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The emerging role of surgery

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Traditionally, metastatic breast cancer is not the province of the surgical oncologist, but of the medical and radiation oncologists. This is due to the non-curability of advanced breast cancer, and surgery generally considered being a too 'toxic' procedure for palliation.

Nevertheless, three different clinical situations can be distinguished where surgery may play a role in patients with advanced breast cancer:

1. Loco regional control in patients with primary breast cancer and distant metastasis at primary diagnosis;
2. Loco regional control in patients with advanced locally recurrent breast cancer and known distant disease;
3. Patients with loco regionally controlled breast cancer but with distant metastases.

Is there evidence that surgery is likely to improve outcome in these situations? I do believe there is.

Ad 1. An increasing number of – retrospective comparative – studies do show that complete excision of the primary breast cancer is associated with an improved survival of patients with metastatic breast cancer. All studies point in the same direction with HRs between 0.5 and 0.63 in favour of those patients who had their cancers completely excised. This is – very – promising, but these results may very well be confounded by selection bias.

Ad 2. In selected patients with extensive loco regional relapse in the presence of distant disease, even extensive surgical procedures with autologous tissue closure may offer important palliation. On average in a number of studies, in over half of the patients local control for life is achieved with a median survival of 25−30 months, not much different from patients without apparent distant disease.

Ad 3. Many studies describe the results of selected patient groups after resection of −mostly isolated or very limited pulmonary or liver metastasis. These usually rather small series report 5-year survival rates of 25−50%. The study of the International Registry of Lung Metastases including 467 cases show a 5-year survival of 38%. So, in selected cases the adagium 'one course of surgical oncology results in a complete remission' may hold promise for a selected group of patients.

As in most primary breast cancers, also advanced breast cancer deserves multimodality treatment with appropriate systemic treatments and timely surgery and radiotherapy. Therefore, it is mandatory that patients with advanced breast cancer are discussed and treated within the multidisciplinary breast team, including the surgeon and radiation therapist.

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Management of early metastatic breast cancer: brain metastases

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Background: Brain metastases usually develop in patients with advanced metastatic disease. Whole brain radiotherapy is the standard treatment, that results in a median survival of 3−6 months, but half of the patients die of progressive systemic disease. In patients with brain metastases as only site of relapse outcome will be more dependent of the management of brain metastases.

Methods: Review of the literature and chart review of patients treated in the Netherlands Cancer Institute regarding incidence, risk factors, treatment and outcome of brain metastasis as first relapse of breast cancer.

Results: In about 20% of patients with brain metastases, the brain is the first site of relapse. Adjuvant systemic treatment is a risk factor for brain as first recurrence. Her2 overexpression, and use of trastuzumab as independent risk factors for brain as first recurrence are disputed. A solitary brain metastasis is a favourable prognostic factor. Treatment includes surgery, stereotactic radiosurgery, whole brain radiotherapy, but also systemic treatment. Neurosurgery and stereotactic radiosurgery of solitary brain metastasis provide the best tumour control with reported median progression free survival of one year or more. Recurrence of brain metastases is not uncommon: in selected cases re-resection or stereotactic radiosurgery affords local tumour control for 6−12 months in about 75% of cases; systemic chemotherapy may induce response or stabilisation in about half of those patients.

Conclusions: If the variety of therapeutic options including surgery, stereotactic radiosurgery, whole brain radiotherapy and systemic therapy is appropriately put into practice, prolonged and meaningful survival may be possible. However, the optimal combination and sequence of the different treatment modalities is not fully defined.

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Response to first line chemotherapy in BRCA1 and BRCA2 mutation carriers with metastatic breast cancer (MBC)

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Background: Data of in vitro and small retrospective neo-adjuvant studies suggest that breast cancer (BC) (cells) without functional BRCA1 or BRCA2 protein have an increased sensitivity to chemotherapeutic agents causing double-strands DNA breaks, such as platinum and anthracyclin-containing regimens. In this study we compared the efficacy of first line chemotherapy in BRCA1- and BRCA2-associated MBC patients with that of sporadic MBC patients.

Patients and methods: We selected from the institutional database 112 BRCA1- and 29 BRCA2-associated patients, diagnosed with MBC before 2007, January 1. Patients were matched on year of birth, diagnosis primary tumor and diagnosis MBC (within 5 years periods) with 141 sporadic BC patients. Response rate (RR) on, progression-free survival (PFS) and overall survival (OS) after start of first line chemotherapy were compared between the 3 groups. Analyses were stratified for different chemotherapy regimens. Multivariate analyses were adjusted for estrogen receptor (ER)-status and adjuvant chemotherapy.

Results: As compared to sporadic patients, BRCA1-associated BC was more often ER-negative (78% vs. 42%; $P < 0.001$) and node-negative (57% vs. 37%; $P = 0.003$), and BRCA2-associated BC more often ER-positive (86% vs.58%; $P = 0.01$). First line chemotherapy consisted of anthracyclin-based regimens ($n = 147$), CMF ($n = 68$), taxane-based ($n = 21$) and other ($n = 6$) regimens. BRCA2-associated patients had a significant higher RR (89% vs. 50%; $P = 0.001$), a longer PFS (hazard ratio $(HR)_{multivariate}$ 0.64; $P = 0.04$) and a longer OS (HR_{mult} 0.53; $P = 0.005$) than sporadic patients. The longer PFS was especially observed for anthracyclin-based regimens (HR_{mult} 0.66) and disappeared for CMF (HR_{mult} 0.98). For BRCA1-associated MBC patients a non-significant trend for a higher RR (66% vs. 50%) and a longer PFS (HR_{mult} 0.79; $P = 0.14$) was observed. OS was not significantly different between BRCA1-associated and sporadic MBC patients (HR_{mult} 0.87).

Conclusion: Chemotherapy is more effective in BRCA2-associated MBC patients in comparison with sporadic BC patients, especially for anthracyclin-containing regimens. For BRCA1-associated MBC, a trend for a higher sensitivity to chemotherapy was observed.

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Trastuzumab plus docetaxel with or without capecitabine as first-line therapy for HER2-positive locally advanced or metastatic breast cancer: a randomised Phase II study

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Background: Trastuzumab (Herceptin®; H) + docetaxel (T) is standard first-line therapy for HER2-positive metastatic breast cancer (MBC). CHAT (Capecitabine, Herceptin And Taxotere), an international, open-label, randomised, Phase II study, evaluated the addition of capecitabine (Xeloda®; X) to the HT combination as first-line therapy for HER2-positive locally advanced breast cancer (LABC)/MBC.

Materials and Methods: Patients (pts) with HER2-positive (IHC 3+ and/or FISH+) LABC/MBC were randomised to receive H (8 mg/kg loading dose then 6 mg/kg q3w) + T (75 mg/m^2 in HTX arm and 100 mg/m^2 in HT arm, q3w) $\pm$ X (950 mg/m^2 bid on Days 1−14 q3w). The primary end point was overall response rate (ORR); secondary end points included duration of response (DoR), progression-free survival (PFS), time to progression (TTP), overall survival and safety.

Results: In total, 222 randomised pts received study medication. Baseline characteristics were generally well balanced. Median follow up for