 ans et moins Cancer/Radiothérapie. 2003. 7: 153.
38. Chan A, Pintilie M, Vallis K, Girourd C, Goss P. Breast cancer in women < or = 35 years: review of 1002 cases from a single institution. Ann Oncol. 2000.11: 1255-1262.
39. Assi HA, Khoury KE, Dbouk H, Khalil LE, Mouhieddine TH, et al. Epidemiology and prognosis of breast cancer in young women, J Thorac Dis. 2013. 5: 2-8.
40. Francis PA. Optimal adjuvant therapy for very young breast cancer patients, The Breast. 2011. 20: 297-302.
41. Rudra S, Yu DS, Yu ES, Switchenko JM, Mister D, et al. Locoregional and Distant Recurrence Patterns in Young versus Elderly Women Treated for Breast Cancer, Int J Breast Cancer. 2015. 213123.