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EDITORIAL – ASO PERSPECTIVES

The EA2108 Clinical Trial and Real-World Data: A Cautionary Tale in Stage IV Breast Cancer

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About 6% of newly diagnosed breast cancer patients present with stage IV disease and an intact breast primary. Retrospective studies have indicated that local-regional treatment (LRT) of the primary tumor may improve overall survival (OS); however, these studies had significant selection bias and patients selected for surgery were younger, had smaller tumors, more favorable biology, and lower metastatic burden.[1,2] Meta-analysis of 30 observational studies primarily based on registry analyses[3,4] showed an improvement in OS with resection of the primary tumor but with a high level of heterogeneity in the studies (hazard ratio [HR] 0.65, 95% confidence interval [CI] 0.61–0.70; $p < 0.001$).[4] Advances in systemic therapy (ST) for breast cancer have improved survival and may warrant re-evaluation of the role of surgery for some patients with stage IV disease.

Given the many hurdles in mounting randomized trials and the years it takes to answer primary endpoints, it is tempting to review data collected retrospectively in the 'real world' to provide quicker answers to key questions. A key source of such data comes from the National Cancer Data Base (NCDB) and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) population cancer registry. These provide case numbers at least an order of magnitude greater than any prospective series or controlled trial but may suffer from inherent biases.

However, registries may not collect sufficient information to compare treatment groups. Data on the extent of metastatic disease are limited, as is timing of surgery in relation to identification of metastases. A case is classified as stage IV if metastases are found within 4 months of diagnosis, irrespective of when surgery was completed. Therefore, those who have surgery for presumed stage I–III disease and then undergo post-surgery imaging that demonstrates metastatic cancer, as well as those with metastases at diagnosis, are both classified as stage IV. Thus, registry studies, even with the optimal matching of cases based on available data, may not be comparing similar cases. Another example of the lack of specificity of registry data is a recent study of surgery versus no surgery in stage IV breast cancer that a priori excluded anyone who received radiation therapy.[5] This is because NCDB and SEER do not record the anatomic site of radiation, making it impossible to know if radiation was to the breast or a metastatic site.

Khan and colleagues recently reported the outcome of the seminal ECOG EA2108 randomized clinical trial addressing this question.[6] The appropriate use of registry data for hypothesis generation on which to base clinical trials was recognized by Dr. Khan in her 2002 NCDB study of surgery in metastatic breast cancer where she recommended evaluation of the role of local therapy in stage IV breast cancer in a randomized trial.[7] Dr. Khan reiterated the

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need for level I evidence in 2013 where she cautioned a "… slippery slope that we embark upon if unbiased empirical evidence and clear concepts do not guide our practice".[8] In 2016, she stated that "Until unbiased data are available, local therapy for asymptomatic primary tumors cannot be recommended in the expectation of a survival benefit".[9]

RANDOMIZED TRIALS

Conflicting results from randomized clinical trials have made the benefit of primary surgery in the setting of de novo stage IV breast cancer seem unclear. One of the first randomized controlled trials was from Tata Memorial Cancer Centre in India,[10] with 350 patients receiving optimal endocrine therapy or anthracycline-based chemotherapy. Patients who achieved a complete or partial response to ST were then randomized to LRT or no LRT. Patients with resectable oligometastatic disease were excluded. Median OS was 19.2 months (95% CI 15.8–22.46) versus 20.5 months (95% CI 16.96–23.98) in the LRT+ST group versus the ST group, respectively (HR 1.04, 95% CI 0.81–1.34; $p = 0.79$). The authors concluded that LRT to the primary tumor did not improve OS in patients with response to first-line ST.

