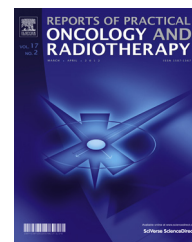


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Review

Breast cancer in young women in southern Tunisia: Anatomical study and clinical prognostic factors: About a series of 83 patients



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ABSTRACT

Purpose: To define epidemiological, clinical, therapeutic and prognostic factors influencing survival of breast cancer in young women younger than 35 in southern Tunisia.

Material and methods: This is a retrospective study of 83 patients younger than 35 years and treated within tumors mammary committee of Sfax.

Results: The mean age was 31.7 years. T2 stage, high grade with positive node tumors were frequent. Breast surgery was performed for 73 patients. Chemotherapy was neo-adjuvant, adjuvant and palliative for respectively 10, 62 and 13 patients. Radiotherapy was delivered for 65 patients with curative intent and for 8 metastatic patients. Endocrine therapy was adjuvant in 38 patients and palliative in 6 cases. The overall survival (OS) at 5 years was 66.8%. Pejorative prognostic factors in uni-variate analysis were clinical T stage (T3, T4), and the number of involved lymph nodes.

Conclusion: Despite adequate treatment, the prognosis of breast cancer in young women remains worse. Early diagnosis is necessary to promote outcome.

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1. Background

The incidence of breast cancer increases with age. The majority of women are diagnosed at the menopause. Nevertheless, 2–20% of women diagnosed with breast cancer are under 35 years old.¹

Breast cancer in young women has particular epidemiological, diagnostic and prognostic features. Its management is a veritable challenge taking into account major medical and emotional issues.²

2. Aim

The aim of this study is to define the epidemiological, anatomo-clinical and therapeutic particularities of breast cancer in young women in south of Tunisia and to determine the features and prognostic factors through a retrospective series of 83 patients treated within the Mammary Committee of Sfax (Tunisia).

3. Material and methods

This is a retrospective study performed between January 2002 and December 2008. Among 781 patients diagnosed by the tumors mammary committee, 83 patients were younger than 35 years.

All patients underwent ultrasound mammography. The diagnosis was confirmed with a biopsy or extemporaneous examination of lumpectomy specimen. All patients underwent a chest X-ray, abdominal ultrasound and bone scan. Tumors were reclassified according to the 2002 TNM system.

Tumors lower than 2 cm or that regressed after chemotherapy were treated with conservative surgery. Radical surgery was made for tumors larger than 5 cm.

The anatomo-pathological exam indicated the histological and immune-histochemical characteristics of the tumor. Hormone receptors study was performed for all patients. Her2 study was not routinely practiced; it was performed only for 17 patients. Chemotherapy was indicated for tumors with poor prognosis including histological lymph node involvement, tumor larger than 2 cm, high-grade SBR form, presence of lympho-vascular involvement, negative hormone receptor (RH) or Her2 over-expression.

Radiotherapy was indicated after conservative surgery or after mastectomy in the case of lymph node involvement, if the tumor size was greater than 5 cm or for T4 tumors. Some patients underwent radiotherapy after mastectomy for pN0 tumors in the case of other loco-regional recurrence risk factors, such as young age or high grade SBR form. Tamoxifen based endocrine therapy was given for all patients with positive RH. Ovarian function suppression by Goserlin or by radiotherapy was associated with patients with worse prognostic factors. After 2008, trastuzumab has been prescribed for patients who are Her2 positive.

All patients with metastatic disease received chemotherapy and/or endocrine therapy. The choice of treatment modalities takes into account the performance status of the patient and the presence or not of visceral metastases.

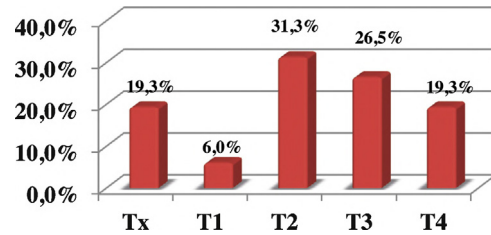


Fig. 1 – T clinical distribution.

