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Personalization of loco-regional care for primary breast cancer patients (part 2)

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The loco-regional management of breast cancer is increasingly complex with application of primary systemic therapies, oncoplastic techniques and genetic testing for breast cancer susceptibility. Personalization of loco-regional treatment is integral to optimization of breast cancer care. Clinical and pathological tumor stage, biological features and host factors influence loco-regional treatment strategies and extent of surgical procedures. Key issues including axillary staging, axillary treatment, radiation therapy, primary systemic therapy (PST), preoperative hormonal therapy and genetic predisposition were identified and discussed at the Kyoto Breast Cancer Consensus Conference (KBCCC2014). In the second of a two part conference scene, consensus recommendations for radiation treatment, primary systemic therapies and management of genetic predisposition are reported and focus on the following topics: influence of both clinical response to PST and stage at presentation on recommendations for postmastectomy radiotherapy; use of regional nodal irradiation in selected node-positive patients and those with adverse pathological factors; extent of surgical resection following downstaging of tumors with PST; use of preoperative hormonal therapy in premenopausal women with larger, node-negative luminal A-like tumors and managing increasing demands for contralateral prophylactic mastectomy in patients with a unilateral sporadic breast cancer.

Postmastectomy radiation therapy (PMRT) is recommended as standard of care for patients with four or more positive nodes, for whom supraclavicular nodal irradiation may also be indicated [1–3]. Even for those patients with limited regional metastatic tumor burden (one to three nodes positive), PMRT should be considered when other adverse pathological features exist such as large tumor size (>5 cm), higher grade (III), extensive lymphovascular invasion and minimal clearance of the deep margin/invasion into muscle. Panel consensus was that PMRT is not indicated for patients with cT1–2N0 and pN0/ypN0 whose tumors have responded well to induction chemotherapy. However, PMRT is recommended for clinical stage III disease regardless of response to primary systemic therapy (PST), or patients with clinical stage I or II disease without a pCR. Omission of PMRT might be a safe option for cT3N0 patients with either a complete or partial pathological response, but cT3N0

KEYWORDS

- breast cancer
- *BRCA1/2* • luminal type
- postmastectomy radiation therapy

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patients who are pathologically node positive or fail to achieve pCR should receive radiotherapy to the chest wall and regional nodes. Decisions for PMRT should be based on a combination of pre-PST clinical stage and post-PST pathological stage with indications for PMRT after PST dependent on therapeutic response to PST in addition to tumor size at presentation [4–6]. It remains unclear whether micrometastases within a sentinel node after PST should influence decisions for radiotherapy, although will usually prompt completion axillary lymph node dissection. The issue of whether PMRT should be based on axillary status pre- or post-PST is being addressed in a large randomized Phase III trial (NSABP-51/RTOG-1304 trial) evaluating PMRT and regional nodal irradiation (RNI) and postlumpectomy RNI in node-positive patients who convert to pathologically negative axillary nodes after PST [7]. Recent results from the NCIC MA-20 and EORTC 22922 have rekindled interest in regional nodal irradiation and the extent of internal mammary node (IMN) capture with standard PMRT [8].

The IMN chain has long been recognized as a primary route for lymphatic drainage from the medial and central zones of the breast and is identified on routine lymphoscintigraphy for sentinel lymph node biopsy in 15% of cases [9]. There is substantial morbidity from surgical removal of IMNs with no gains in overall survival from these aggressive resections [10]. The biological significance of IMN disease is uncertain and adjuvant therapies are often prompted by axillary nodal disease rather than metastases in the IMNs. Whether or not the volume of PMRT fields in patients treated with PST should include IMN remains controversial, although preliminary evidence from the NCIC MA-20 [8] and EORTC 22922 [8] has demonstrated overall survival benefit. Consensus recommendations for breast

irradiation, PMRT and RNI are summarized in **Box 1**.

