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Onco-metabolism: defining the prognostic significance of obesity and diabetes in women with brain metastases from breast cancer

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Abstract

Purpose—Metabolic dysregulation has been implicated as a molecular driver of breast cancer in preclinical studies, especially with respect to metastases. We hypothesized that abnormalities in patient metabolism, such as obesity and diabetes, may drive outcomes in breast cancer patients with brain metastases.

Methods—We retrospectively identified 84 consecutive patients with brain metastases from breast cancer treated with intracranial radiation therapy. Radiation was delivered as whole-brain radiation to a median dose of 3000 cGy or stereotactic radiosurgery to a median dose of 2100 cGy. Kaplan Meier curves were generated for overall survival (OS) data and Mantel-Cox regression was performed to detect differences in groups.

Results—At analysis, 81 survival events had occurred and the median OS for the entire cohort was 21.7 months. Despite similar modified graded prognostic assessments, resection rates, and receptor status, BMI ≥ 25 kg/m² ($n = 45$) was associated with decreased median OS (13.7 vs. 30.6 months; $p < 0.001$) and median intracranial progression-free survival (PFS) (7.4 vs. 10.9 months; $p = 0.04$) compared to patients with BMI < 25 kg/m² ($n = 39$). Similar trends were observed among all three types of breast cancer. Patients with diabetes ($n = 17$) had decreased median OS (11.8 vs.

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26.2 months; $p < 0.001$) and median intracranial PFS (4.5 vs. 10.3 months; $p = 0.001$) compared to non-diabetics ($n = 67$). On multivariate analysis, both BMI ≥ 25 kg/m² [HR 2.35 (1.39–3.98); $p = 0.002$] and diabetes [HR 2.77 (1.454–5.274); $p = 0.002$] were associated with increased mortality.

Conclusions—Elevated BMI or diabetes may negatively impact both overall survival and local control in patients with brain metastases from breast cancer, highlighting the importance of the translational development of therapeutic metabolic interventions. Given its prognostic significance, BMI should be used as a stratification in future clinical trial design in this patient population.

Keywords

Breast cancer; Brain metastases; Radiation; Obesity; Diabetes; Radiosurgery

Introduction

Among women, breast cancer is the most common malignancy as well as the most common cause of brain metastases [1]. As many as 30% of women with breast cancer develop brain metastases, and the incidence of brain metastases from breast cancer (BMBC) has increased two-to three-fold in recent decades [2]. Improvements in overall survival (OS) for patients with breast cancer have largely been a function of earlier detection and improved extra-cranial disease control [3]. Penetration of the blood–brain barrier and central nervous system (CNS) efficacy is limited to a select few systemic therapies, and BMBC portends a dismal prognosis and is capable of inflicting debilitating neurologic sequelae [2, 4].

Local control of brain metastases using radiation with or without surgery, the mainstays of treatment for brain metastases, is critical to prevent neurologic disability, and can potentially improve OS [5]. Historically, radiation for brain metastases has been delivered as whole-brain radio-therapy (WBRT); however, high-dose stereotactic radio-surgery (SRS) achieves comparable OS while decreasing the neurocognitive disability associated with WBRT in patients with limited numbers of brain metastases [6]. Although these advances have improved quality of life, they have not changed the palliative nature of treatment for intracranial metastases. Median survival of patients with triple negative BMBC, for example, remains less than 6 months [7, 8], indicating a clear need for novel therapeutic strategies.

Both obesity and diabetes have been associated with larger, higher grade tumors with increased metastatic and recurrent potential [9, 10]. Preclinical studies implicate obesity as a driver of a number of the hallmarks of cancer. Obesity-related increases in IGF-1R signaling augment breast cancer cell proliferation and decrease apoptosis [11]. The consequential chronic inflammatory state caused by obesity facilitates immune dysregulation and angiogenesis [12]. Additionally, excess body fat creates an environment conducive to the enhanced glycolytic metabolism in cancer cells [13].

These metabolic drivers of tumorigenesis become even more relevant within the CNS, where glucose is the sole source of energy. Therefore, tumors that have penetrated the CNS may be more susceptible to manipulations in glucose metabolism [14]. Preclinical research shows that breast cancer cells may alter several metabolic pathways to utilize glucose but minimize

production of reactive oxygen species as a means to promote survival and proliferation of intracranial metastasis [15]. The observation in our lab that caloric restriction reduces the likelihood of metastases and therapeutically synergizes with radiation to improve treatment response of both primary tumors and lung metastases in murine models supports the critical role of metabolism in breast cancer [2, 16]. We hypothesized that altered metabolism manifesting as obesity or diabetes would portend a worse prognosis in BMBC patients as compared to those patients who are not obese or diabetic. This retrospective analysis examines the role of obesity as measured by body-mass index (BMI) and the presence or absence of diabetes on clinical outcomes in patients with BMBC treated with either SRS or WBRT.