Table 1 – Distribution of patients by metastasis location.

| Metastasis location | Number of patients |
|---------------------|--------------------|
| Bone | 9 |
| Liver | 2 |
| Lung | 4 |
| Cervical nodes | 2 |
| Skin | 1 |

Survival estimates were performed according to the Kaplan Meier. Log-rank model was used to compare survival curves according to prognostic factors. The statistical significance was set at 5%. The test is significant if the p -value ≤ 0.05 .

4. Results

4.1. Clinical characteristics

The mean age at diagnosis was 31.7 years (19–35 years). Seventeen patients (20.5%) had a family history of breast cancer with a relationship of first degree in 7 cases. Only 6 patients had early menarche (<12 years). Nulliparity was found in 25 patients (30.1%). The mean age of the first pregnancy was 23.3 years. Only 4 patients had oral contraception with an average duration of 44 months.

Palpation of a breast nodule was the most common circumstance for the revelation of the disease. The mean tumor size at diagnosis was 5.4 cm. It was superior to 3 cm in 52 cases (78.8%). Only 14 patients (21.2%) had a tumor sized less than 3 cm. Thirty-eight patients (45.8%) had locally advanced disease at diagnosis (T3, T4) (Fig. 1). Thirteen patients (15.7%) were metastatic at diagnosis. Bone metastases were the most common (Table 1).

4.2. Histological features

Infiltrating ductal carcinoma (CCI) was the most common histological type (73.5%). Seventeen patients (12%) had intraductal carcinoma (CIS) and 3 patients (3.6%) had an inflammatory carcinoma. High-grade SBR forms (SBR II and III) were found in 95.2% of cases. Twenty-two patients had multifocal tumors. The mean tumor size was 4.2 cm. The majority of tumors were larger than 2 cm. Histological lymph node involvements were seen in 52 patients (74.3%) with more than four lymph nodes in 29 patients (41.4%). Tumors expressed hormone receptor in 46 cases (55.4%). Among the 17 patients who had the Her2 study, 5 patients (29.4%) over-expressed this marker (Table 2).

Table 2 – Histological characteristics of patients.

| | Number | Percentage (%) |
|------------------------------------|--------|----------------|
| Histological type | | |
| CCI | 61 | 73.5 |
| CIS | 11 | 13.2 |
| Mixed carcinoma | 4 | 4.8 |
| Inflammatory carcinoma | 3 | 3.6 |
| Others | 4 | 4.8 |
| Grade SBR | | |
| SBRI | 3 | 3.6 |
| SBRII | 35 | 42.2 |
| SBRIII | 25 | 30.1 |
| Unknown | 20 | 24.1 |
| Histological tumor size | | |
| ≤2 cm | 13 | 15.7 |
| >2 cm et ≤5 cm | 38 | 45.8 |
| >5 cm | 12 | 14.4 |
| Unknown | 20 | 24.1 |
| Lymph nodes involvement (N) | | |
| N– | 18 | 25.7 |
| 1à 3 N+ | 23 | 32.9 |
| ≥4 N+ | 29 | 41.4 |
| Lympho-vascular involvement | | |
| Yes | 30 | 41.1 |
| No | 43 | 58.9 |
| Hormonal receptor (RH) | | |
| Positive | 46 | 55.4 |
| Negative | 32 | 38.6 |
| Unknown | 5 | 6 |

4.3. Therapeutic management

Breast surgery was performed for 73 patients. Ten patients had an important metastatic dissemination and had no surgery. Patey as radical treatment was performed for 62 patients. Ten patients had conservative treatment. Breast conservation was performed after neoadjuvant chemotherapy in one case. The axillary dissection had taken more than 10 lymph nodes in 55 cases (78.6%). Only two patients had no axillary dissection for CIS.

Ten patients had neo-adjuvant chemotherapy with anthracyclines. This chemotherapy was given in 5 cases for locally advanced tumor (T4) and for breast conservation in 5 patients. Conservative surgery was performed for one patient.

Sixty-two patients (88.6%) had adjuvant chemotherapy. Anthracyclines were administered in 59 patients (95.2%) and were combined with taxanes in 22 patients.