The panel confirmed that PST schedules are based on tumor subtypes and luminal A-like cancers are usually considered less suitable for cytotoxic PST because of their relatively poor response to chemotherapy [11]. A pCR is more likely for triple-negative and HER2-positive tumors treated with neoadjuvant anti-HER2 therapies, with prognosis being much more favorable for pCR than non-pCR [12]. High local control rates are achievable using a combination of anti-HER2 therapy with multiagent chemotherapy, which permits more conservative breast resections (irrespective of initial tumor footprint). Triple-negative disease has a broad spectrum of sensitivities to chemotherapeutic agents with response determined by subgroup characteristics. While triple-negative tumors show a higher pCR rate to chemotherapy alone they also have a poorer long-term outcome than most other tumor types. For HER2-positive disease, limited surgical resection for responders would appear reasonable, particularly bearing in mind the continuation of anti-HER2 therapy. However, there is a paucity of randomized controlled data pertaining specifically to breast recurrence for HER2-positive tumors treated with breast conserving surgery (BCS) after PST [13]. MRI is often used to measure tumor response [14]. More sophisticated modalities such as PET have predictive capacity for response to PST, but the clinical role of positron emission tomography is limited in terms of assessing response within the breast. Ultrasound can also be used and represents a more cost-effective alternative to MRI. PST is appropriate when the purpose is BCS following downstaging and is best suited to tumors measuring between 3 and 5 cm, with pCR less likely for tumors >6 cm at presentation. Rates of ipsilateral breast tumor

Box 1. Radiation treatment.

- For node-negative patients and those with one to three positive nodes, decisions for PMRT should take account of tumor size, grade and the presence/absence of lymphovascular invasion
- Estimated risk of local recurrence according to pathological results after PST is very different to clinical status prior to chemotherapy.
- Recommendations for PMRT should be based on both clinical response to PST and stage at presentation. In general, these will include most stage III and any pathologically node-positive tumors postchemotherapy
- Stage II patients with a pCR may avoid PMRT, but otherwise can be enrolled in the N9353 trial.
- Based on recent trials results (MA-20 and EORTC 22922), regional nodal irradiation should be considered in patients with one to three positive axillary nodes and adverse pathological factors (high grade, LVI, ER negative, HER2 positive)
- Irradiation of the internal mammary nodes should be considered for patients with medially located node-positive tumors who require either breast irradiation or PMRT

pCR: Pathological complete response; PMRT: Postmastectomy radiotherapy; PST: Primary systemic therapy.

Box 2. Patients with *BRCA* mutations.

- Systemic therapies for early stage patients with *BRCA* gene mutations should be similar to sporadic disease but platinum salts and PARP inhibitors may be appropriate for some cases of metastatic disease (outside or within a clinical trial)
- Ongoing trials will determine whether *BRCA* mutations confer a general increase in sensitivity to chemotherapy or specifically to platinum compounds and whether neoadjuvant cisplatin is the optimal choice of agent for *BRCA1* gene-positive breast cancer patients
- Breast conserving surgery can safely be offered to *BRCA1* and *BRCA2* mutations carriers without elevated risk of ipsilateral breast tumor recurrence but there is a greater chance of second ipsilateral and contralateral tumors that are age-related
- Risk of contralateral disease can be reduced for *BRCA2*-positive patients with bilateral oophorectomy
- Contralateral prophylactic mastectomy should not be routinely recommended for patients undergoing unilateral mastectomy for sporadic breast cancer
- Diagnostic mammography may increase breast cancer risk and periodic MRI should be undertaken in *BRCA* mutation carriers <50 years without a personal history of breast cancer

