Journal of Clinical Neuroscience 43 (2017) 6–10

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Review article

Leptomeningeal failure in patients with breast cancer receiving stereotactic radiosurgery for brain metastases

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ARTICLE INFO

Article history:
Received 4 February 2017
Accepted 22 April 2017

ABSTRACT

Purpose: Prior studies suggest a high incidence of leptomeningeal failure (LMF) in breast cancer metastatic to brain. This study examines breast cancer-specific variables affecting development of LMF and survival after Gamma-Knife Radiosurgery (GKS).

Methods: Between 2000–2010, 149 (breast) and 658 other-histology patients were treated with GKS. Hormone/HER2, age, local/distant brain failure, prior craniotomy, and prior whole-brain radiotherapy (WBRT) were assessed. Median follow-up was 54 months (range, 0–106). Serial MRI determined local and distant-brain failure and LMF. Statistical analysis with categorical/continuous data comparisons were done with Fisher's-exact, Wilcoxon rank-sum, log-rank tests, and Cox-Proportional Hazard models.

Results: Of 149 patients, 21 (14%) developed LMF (median time of 11.9 months). None of the following predicted for LMF: Her2-status (HR = 0.49, $p = 0.16$), hormone-receptor status (HR = 1.15, $p = 0.79$), prior craniotomy (HR = 1.58, $p = 0.42$), prior WBRT (HR = 1.36, $p = 0.55$). Non-significant factors between patients that did (n = 21) and did not (n = 106) develop LMF included neurologic death ($p = 0.34$) and median survival (8.6 vs 14.2 months, respectively). Breast patients who had distant-failure after GKS (65/149; 43.6%) were more likely to later develop LMF (HR 4.2, $p = 0.005$); including 15/65 (23%) patients who had distant-failure and developed LMF. Median time-to-death for patients experiencing LMF was 6.1 months (IQR 3.4–7.8) from onset of LMF. Median survival from LMF to death was much longer in breast (6.1 months) than in other (1.7 months) histologies

Conclusion: Breast cancer patients had a longer survival after diagnosis of LMF versus other histologies. Neither ER/PR/HER2 status, nor prior surgery or prior WBRT predicted for development of LMF in breast patients.

1. Introduction

Breast cancer that spreads intracranially is at an increased risk for development of further brain metastases and also of leptomeningeal failure (LMF), also known as leptomeningeal carcinomatosis, neoplastic meningitis, carcinomatous meningitis, or leptomeningeal disease [1]. Prior studies suggest a higher incidence of leptomeningeal disease in patients with breast cancer as compared to other histologies [2]. It has been unclear if the prior use of whole brain radiotherapy (WBRT) decreases the likelihood of LMF. The use of WBRT for breast cancer brain metastases has declined over the last two decades in favor of radiosurgery as a means to preserve quality of life of patients with brain metastases [3,4]. The use of radiosurgery instead of WBRT has allowed for the sparing of cognitive decline that is often seen after WBRT [5]. Unfortunately, the increased cost of stereotactic radiosurgery and continued risk of distant failure of unaddressed at-risk regions in the brain make some patients less than ideal candidates for radiosurgery. A number of prognostic algorithms have emerged to predict for prolonged survival in patients with breast cancer brain metastases [6] and for those who may rapidly develop more brain metastases [7], as well as recommendations for routine imaging

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http://dx.doi.org/10.1016/j.jocn.2017.04.033
0967-5868/

surveillance for those patients who undergo radiosurgery [8]. These data have proven helpful in determining the proper patients for use of radiosurgery and for following them appropriately.

Development of LMP is a dreaded consequence of distant progression of intracranial disease. Historically, LMF confers a dismal prognosis characterized by development of metastases in the spinal fluid and leptomeninges, and can lead to severe neurologic symptoms (headache, vomiting, confusion, diplopia, extremity weakness, loss of continence), rapid neurologic demise, and resultant death [9]. Accurate predictive tools are being refined, but it is still unclear which patients may or may not develop LMF [2]. Previous studies have identified risk factors for LMF in patients with any histology to include history of craniotomy, particularly with piecemeal surgical resection [10–13]. Histologically, metastases of gastrointestinal, melanoma, breast cancer, or lung origin, have been identified as those having higher rates of leptomeningeal disease [2]. Patients at increased risk of early LMF may not be ideal candidates for upfront radiosurgery given the cost and need for early salvage treatment that make radiosurgery less useful as part of the overall management strategy of such patients. Because breast cancer patients are at higher risk of LMF, this is a particularly relevant clinical question for breast cancer patients with intracranial spread of disease.

