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Treating male breast cancer: Role of Oncotype Dx in early stage male breast cancer patients. A case series and review of literature

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Introduction

Male breast cancer is rare, and reportedly accounts for less than 1% of all breast cancers [1]. *But the incidence is increasing with a mortality rate comparable to female breast cancer [2].* Although the histology is similar as female breast cancer, but emerging research points at the unique molecular profile associated with male breast cancer [3]. Most of the data on male breast cancer comes from small-single institution studies so assessment and treatment relies on experiences and guidelines that have been developed for female patients. It is estimated that about 2,140 new cases are diagnosed annually in the United States (US) and about 300 in the United Kingdom (UK). The number of annual deaths in the US is about 450 [4,5]. The relative risk of breast cancer for a female with an affected brother is approximately 30% higher than for a female with an affected sister [6]. The highest risk for male breast cancer is carried by men with Klinefelter syndrome [6]. Male BRCA mutation carriers are thought to be at higher risk for breast cancer as well, with roughly 10% of male breast cancer cases carrying BRCA2 mutations, and BRCA1 mutation being in the minority [7].

Treatment largely follows patterns that have been set for the management of postmenopausal breast cancer. The initial treatment is surgical followed by adjuvant care with chemo/ hormonal or radiation therapy. The decision to use adjuvant chemotherapy in male patients with early stage breast cancer involves the consideration of many factors that traditionally rely heavily on tumor size and lymph node involvement and a limited set of biologic characteristics such as estrogen receptor and HER2 expression. Overtreatment with cytotoxic chemotherapy is a significant concern among patients and physicians.

Gene expression profiling is a technology developed to help improve risk stratification of patients and to predict outcomes. The Oncotype DX trade mark assay is one example of a gene expression profile validated in women with lymph node-negative, estrogen receptor-expressing breast cancer. Patients with a low recurrence score may be able to receive only hormone therapy and avoid chemotherapy. The test measures multiple genes at once to estimate the risk of breast cancer recurrence. Oncotype DX is an assay performed on RNA extracted from paraffin-embedded tumor tissue. The test analyzes the expression of 21 genes: 16 are cancer-related genes and 5 are reference genes.

As the treatment strategy in male breast cancer patients follows the guidelines for postmenopausal women, using Oncotype DX in early stage, node negative, breast cancer patients makes sense. However there are no validation studies in this cohort. This case series and review of literature will help us identifying the role Oncotype DX in male breast cancer patients.

Case series

Patient 1

66 year old male presented with a palpable left sub-areolar breast mass and nipple inversion and underwent left sided mastectomy with sentinel lymph node dissection (SLND). He was found to have Stage IIa, T2N0M0 Invasive ductal carcinoma of left breast, ER-98%, PR-80%, Her-2 – non amplified by FISH and Ki-67-10%. Oncotype DX was requested and it showed a recurrence score (RS) of 24. After a detailed discussion, he was offered hormonal therapy with Letrozole as he had many co morbid conditions and was at higher risk of thrombosis.

Patient 2

35 year old otherwise healthy male presented with palpable mass in his right breast and underwent bilateral mastectomies with right sided SLND. He was staged as Stage I T1bN0M0 Invasive ductal carcinoma of right breast. Tumor profile showed ER 100%, PR 10%, HER2 1+, Ki-67 10%. The Oncotype DX revealed a RS of 17. Patient was started on hormonal therapy with Tamoxifen for 5 years.

Patient 3

Our last patient was a 50 year old otherwise healthy male who also was diagnosed after a palpable with Stage IIA T2N0M0, Invasive ductal carcinoma of left breast. Pt had a left mastectomy with sentinel lymph node dissection. Tumor profile shows ER 100%, PR 45%, HER 2 was equivocal, Ki-67 95%. Oncotype Dx RS was high risk at 47. Repeat IHC of specimen confirmed HER2 to be 3+. Pt received adjuvant chemotherapy with Taxotere/Carboplatin/Herceptin for 6 cycles and Herceptin for a total of 1 year. He also received Tamoxifen after chemotherapy.

Discussion

Oncotype DX represents a step further in individualized care for patients with cancer. The ultimate goal of individualized care is that all patients can achieve optimal benefit from treatment and delivery of

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Table 1. Patient characteristics.

AGE	Race	Path	ER	PR	Her-2	Ki-67	Surgery	Oncotype (RS)	Stage
66	Caucasian	IDC	98%	80%	Negative	10%	mastectomy	24	T2N0M0
35	Caucasian	IDC	100%	10%	Negative	10%	B/L mastectomies	17	T1bN0 M0
50	Caucasian	IDC	100%	45%	Positive	95%	Mastectomy	47	T2N0M0

unnecessary therapy is minimized. Using a prospectively defined gene-expression assay and an algorithm for calculating recurrence scores, it was possible to quantify the likelihood of distant recurrence in patients with node-negative, estrogen-receptor–positive breast cancer [8,9].

Breast cancer is not just women's disease, yet treatment for men is typically extrapolated from our experience in the female population since it is rare and there is little known about the biology of male breast cancer. Oncotype became available in 2004 for early stage breast cancer after it was validated in several retrospective studies. The Recurrence Score (RS) generated by the assay has proved to be a prognostic and predictive marker for patients with hormone receptor positive node negative breast cancer providing information beyond that provided by traditional prognostic marker.

There is not much literature available but we were able to find two studies. First one was presented in ASCO 2009 as a poster by Genomic Health. This was the first large genomic study focusing on male breast cancer. The study analyzed 347 male breast cancer samples and over 82,000 female breast cancer samples using Oncotype assay. A wide inter-patients variation was observed in gene expression in male breast cancer. They reported 53.6% low risk tumors based on RS score in males and 53.4% in females. Intermediate risk 35.2% in males vs 36.3% in females, and high risk 11.2% in males and 10.3% in females. They demonstrated male breast cancer displays the similar gene signatures to female breast cancer [10].

Although there were many similarities between the two patient groups but there were some differences too. Male breast cancer patients had higher mean expression of the hormone receptor genes, likely due to the different hormonal context of men and women. Male breast cancer patients were older than the females. And lastly, they were less likely to have the lobular form of breast cancer.

The other study was reported in 2014 and included 65 male patients and compared there RS score with 2,455 female patients. Mean reported age was 65 years. 44.6% male breast cancer patients had low risk, 41.5% intermediate risk, and 13.9% had high risk disease. They also noticed the same distribution of genomic expression as 2,455 female breast cancers [11].

Few case reports were also found where Oncotype was used as a decision making tool and overtreatment was avoided in male breast cancer patients [12,13].

Conclusion

The distribution of Recurrence Score in male breast cancer may be similar to female breast cancer. For this reason, Oncotype Dx may be a considerably good tool to be used to determine therapeutic strategy in a similar manner in male breast cancer patients as it is used in female breast cancer patients to evaluate the possible benefit of adjuvant chemotherapy and to avoid chemotherapy toxicity in over treatment of patients.

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