Another multicenter, randomized, phase III trial showed differing results.[11] The Turkish MF07-01 study randomized 274 patients to LRT+ST versus ST alone; however, those undergoing LRT received surgery prior to ST. The hazard of death was 34% lower in the LRT+ST group compared with ST alone (HR 0.66, 95% CI 0.49–0.88; $p = 0.005$). In a subgroup analysis, a lower risk of death was seen in the LRT+ST group, for the following subgroups: HR 0.64 (95% CI 0.46–0.91) for estrogen receptor (ER)-positive ($p = 0.01$); HR 0.64 (95% CI 0.45–0.91) for human epidermal growth factor receptor 2 (HER2)-positive ($p = 0.01$); HR 0.57 (95% CI 0.38–0.86) for age <55 years ($p = 0.007$); and HR 0.47 (95% CI 0.23–0.98) for solitary bone-only metastasis ($p = 0.04$), respectively.

The ABCSG-28 POSYTIVE trial closed early due to poor accrual and failed to show either an OS benefit or difference in time to distant progression (TTDP) with surgical resection of the breast primary in patients presenting with stage IV disease (HR for OS 0.69, 95% CI 0.36–1.33, $p = 0.27$; and HR for TTP 0.60, 95% CI 0.34–1.04, $p = 0.07$).[12]

ECOG EA2108

The ECOG-ACRIN 2108 (EA2108) trial led by Seema Khan was developed to assess the role of early LRT for patients with an intact primary and metastatic breast cancer who responded to ST.[6] The primary endpoint was OS, with locoregional disease control as a secondary endpoint. This prospective, randomized, phase III trial enrolled 390 patients from February 2011 to July 2015. Tumor biology was 59% hormone receptor-positive (HR+) and HER2-negative, 11% triple negative, and 30% HER2-positive. Those without progression of distant disease following 4–8 months of ST were eligible for randomization ($n = 256$) to continue ST alone ($n = 131$) versus proceed with LRT ($n = 125$). LRT included complete tumor resection with mastectomy in 76 patients and breast-conserving surgery in 31 patients. Negative margins were achieved in 91.6%. Axillary surgery was sentinel lymph node (SLN) surgery alone in 13 patients, axillary dissection (with or without SLN surgery) in 82 patients, while 9 patients had no axillary surgery. Adjuvant radiotherapy was utilized in 57.6% of patients (27/31 patients treated with breast conservation and 44/76 undergoing mastectomy). ST was continued as determined by the treating oncologist. For those randomized to ST alone, delayed LRT was permitted for palliation at the discretion of the treating team, with 22/131 patients undergoing breast surgery and 15 receiving adjuvant radiation.

With a median follow-up of 53 months, there was no difference in OS, 3-year OS of 67.9% in the ST-alone group and 68.4% in the LRT group. Median survival was 53.1 months in the ST-alone group versus 54.9 months in the LRT arm (HR 1.11; $p = 0.57$).[6]

Locoregional progression was more common in patients without early local therapy, with a locoregional progression 3-year cumulative incidence of 39.8% in the ST-alone group and 16.3% in the LRT group (HR 0.34; $p < 0.001$).

An exploratory post hoc subgroup analysis based on subtype showed no difference in OS for patients with HER2-positive disease or those with HR+, HER2-negative disease. Among the 20 patients with triple-negative breast cancer, survival was worse (HR 3.33) in the early local therapy arm.

QUALITY OF LIFE IN EA2108

The possibility of improvement in quality of life (QoL) is a frequently cited reason to support the use of LRT in de novo stage IV disease. The EA2108 study evaluated health-related QoL (HRQoL) measures, including depression, anxiety, and well-being, using the FACT-B Trial Outcome Index. At 18 months post-randomization, HRQoL was significantly worse in the LRT group compared with the ST-alone group ($p = 0.01$) but no differences were seen at 6 or 30 months. Despite the higher risk of local disease progression in patients who did not receive LRT (39.8% at 3 years vs. 16.3% in the LRT arm), this progression did not

translate into worse QoL. In addition, no differences were seen between the groups regarding symptoms, worry, or functionality.[6] This may be because adverse effects of extensive surgery and radiation could offset any improvement in QoL. Neither improved OS nor improved QoL was seen with LRT.

OLIGOMETASTATIC DISEASE

Importantly, there was no survival difference with LRT of the breast primary among women who had oligometastases (HR 1.18); however, only 16% of patients randomized had oligometastatic disease and thus this group may be understudied.