All metastatic patients underwent chemotherapy with anthracyclines combined with taxanes in 2 cases.

The irradiation was performed for 65 patients including 10 after conservative treatment.

The radiation after mastectomy was performed for tumors with lymph node involvement (N+) and for tumors larger than 5 cm without any node involvement. The dose was 50 Gray (Gy) for 55 patients. An additional boost of 14–16 Gy was given in the case of economic or invaded margins (n=10). The dose was 50 Gy in the mammary gland after conservative treatment with an additional boost of 14 to 16 Gy in the tumor bed.

Supra-clavicular area irradiation was performed for 52 patients at a dose of 44–50 Gy. It was indicated for patients

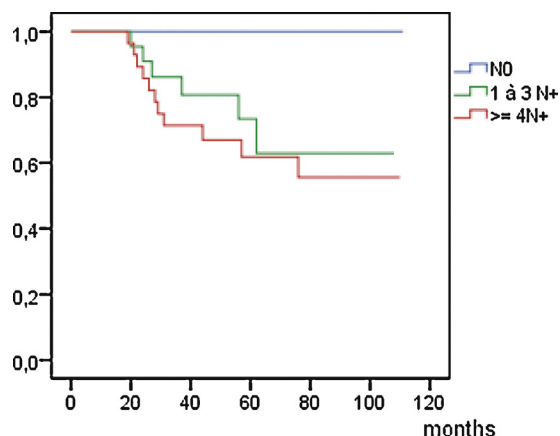


Fig. 2 – Kaplan Meyer estimates of OS by number of involved lymph nodes.

with histological lymph node involvement. Radiotherapy for metastatic patients was loco-regional in 4 cases and for metastatic sites in 4 cases.

Thirty-eight patients had adjuvant endocrine therapy. The combination tamoxifen-castration (chemical or by radiotherapy) was indicated for 24 patients. Fourteen patients had tamoxifen alone. Nineteen patients had chemical function suppression by Goserlin. The other patients had ovarian radiotherapy.

Six immediately metastatic patients underwent endocrine therapy with tamoxifen alone (n=3) or by a combination of tamoxifen and ovarian function suppression in 3 other cases.

After a median follow up of 75 months, 25 patients initially classified M0 relapsed. Seventy patients had a metastatic relapse after an average period of 21.4 months. Local recurrences were isolated in 6 patients or associated with regional lymph node metastases in 6 patients. In addition, five patients had a contro-lateral recurrence.

Eight patients are metastatic and progressed after an average period of 15.5 months. Overall survival (OS) at 5 years was 66.8%. OS at 5 years for non-metastatic patients was 75.2%.

On uni-variate analysis, locally advanced tumor (T3, T4), the presence of histological lymph node involvement and the number of involved lymph nodes were prognostic factors for overall survival (p<05) (Figs. 2 and 3). A clinical tumor size larger than 4 cm, the presence of capsular effraction (R) and the negativity of the RH did not influence OS (Table 3).

5. Discussion

The rate of breast cancer among young women varies between 2 and 20%. In fact, there is heterogeneity on the definition of young women in the literature. According to various studies, young women are defined by an age under 35, under 40 years, or simply premenopausal status.^{1,2} In our study, we take a cut-off of age of 35 years. In Tunisia, young women account for 10.7% of all patients. Family history of breast cancer is variously appreciated in the series of young women with breast cancer. The presence of family history ranged between

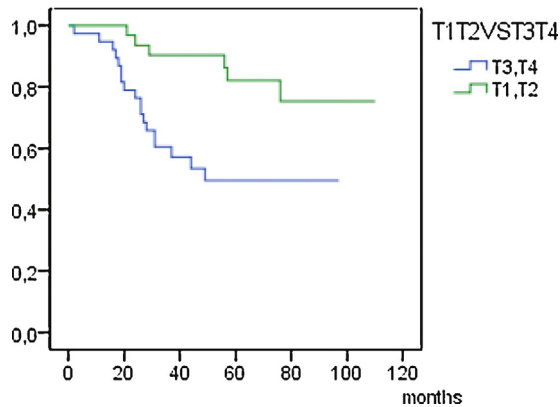


Fig. 3 – Kaplan Meyer estimates of OS by T stage.

