JOURNAL WATCH

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Our panel of experts highlight the most important research articles across the spectrum of topics relevant to the field of breast cancer management

Expert panel: Dhwani Parikh, Rutgers Cancer Institute of New Jersey, NJ, USA; Bruce C Haffty, Rutgers Cancer Institute of New Jersey, NJ, USA; Debora Gagliato, MD Anderson Cancer Center, Houston, TX, USA; Joana Ribeiro, Breast Unit, Champalimaud Cancer Center, Lisbon, Portugal

Haviland JS, Owen JR, Dewar JA et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol.* 14(11), 1086–1094 (2013).

The much awaited 10-year follow-up results of the UK START A and B trials have now been published in *Lancet Oncology*. The UK START trials were conducted to compare standard radiotherapy with hypofractionation schemes in over 4000 women with early-stage breast cancer. The primary end points were locoregional control and normal tissue effects. The START A trial compared standard fractionation of 50 Gy in 25 fractions over 5 weeks with 41.6 or 39 Gy in 13 fractions over 5 weeks. Patients in START B were randomized to 50 Gy in 25 fractions in 5 weeks versus 40 Gy in 15 fractions over 3 weeks. The initial results from these studies that were previously published were promising in favor of the hypofractionated regimens.

At longer follow-up, there continues to be a benefit to hypofractionation over standard fractionation. Rates of locoregional failure and late tissue effects, including moderate/marked breast induration, telangiectasia and breast edema, were significantly lower in the hypofractionated arms. The rates of ischemic heart disease, symptomatic rib fracture and symptomatic

lung fibrosis were low and similar among the different arms. Furthermore, the hypofractionated arm in START B had lower distant relapse rates, which resulted in higher rates of disease-free survival and overall survival compared with the standard arm.

In conclusion, the 10-year follow-up confirms that hypofractionation is both safe and effective in early-stage breast cancer and has now been adopted as the standard of care by most UK centers.

– Written by Dhwan Parikh
& Bruce G Haffty

Olivetto IA, Whelan TJ, Parpia S et al. Interim cosmetic and toxicity results from RAPID: a randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiation therapy. *J. Clin. Oncol.* doi:10.1200/JCO.2013.50.5511 (2013) (Epub ahead of print).

It has been well established that whole-breast radiation in the setting of breast conservation therapy improves local control and survival. Furthermore, several studies have shown that hypofractionated regimens provide equivalent efficacy and toxicity as compared with standard fractionation. Findings have also suggested that the majority of local recurrences after breast-conserving surgery occur in

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the region of the tumor bed. The results of these studies have since paved the way for the use of accelerated partial breast irradiation (APBI).

This large Canadian noninferiority study randomized 2135 women with early, favorable-risk breast cancer to 3D-conformal APBI versus whole-breast irradiation (WBI). This interim report evaluates cosmetic and toxicity results at a median follow-up of 36 months.

Cosmetic results were prospectively recorded by trained nurses and a panel of physicians as well as self-reported by the patients at baseline, 3 years and 5 years.

The study shows that adverse cosmesis (defined as fair or poor global cosmetic score) was more common in patients treated with APBI as assessed by the nurses (29 vs 17%; $p < 0.001$), patients themselves (26 vs 18%; $p = 0.002$) and blinded physician reviewers (35 vs 17%; $p < 0.001$). Also, grade 1 and 2 toxicities were more common among patients treated with APBI compared with WBI ($p < 0.001$).

This is the first published randomized trial to report comparisons of cosmetic outcomes between 3D-conformal radiation therapy APBI and standard WBI, and it shows worse cosmetic outcomes with APBI. The study suggests that until there are more data available, physicians should proceed with caution when using 3D-conformal APBI outside of a clinical study.

– Written by Dhvani Parikh
& Bruce G Haffty

Donker M, Litière S, Werutsky G *et al.* Breast-conserving treatment with or without radiotherapy in ductal carcinoma *in situ*: 15-year recurrence rates and outcome after a recurrence, from the EORTC 10853 randomized Phase III trial. *J. Clin. Oncol.* doi:10.1200/JCO.2013.49.5077 (2013) (Epub ahead of print).

Patients with localized ductal carcinoma *in situ* (DCIS) can be managed with lumpectomy alone or lumpectomy plus radiotherapy. None of the previous

controlled randomized trials comparing adjuvant radiotherapy versus no further treatment after breast-conserving surgery (BCS) for DCIS demonstrated an overall survival (OS) benefit for the addition of radiotherapy.

Efforts are being made to identify patients that could be spared from radiotherapy. Widespread use of screening mammography is leading to diagnosis of small lesions with a lower risk of recurrence. Patients older than 50 years, with small DCIS classified with low or intermediate histologic grade, could potentially represent this favorable prognosis subgroup.

