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Survival of breast cancer patients with synchronous or metachronous central nervous system metastases

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Abstract ***Background:*** Central nervous system (CNS) metastases represent a devastating complication for advanced breast cancer patients. This observational study examines the influence of patient, tumour and treatment characteristics on overall survival after synchronous or metachronous CNS metastases.

Methods: Information on 992 breast cancer patients with CNS metastases (whose primary tumour was diagnosed between 2004 and 2010) was retrieved from the Netherlands Cancer Registry (NCR). Overall survival was calculated from the date of CNS metastatic diagnosis, and the impact of prognostic factors on survival was assessed using univariate and multivariate extended Cox-regression models.

Results: We identified 165 patients with synchronous and 827 patients with metachronous CNS metastases. The majority of patients (88%) presented with brain metastases only, 12% had leptomeningeal metastases. Overall median survival was 5.0 months. Non-triple-negative breast cancer and systemic therapy were associated with improved survival in both groups. In patients with synchronous CNS metastases, surgery for the primary tumour and the metastases also improved survival. In patients with metachronous metastases, younger age (<50 years), lower initial tumour stage (I), ductal carcinoma, a prolonged time interval until diagnosis of CNS metastasis (>1 year), and absence of extracranial metastases

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were associated with improved survival. Metastasectomy and radiation therapy did not provide benefit beyond the first six months.

Conclusions: No difference in survival was established between synchronous and metachronous CNS metastases. Triple-negative disease is prognostically unfavourable in both groups, while those receiving treatment have a better outcome. Metastasectomy and radiotherapy improve survival within the first six months, and additional benefit may be derived from systemic therapy.

1. Introduction

Central nervous system (CNS) metastases represent a devastating complication in patients with advanced breast cancer. Population-based studies have reported incidence rates for brain metastases of approximately 5% in all breast cancer patients [1,2], but actual figures may well exceed this estimate because of underreporting. Autopsy findings in the past have suggested incidences of up to 30%, with the majority of cases not being clinically diagnosed or suspected before death [3,4]. A minority of CNS metastases develop in the spinal cord and leptomeninges.

The prognosis after detection of CNS metastases is generally poor, partly due to the CNS metastases themselves. Importantly, however, the majority of CNS metastases are diagnosed in patients already suffering from progressive extracranial disease activity after multiple treatment lines. Median overall survival among patients diagnosed with brain metastases ranges between 4 and 6 months, and only about 20% of patients survive the first year [5–7]. Since the introduction of trastuzumab for HER2-positive disease, prognosis of CNS metastases has improved for this specific subgroup of patients [8–11]. Important factors affecting survival include the breast cancer subtype and the performance status of the patient [12,13].

Patients with single or few (i.e. 1–3) metastatic foci in the brain may be treated with metastasectomy or stereotactic radiosurgery. For those with extensive brain metastases, whole-brain radiotherapy (WBRT) forms the mainstay of clinical management. The role of adjuvant WBRT after surgery or stereotactic radiosurgery remains subject of debate. Although it decreases the number of intracranial relapses, it has no significant effect on overall survival [14,15], and may induce substantial cognitive side-effects in patients [16]. Depending on the patient's condition, the extracranial tumour activity and the sensitivity of the tumour for (further) cytotoxic treatment, patients may also be offered systemic therapy [17,18]. Possible therapies for leptomeningeal metastases include focal radiation therapy, intrathecal cytotoxic therapy and systemic chemotherapy [19].

Synchronous CNS metastases in breast cancer patients are relatively rare [20]. Sometimes neurological complaints due to CNS metastases may represent the initial symptom of (disseminated) breast cancer, while in exceptional cases asymptomatic CNS metastases may be detected upon extensive breast cancer staging including an MRI of the brain [21]. Most CNS metastases occur metachronously after variable length of follow-up time or during palliative treatment for systemic metastases. Not uncommonly, malignant cells may lie dormant behind the blood–brain barrier for months or years before causing any symptoms [22]. Hence, synchronous and metachronous CNS metastases may represent distinct entities with respect to their biological behaviour. In addition, prior lines of systemic treatment and active follow-up of patients after primary breast cancer treatment could modify the course of metachronic disease. Indeed, optimal clinical management may require different strategies for synchronous and metachronous CNS metastases [23].

In this observational cohort study, we examined overall survival of breast cancer patients diagnosed with either synchronous or metachronous CNS metastases. Our aim was to evaluate patient and tumour characteristics as well as treatment modalities that affect patients' prognosis in each setting.

2. Patients and methods

Patients' records were retrieved from the database of the nationwide Netherlands Cancer Registry (NCR). For the NCR, information on patient and disease characteristics (including recurrent disease status), diagnostics and therapy is collected from hospital records by trained registry personnel upon notification by PALGA, the Dutch network and registry of histo- and cyto-pathology. Case ascertainment is provided by the national hospital discharge database, which receives discharge diagnoses of all patients admitted in Dutch hospitals. Under-registration by the NCR has been estimated to be less than 2% [24]. Follow-up information on vital status is obtained through linkage with the Municipal Personal Records Database. Consent for the design, data abstraction process as well as storage protocols is obtained from the national supervisory committee of the NCR.

Data registered in the NCR include patients' age at diagnosis, histological subtype, tumour grade