recurrence are higher postchemotherapy when mastectomy would otherwise be necessary at the outset. Surgery after PST should neither be tailored according to tumor subtype nor aim to excise the initial tumor footprint when there is evidence of concentric tumor shrinkage radiologically or clinically (residual calcium likely to represent ductal carcinoma *in situ* should be removed). The width of margin clearance for wide local excision specimens after PST should be based on tumor status post-PST, unless there is extensive ductal carcinoma *in situ*. The margin mandate in this setting has not been defined and current recommendations relate exclusively to patients treated with primary surgery. It would seem sensible to aim for a margin clearance of 2 mm, although 'no tumor at ink' appears to be satisfactory for invasive disease treated with surgery at the outset [15]. There was panel consensus that surgery cannot safely be omitted after PST when there is a complete clinical and radiological response – there are higher rates of ipsilateral breast tumor recurrence despite similar overall survival between surgery and nonsurgery patients.

Primary hormonal therapy has hitherto been under-utilized as a neoadjuvant strategy and PST should be tailored using biomarkers such as ER/HER2 status to select optimal loco-regional care. Preoperative hormonal therapy (PHT) can yield favorable clinical responses in patients with HER2-negative luminal A-like disease compared with multiagent chemotherapy which generally shows modest clinical benefit for this subgroup [16]. Decisions on PHT are most strongly influenced by levels of hormone receptor expression (ER/PgR) but also tumor size, stage, grade, proliferation (Ki67 labeling index) and multigene assay score (e.g., Oncotype DX®). PHT is anticipated to have significant impact for ER-positive lesions with lower proliferative potential, namely

luminal A-like tumors [17]. HER2-positive disease is the most frequent reason for exclusion of PHT in more than three-quarters of cases. However, PHT should be considered more often in premenopausal women with larger, luminal A-like tumors and a negative upfront sentinel lymph node biopsy. PHT for postmenopausal patients reduces tumor size, improves the chance for BCS and provides information on drug sensitivity. The panel agreed that MRI or ultrasound is the preferred method for monitoring response to PHT in more than three-quarters of cases. For premenopausal patients with HER2-negative and luminal disease, a preoperative schedule involving a combination of a luteinizing hormone-releasing hormone analogue with an aromatase inhibitor can induce objective response in a high proportion of patients [18]. Minimal data are available on local recurrence rates following neoadjuvant endocrine therapy which may be appropriate for selected premenopausal patients depending on clinical circumstances. These women may benefit specifically from induction of tumor regression without the use of cytotoxic agents. Expression levels of ER and progesterone receptor together with Ki67 labeling index and perhaps recurrence score (Oncotype DX) would aid selection for PHT [19]. Only a limited number of small studies have directly compared neoadjuvant endocrine treatment with aromatase inhibitors and cytotoxic chemotherapy in luminal disease.

An increasingly common issue is management of high-risk patients who may request risk-reduction-surgery due to carriage of germline mutations such as high penetrance (*BRCA1/2*) or low penetrance (*PTEN*, *p53*, *CDH1* and *STK11*) genes. Bilateral prophylactic mastectomy reduces risk of subsequent breast cancer by >90% which is increased to >95% when combined with bilateral oophorectomy [20,21]. The latter reduces breast cancer risk by 50% in *BRCA1/2* gene carriers and risk

of contralateral disease in *BRCA2* mutation carriers with unilateral breast cancer. MRI has proven greater sensitivity for cancer detection in high-risk women but any additional benefit of MRI to preoperative work up of tumors diagnosed with conventional imaging in this high-risk population remains uncertain. Contralateral prophylactic mastectomy might be requested by patients with unilateral cancer and a strong family history or a proven *BRCA1/2* mutation, but clinicians should actively dissuade misinformed patients from contralateral surgery in the absence of any confirmed gene mutation or familial breast or ovarian cancer. **Box 2** summarizes consensus opinion on patients management with *BRCA* mutations.

Conclusion

Current trends in clinical and basic science research continue to tailor breast cancer treatment to optimize therapeutic, cosmetic and quality of life outcomes. The challenge for the future is to successfully integrate molecular technologies, bioinformatics and conventional clinical/histopathological parameters for improved personalization of breast cancer treatments.

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