Resection of Metastatic Sites in Oligometastatic Disease

Some investigators have opined treatment of the metastatic site may be appropriate for limited metastatic disease that can be treated with ablation for cure. Similar to other solid organ cancers, ablation of imaging-detected metastases, with either surgery or radiation, has been associated with long disease-free intervals in breast cancer patients. Retrospective series have shown an improvement following resection of liver or lung metastasis in patients with primary sites that are controlled.[13] In terms of stereotactic ablation, the largest retrospective study in breast cancer patients pooled an analysis of 40 women with limited metastases showing a progression-free survival (PFS) at 4 years of 38%, and the treated metastasis control per patient was 80%. Patients with bone-only disease had improved outcomes and patients with a solitary metastasis had improved PFS and OS compared with those with more than one metastasis ($p = 0.028$).[14]

There are several prospective studies examining the benefit of ablation of metastatic disease. In these trials, the primary tumor must be controlled with no tumor detectable on imaging or no progression for more than 3 months locally. NRG BR001 (NCT02206334), a phase I dose escalation study, included patients with breast, lung, and prostate cancer with two metastases in close proximity (< 5 cm) or those with three to four metastases who received radiation to all known sites of disease.[15] The trial completed accrual and was deemed safe to proceed to phase II. NRG BR002 is a phase II randomized trial that studies whether ablation of all known metastases in addition to standard of care improves PFS in women with one to two metastases. If an improvement in PFS is seen, then investigators will proceed with a phase III study to determine if ablation of all metastases can improve OS. The SABR COMET study (NCT01446744) is a dose-stratified method for ablation of limited metastasis in patients with definitive treatment of the breast primary.[16] Stereotactic ablative radiotherapy (SABR) was associated with an improvement in OS, meeting the primary endpoint, but three of 66 (4.5%) patients in the SABR group had treatment-related death. A phase III trial is needed to conclusively show an OS benefit and to determine the maximum number of metastatic lesions wherein SABR provides benefit. In terms of surgical ablation, there is the newly activated OMIT trial in China—A Trial Evaluating the Efficacy of Metastasectomy in Patients with Oligo-Metastatic Breast Cancer—that randomizes patients to surgical resection plus ST versus ST alone. Although ablative therapies are gaining in popularity, only now are prospective trials open to identify the role of ablative therapy in oligometastatic breast cancer.

In addition to heterogeneity in the treatment of metastatic sites, there is significant variability in the management of local-regional disease in stage IV patients. Some are treated with breast surgery alone without any assessment of the regional nodes. There is also variability in the type of axillary surgery in patients undergoing LRT, and it is often left to the treating surgeon. Patients with positive margins (7.4% in EA2108) generally do not undergo re-excision surgery and it is unclear whether patients with positive margins are receiving radiation therapy, as would be standard in the curative treatment setting. Not all patients undergoing breast-conserving surgery receive adjuvant radiation therapy in the stage IV setting, and standard indications for postmastectomy radiation therapy may not be followed in these patients. In a single-institution study of stage IV patients with an intact primary tumor, investigators found that radiation treatment to the primary was associated with improved survival but only after adjustment for the effect of surgery.[17] These data are hypothesis-generating but do suggest that standardization of the 'optimal' LRT is important to assess the true impact on survival outcomes in stage IV patients.

In summary, the EA2108 prospective randomized controlled trial provides definitive data that early local therapy does not improve survival in patients with de novo metastatic breast cancer who present with an intact primary tumor and respond to ST. Thus, surgical resection of the breast primary in a patient with stage IV disease should not be routinely offered. Clinicians should clearly communicate the lack of OS benefit and assure that patients understand that locoregional disease most often remains asymptomatic when treated with optimal ST without LRT. While the EA2108 study shows a clear lack of survival benefit, the role of locoregional therapy in patients with stable primary disease, along with treatment of oligometastatic sites, will continue to be debated and evaluated in the era of advancing systemic therapies.

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