Table 3 – Uni-variate analyses of prognostic factors of survival.

| Prognostic factor | OS at 5 years (%) | P |
|---|-----------------------|-------|
| Clinical tumor size (≤ 4 cm vs. > 4 cm) | 73.3 vs. 72.2 | 0.519 |
| T clinical stage (T1, T2 vs. T3, T4) | 79.2 vs. 42.9 | 0.026 |
| Lymph nodes involvement | | |
| N0 vs. N+ | 100 vs. 66.9 | 0.005 |
| N– vs. 1 à 3 N+ vs. ≥ 4 N+ | 100 vs. 73.4 vs. 61.8 | 0.013 |
| Capsular effraction (R+ vs. R–) | 70 vs. 78.2 | 0.5 |
| Lympho-vascular involvement (Yes vs. No) | 66.3 vs. 70.8 | 0.3 |
| Hormone receptor expression (Positive vs. Negative RH) | 71.5 vs. 61.5 | 0.5 |

8.5% and 29% depending on the series.^{3,4} In our series, 20% of patients had a family history of breast carcinoma.

In young women, the genetic predisposition is an important factor. Three genes are now recognized as the cause of hereditary forms: TP53 in Li-Fraumeni syndrome,⁵ the BRCA1 and BRCA2 genes.⁶ Several studies have shown that young women with breast cancer are often the founding members, being the first of the family to carry a mutation in a susceptibility gene, BRCA1, in particular.⁷

5.1. Clinical characteristics

There are no clinical particularities for breast cancer in young women, but several authors report larger tumors.^{8,9} Tumor size ranges between 3 and 4 cm^{4,8} in different series.

In our series, tumor size at diagnosis was 5.4 cm compared with an average size of 4.5 cm in Tunisia.¹⁰

The tumors are mostly classified T2 in different series.^{8,9,11} T4 forms are found in 7–10% of cases.^{8,10} In our series, tumors were classified T4 in 19.1% of cases.

The literature reported a rate of 2.4 up to 30% of metastases at diagnosis.¹² In our series, the rate was 15.7%. This rate is similar to those of other Tunisian series.¹¹

5.2. Histological characteristics

The CCI is the most common histological type. Lobular type is less common in young women, whereas medullary forms

are more frequent.¹³ In our series, the infiltrating ductal carcinoma was the most common histological type (73.5%). No lobular form was found.

Several authors have reported an important frequency of high-grade SBR forms and the presence of diffuse intraductal component among young women.¹⁴ High grade SBR forms were found in our series in 90% of cases.

Nodal involvement rate is estimated at 50% in the literature.⁸ Bollet et al.¹ found a higher rate of nodal involvement among women younger than 35 years of age compared to those with age between 35 and 50 years. In our series, 74.4% of patients had lymph node involvement.

Most studies agree on the lower frequency of tumors expressing hormone receptors. Colleoni et al. reported the rates of 38.8% and of 49.1% of tumors with negative estrogen and progesterone receptor, respectively.¹⁵ In older women, those rates are 21% and 35.6%, respectively.

In our series, 39.1% of patients did not express hormone receptors.

The triple negative tumors are more common in young women. Most studies report a rate of 34–39%. This rate is between 14% and 16% in the general population.¹²

5.3. Treatment features

5.3.1. Surgery

The decision to perform a conservative or radical surgery is taken independently of age. However, the local recurrence rate is higher in young women after conservative treatment. It is five times higher compared to older women.¹⁶ Several authors agree that young age is an independent predictor of local recurrence after conservative treatment.¹⁷ However, it allows conservative surgery. After mastectomy, the local recurrence rate is similar to that of older women.¹⁸

In our series, only 13.7% of patients had conservative treatment. The frequency of conservative treatment in Tunisian series is about 20%.¹¹ In fact, 78.8% of our patients had clinical tumor size superior than 3 cm.

