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Case Report

Quantitative mRNA Expression Assays and Synchronous Breast Cancers: A Case Report

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Synchronous · Risk assessment · Quantitative RNA

Abstract
Quantitative mRNA analysis of breast tumors represents a routinely applied example of precision oncology. Currently the National Comprehensive Cancer Network (NCCN) recommends quantitative mRNA profiling (e.g., 21-gene RT PCR or Oncotype Dx assay) for nearly all surgically resected lymph node (LN) negative hormone receptor (HR) positive, HER2 negative breast cancers in order to predict recurrence risk with endocrine therapy compared to chemotherapy followed by endocrine therapy after surgery. The incidence of synchronous breast cancers is low and evidence concerning distant recurrence risk is limited, but the risk of distant recurrence from one or the other of two primary breast cancers appears to be higher than the recurrence risk of the single largest of the two cancers. In this report, a woman with synchronous primary breast cancers is described. Oncotype Dx testing was done on each of her two cancers. By assuming that the recurrence risk from each with adjuvant endocrine therapy is an independent event, the recurrence likelihood from one or the other or both is calculated. I propose that this calculated value more accurately should predict the recurrence from one or the other or both tumors with endocrine therapy or chemotherapy followed by endocrine therapy compared with using only the higher of the two Oncotype Dx estimated risks.

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Case Report

A 60 year old woman underwent bilateral mastectomies in 2017 for synchronous breast cancers. The left-sided invasive ductal carcinoma (IDC) (Tumor A) was grade 1, measuring 2.5 cm. 1 of 2 sentinel lymph nodes sampled showed a 0.3 cm focus of carcinoma (T2N1a) ER >99%, PR >99%, HER2 "0." A right sided IDC (Tumor B) was grade 1, 1.5 cm with 0/3 sentinel LNs positive (T1N0) IHC ER 95%, PR 95%, HER2 "0".

Each tumor was analyzed for quantitative mRNA expression (21-gene RT-PCR or Oncotype Dx, Genomic Health, Inc, Redwood City, CA, USA, 94063). The 10-year risk of distance recurrence from the left sided tumor and right sided tumors were estimated to be 14% and 12% respectively with treatment using 5 years of adjuvant tamoxifen therapy. Each Oncotype Dx result was consistent with no statistically significant benefit from adjuvant chemotherapy preceding the tamoxifen. The patient completed 4 cycles of adjuvant chemotherapy with dose dense doxorubicin/cyclophosphamide followed by 12 weekly doses of paclitaxel and she has since been taking adjuvant aromatase inhibitor therapy daily without evidence of recurrence.

Discussion

Informed decisions regarding the absolute benefit from adjuvant chemotherapy for patient with HR positive breast cancers are initially considered based on accurately estimating the risk of recurrence with endocrine therapy alone. Recently, the NCCN has endorsed the 21-gene RT-PCR assay or Oncotype Dx testing for most endocrine receptor positive breast cancers to determine the likelihood of adjuvant chemotherapy followed by adjuvant endocrine therapy compared to adjuvant endocrine therapy alone [1]. However, the NCCN guideline does not address how to apply the assay to estimate of recurrence risk from one or the other or both cancers for that small percentage of patients with synchronous breast cancers (1–3%), although studies have shown that the risk of recurrence from one, the other or both, is higher than the risk from either of individual cancer [2–4].

Assuming that the risk of recurrence from each of the two tumors above with adjuvant endocrine therapy to be "independent events," than the risk of recurrence from either or both tumors would be calculated to be:

Likelihood of no recurrence from A = 100–14% = 86%.

Likelihood of no recurrence from B = 100–12% = 88%.

Likelihood of no recurrence from A or B = 0.88 × 0.86 = 75%.

Likelihood of recurrence from A or B or both = 100–75% = 25%.

Per the NCCN Guidelines, for either the A or B cancers described above, there is no proven benefit from adjuvant chemotherapy preceding endocrine therapy [1]. However, by considering the risk of recurrence from A or B to be independent events (25% risk of recurrence from A or B or both with endocrine therapy alone), chemotherapy becomes a consideration. In other words, whereas the absolute predicted benefit from chemotherapy for a patient with a 14% risk of recurrence would typically be inadequate for most patients (and statistically not proven), the absolute chemotherapy benefit if the risk with endocrine therapy alone is 25% would be significant to many patients (and is more of a consideration per the NCCN Guidelines) [1].

It remains unproven whether the risk of recurrence from one or the other or each of two synchronous cancers can be considered truly independent events. It is possible that chemotherapy works less well or better when applied to micrometastatic disease from two

primaries as opposed to one. It is possible that having one cancer somehow affects favorably or adversely the prognosis of another cancer of the same origin. However, I could find no evidence in the literature to support this possibility.

The method of assessing risk of recurrence for synchronous cancers might also be applied to other cancers. For example, without high risk features there is no proof of an adjuvant chemotherapy benefit for stage 2 colon cancer. However, were a patient to have two stage II colon cancers, each with a 20% risk of recurrence, the risk of recurrence from one or the other or both would be calculated to be 36%, assuming that each tumor's risk of recurrence is independent of the other tumor's risk of recurrence. With the known relative reduction in risk using chemotherapy for patients with stage 3 and high-risk stage 2 colon cancers, many patients and oncologists might think it reasonable to consider adjuvant chemotherapy use with two stage colon 2 cancers, even if neither contains a high-risk feature.

Conclusions

How best to estimating the risk of distant recurrence with adjuvant systemic therapy from one or both of synchronous breast cancers has not been well defined. It seems reasonable to consider the recurrence risk from each of two synchronous breast cancers to be independent events. Using the 21-gene RT-PCR assay the risk of recurrence from one, the other or both tumors will be higher than the risk estimated using only the risk from the tumor with the highest score, and patients who would not have chosen adjuvant chemotherapy might instead elect for adjuvant chemotherapy followed by endocrine therapy based on this more accurate assessment of risk with adjuvant endocrine therapy alone.

Statement of Ethics

The patient described gave written informed consent for publication of her case.

Disclosure Statement

There are no conflicts of interest relevant to this article.

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