EORTC 10853 is a prospective randomized Phase III trial that evaluated adjuvant radiotherapy post-BCS for patients with DCIS. This is the third analysis from this trial. The first was performed at 4.25 years, the second at 10.5 years and the present one takes place at 15.8 years of follow-up. In the present analysis, the benefit in local control achieved at 10.5 years of follow-up was maintained. Radiotherapy reduced the risk of locoregional recurrence (LR) by 48% (hazard ratio: 0.52; 95% CI: 0.40–0.68; $p < 0.001$). Of note, all patients' subgroups achieved a benefit from adjuvant radiotherapy and investigators could not find any specific subgroup in which radiotherapy was not beneficial. Women who experienced an invasive LR had worse breast cancer-specific survival (BCSS). Nevertheless, the two groups did not have differences in BCSS or overall survival.

It is important to emphasize that this trial was not powered to find a difference in the occurrence of distant metastases, BCSS or OS, and that prognosis after BCS for DCIS is excellent. In addition, treatment after a LR might have an effect in OS, minimizing the potential impact from adjuvant radiotherapy in OS.

Thus, the present trial ratifies the benefit from radiotherapy in preventing invasive and noninvasive breast local recurrences to subgroups of woman with DCIS. Although no difference in BCSS and OS was observed, patients who experienced invasive LR had worse OS compared with those who did not have invasive LR. Adjuvant

radiotherapy should be recommended to all patients after a BCS for DCIS.

– Written by Debora Gagliato

Ciriello G, Sinha R, Hoadley K *et al.* The molecular diversity of luminal A breast tumors. *Breast Cancer Res. Treat.* 141, 409–420 (2013).

Breast cancer is a heterogeneous disease composed of subgroups with different prognosis and therapeutic options. In 2000, Perou *et al.* identified five intrinsic breast cancer subtypes largely segregated by expression of hormone receptors and HER2 status [1]. Two HR-positive subgroups were identified, luminal A and luminal B, and these are the most frequently occurring types of breast cancer seen in the clinic. However, since then, several genomic studies and RNA expression-based signatures clearly provided insights into the diversity within these subgroups [2,3].

In this article Ciriello *et al.* explore the molecular heterogeneity of luminal A breast cancer to provide a molecular stratification of this group with potential clinical implications. Using genomic data from over 1000 luminal A tumors across multiple studies the authors analyzed the copy number and mutational landscape of this subgroup and identified four major subtypes, each showing distinct DNA copy number alterations, somatic mutations, pathway alterations and clinical outcomes.

One subgroup (copy number high) was associated with worse prognosis, and showed a high level of copy number alterations, recurrent TP53 mutations and overexpression of mitotic regulators (e.g., Aurora kinases A and B). This may be particularly important since Aurora kinases are targets of specific inhibitors currently in clinical trials [4]. The poor clinical outcome of this subgroup was independent of other markers, such as tumor size, grade and stage, and patient age at diagnosis. Another subgroup presented with whole-arm events on chromosomes 8 and 16 and multiple inactivating mutations in *MAP3K1*. These alterations point to deregulated AKT and MAPK signaling, the last being especially important since deregulations in this pathway may

compromise the response to chemotherapy [5]. A third group of tumors characterized by 1q gain and 16q loss showed a significant prevalence of *GATA3* and *PIK3CA* hotspot mutations. The PI3K pathway mutations are of particular interest with the advent of PIK3CA inhibitors, which are currently in clinical trials. The last group, copy number quiet, was characterized by the absence of copy number alterations or whole-arm events. PIK3CA and AKT1 mutations were observed in this subgroup.

These results clearly shed new light on the intrinsic heterogeneity of luminal A breast cancer and open new perspectives in a more individualized treatment for these patients.

– Written by Joana Ribeiro

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Widschwendter M, Rosenthal A, Philpott S *et al.* The sex hormone system in carriers of *BRCA1/2* mutations: a case–control study. *Lancet Oncol.* 14(12), 1226–1232 (2013).

Germline mutations present in inherited cancer syndromes are thought to have a local effect in an organ that is predisposed to the development of cancer. This may explain the organ-specific cancer penetrance seen for example with breast and ovarian tumors in *BRCA1* and *BRCA2* mutation carriers. In fact, evidence from preclinical models suggest that both hormone production and sensitivity of end organs is altered in carriers of *BRCA1* mutations [1,2]. In this article the authors postulate that both endometrial thickness, as a surrogate of hormonal activity, and serum ovarian steroid hormone titers at particular stages of menstrual cycle, differ between carriers of the *BRCA1/BRCA2* mutations and women without these mutations. Participants, women aged above 35 years with no previous or subsequent history of cancer, were recruited from the UK Familial Ovarian Cancer Screening Study between June 2002 and September 2010. Endometrial thickness and date of the last menstrual period were routinely recorded during sonography performed in the context of ovarian cancer screening, germline mutations in the coding sequence of *BRCA1* and *BRCA2* were assessed, and estradiol and progesterone were measured with automated immunoassays. Results showed

clear differences in cyclical endometrial thickness and sex hormone titers between carriers of *BRCA1/BRCA2* mutations and wild-type controls. These results support the hypothesis that the organ-specific cancer penetrance in carriers is, in part, due to hormonal dysregulation and might be the basis for novel chemoprevention trials using strategies (e.g., anti-RANKL monoclonal antibody or progesterone antagonist/modulator) that exploit them.

– Written by Joana Ribeiro

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