5.3.2. Radiotherapy

Radiotherapy has the same indication in young women. Its benefit is independent of age after conservative treatment or after mastectomy for tumor with lymph node involvement.¹⁹ However, the indication of radiotherapy after mastectomy for pN0 tumors takes into consideration other prognostic factors including young age.²⁰

The EORTC randomized trials have demonstrated the benefit of an additional boost to the tumor bed²¹ but the benefit depends on age. The technique of partial breast irradiation is not recommended in young women.²²

Indication and dose irradiation for the lymph area are the same in young women.²³ Conventional fractionation regimen is recommended. Hypo-fractionated regimen is an option for older women > 50 years.²³

5.3.3. Chemotherapy

Adjuvant chemotherapy provides a benefit for women younger than 50 years, regardless of the nodal status with a reduced risk of recurrence of 12.4% and a 10% gain in terms of specific survival.²⁴ Kroman et al. found a significantly

increased risk of death from cancer in women younger than 35 years.²⁵ In the study of the MD Anderson Cancer Center, women under 30 years without any other poor prognostic factor did not receive chemotherapy.²⁶ The relapse-free survival rate was significantly lower for those patients. Experts from St. Gallen in 2005 found that young age under 35 years is an independent predictor of poor prognosis. Young age alone as a poor prognostic factor indicates adjuvant chemotherapy and/or endocrine therapy.²⁷ This indication is still maintained at St. Gallen 2013.²⁸ Patients who develop chemotherapy induced amenorrhea have a better prognosis.²⁹ Six months amenorrhea significantly improves the OS whatever the status of RH.²⁹

The superiority of taxanes compared with anthracyclines has been demonstrated for tumors with lymph node involvement³⁰ and even without any lymph node metastases, regardless of age.³¹

In our series, only 88.6% of patients had chemotherapy. Anthracyclines were the most used.

5.3.4. Endocrine therapy

Tamoxifen is the gold standard for young women. A period of 5 years is recommended.¹⁸ Association of ovarian function suppression and tamoxifen remains always a point of controversy. The ZIPP trial³² showed a benefice of chemical suppression by Goserlin in terms of relapse-free survival and overall survival. Chemotherapy associated with endocrine therapy by tamoxifen and castration is the better sequence for some authors, for others, this association does not improve outcomes compared with chemotherapy alone.³³

5.3.5. Follow-up and prognostic aspects

Local recurrence and metastases occur more frequently in younger women.¹² Median survival is shorter. Boufettal et al.⁴ found no significant difference in terms of local and distant recurrence rates between the young and older women. Several authors found that young age is correlated with poor prognosis in terms of OS.³⁴ Analysis of other series showed no significant difference in term of overall survival or disease-free survival among young women aged under 40 years compared with older women, both on uni and multivariate analysis.¹¹

5.3.6. Fertility

Fertility is affected by the treatment of breast cancer¹⁸ including chemotherapy that may induce early menopause by decreasing the ovarian reserve. This risk is increased in women older than 30 years and must be recognized especially for nulliparous and pauciparous women still wishing pregnancies.

The various techniques of fertility preservation in women with breast cancer are more complex than in other cancers. In fact, fertility preservation strategies may increase the risk of cancer recurrence, particularly with tumors expressing RH.³⁵ The best technique to preserve fertility is embryo cryopreservation. But this technique requires ovarian stimulation which can cause a peak of estradiol.¹⁸

OS rate at 5 years was comparable to that of older women in Tunisia.¹¹ However, it remains lower than in Western countries where OS at 5 years is above 80%.²⁸

6. Conclusion

Although the incidence of breast cancer in young women is declining in our country, this entity represents a problem of management and prognosis because of its medical and emotional challenges. Tumor diagnosis is usually late with more aggressive histological types making the prognosis worse. Therapeutic indications are not generally different from those of older women. However, the optimal endocrine therapy regimen is still not validated. The search for mutations in BRCA1, BRCA2, and in some cases P53 can be proposed. The preservation of fertility must be considered in these young patients. New techniques are now being evaluated to enable these women to keep gestational opportunities.

Conflict of interest

None declared.

Financial disclosure

None declared.

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