Across breast cancer subtypes, there are differences in biologic behavior of brain metastasis following radiosurgery [14,15]. Hormone receptor negative status, human epidermal growth factor receptor 2 (HER2) negative status, extent of extracranial disease, number of brain metastases, Luminal B subtype, omission of WBRT, poor Karnofsky performance status (KPS), have all been identified as risk factors for progression of disease and death after radiosurgery [16,17]. There have also been prognostic studies to help identify patients at risk for brain metastases after breast-conservation therapy for early stage disease; identified risk factors for this include triple negative disease, HER2 positive, and Luminal B subtypes [18]. To date, there are few prognostic tools that exist to identify breast cancer patients at highest risk of leptomeningeal disease [19].

Thus it would be helpful to further understand which risk factors may predispose patients to the development of LMF, so that clinical decisions about radiosurgery can be made to best suit the patient's expected survival and expected pattern of spread of disease. Understanding the prognosis and various treatment options available to breast cancer patients that do eventually develop LMF may also help inform patients and clinicians and aid in therapeutic decision making at onset of LMF.

In this study, we investigate breast cancer-specific variables affecting the probability of developing LMF after Gamma Knife Radiosurgery (GKS) for brain metastases and examine survival of patients with LMF in breast cancer as compared with other histologies.

2. Material and methods

2.1. Data acquisition

The Wake Forest Health Sciences Institutional Review Board approved this study. Between the years 2000–2010, a total of 149 patients with breast cancer and 658 patients with other cancers (lung, melanoma, genitourinary, colon/rectal, esophageal, and gynecologic cancers) were treated with GKS for brain metastases at the Wake Forest School of Medicine. Electronic medical records were reviewed to determine patient characteristics and outcomes. Several factors were analyzed including hormone status, HER2 status, age, local failure, distant intracranial failure, history and date of surgery prior to GKS, and history of prior WBRT were assessed.

2.2. Patient follow-up, response assessment, and criteria for determining leptomeningeal dissemination

Patients were followed 4–6 weeks after GKS with an MRI of the brain. Subsequent MRI of the brain was conducted every three months for the first 1–2 years following GKS, and then every 6 months after that unless there were recurrences. Local failure was defined as a either a pathologically proven recurrence or imaging evidence of a 25% increase in area of enhancement on an axial MRI alice along with corresponding increased perfusion on perfusion-weighted imaging for a tumor that was originally within the prescription treatment volume. If patients were found to have new brain metastases over time, additional GKS treatment was offered when possible, provided there was not numerous or rapid multifocal new brain metastases. WBRT was reserved for salvage of four or more total brain metastases over time or in the setting of short interval distant brain failure and/or uncontrolled distant extracranial metastases [7]. Using the same technique as previously described by Huang et al. [2], the development of LMF was determined by magnetic resonance imaging (MRI), computerized tomography (CT) scan, or lumbar puncture with cerebral spinal fluid (CSF) sampling. The MRI and CT were read by our institutional neuroradiologists. Their reports as well as CSF cytology, when available, were reviewed for evidence of LMF. Neurologic death was defined as progressive neurologic dysfunction in the context of stable systemic disease as previously described by Patchell et al. [20].

2.3. Statistical analysis

Categorical and continuous data comparisons were done using the Wilcoxon Rank-Sum test or two-sided T test for continuous variables, or Chi squared or Fischer Exact tests for categorical variables. Log-Rank tests were used to compare survival distributions. Predictors of LMF were evaluated using Cox proportional hazard models. Data was managed and analyzed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA). To identify predictors of LMF, Cox proportional hazards models were developed using PROC PHREG. The proportional hazards and modeling assumptions were evaluated using the "assess" function of PROC PHREG. WBRT and distant brain failure were time-varying covariates and thus were modeled using the Andersen-Gill approach. All variables were assessed with univariate analysis, then stepwise selection was used to build the multivariable model. Any variables with p values <0.3 were added to the model and were kept if the p-values remained below 0.15. In addition, we employed a cause-specific competing risk analysis (SAS%CIF macro) as there was a high occurrence of death in this cohort. Robust covariance matrixes were used to construct 95% confidence intervals.

To assess the association between LMF and surgery to the posterior fossa, we identified all patients in our cohort who underwent surgical resection of one or more brain metastases. We excluded patients who developed LMF before surgical resection as well as patients who underwent surgery to both an infratentorial and supratentorial lesion. Infratentorial structures included the cerebellum, medulla, and pons.

3. Results

3.1. Characteristics of patients with leptomeningeal failure

Between 2000 and 2010, 149 patients with breast cancer and 658 patients with other cancers were treated with GKS for brain metastases. Their characteristics are detailed in Table 1. The patients had a KPS range of 50–100 with a median KPS of 80. Of