Methods

Patient selection

This single institution, retrospective cohort study was designed to investigate whether BMI may be prognostic of OS in patients with BMBC who were treated with SRS or WBRT. After IRB approval was obtained, our institution's radiation-specific electronic health record, MOSAIQ® was queried for patients with BMBC treated at Thomas Jefferson University Hospital. Inclusion criteria included only the presence of intracranial metastasis presumed or biopsy-proven to be of breast carcinoma origin and subsequent treatment with either SRS or WBRT. No exclusion criteria were identified.

Patient demographics, history of diabetes mellitus, histopathology (including histology type, receptor status, proliferation index), radiology, prior treatment, height and weight, radiotherapy technique, and survival data were collected from the electronic health record. BMI, calculated as weight in kilograms (kg) divided by the square of height in meters, was defined by values at the time of radiographic diagnosis of BMBC. Patients were subsequently divided into two groups: BMI < 25 kg/m² and BMI ≥ 25 kg/m². Stable extra-cranial disease was defined as the absence of extra-cranial progression of disease over 3 months prior to the identification of BMBC. Receptor status and histologic grade were defined as previously described by immunohistochemistry and/or fluorescence in situ hybridization [17]. Briefly, tumors were classified as hormone receptor-positive (HR+) if the estrogen or progesterone receptors were detected on ≥ 1% of tumor cells. HER2 status was first scored by immunohistochemistry and categorized from 0 to 3+. Further classification of 2 + results was performed with fluorescence in situ hybridization.

Primary and secondary endpoints

The primary objective of this study was to determine whether BMI and diabetes affect OS in patients progression-free survival (PFS) as defined on imaging. Additionally, OS was determined for each tumor subtype including triple negative, HER2+, and HR+ triple negative. To determine the relative prognostic indices between the two groups, breast cancer disease-specific graded prognostic assessments (GPA) and modified breast-GPA, two validated models for predicting survival in patients with BMBC were calculated as previously described [18, 19].

Radiation therapy

Radiation was delivered as either whole-brain radiation (WBRT) or stereotactic radiosurgery (SRS) based on physician discretion. Patients who received WBRT had a median number of four lesions. WBRT was delivered with opposed lateral fields planned with CT-based simulation to a median dose of 3000 cGy (range 2700–4750 cGy) in a median number of ten fractions. SRS was delivered either as single fraction or fractionated stereotactic radiosurgery (FSRT) depending on the size and location of the lesion. The median dose for lesions treated with SRS or FSRT was 2100 cGy (range 1200–2800 cGy) with a median number of three brain lesions treated. Target lesions were delineated on pre-treatment MRI with a 1.25 mm cut sequence and iPlan RT® software from Brainlab was used to create treatment plans. Our institutional practice for SRS is to use a mask-based linear accelerator technique for delivery of external beam radiation with 6MV photons. A portion of patients treated in the last 5 years of inclusion were treated with flat-tening filter-free mode.

Statistical analysis

Statistical analyses were performed using t-tests for continuous variables, Wilcoxon rank-sum test for non-normally distributed variables, and Chi square for categorical variables. Univariate risk factors hazard ratios for death from BMBC were used to generate a full multivariate model. A backwards elimination model selection procedure was implemented to sequentially remove other predictors until all predictors were $p < 0.10$. All statistical analyses were performed using SPSS, IBM Analytics. Kaplan Meier curves were generated using commercially available Graph Pad Prism® software (La Jolla, CA).

Results

Sample characteristics

Eighty-four consecutive patients with BMBC who were treated with WBRT, SRS, or a combination of the two modalities at Thomas Jefferson University Hospital between December 1, 2003 and March 1, 2016 were identified. No patients were excluded from analysis. Characteristics of the study population are presented in Table 1. The majority of patients was over the age of 50; however, 38.1% of the population was younger than 50 years, 35.7% had TNBC, 53.5% had a BMI ≥ 25 kg/m², and 20.2% had diabetes.

Patients were stratified according to BMI < 25 kg/m² versus ≥ 25 kg/m². These groups represented 46.4 and 53.5% of the study population, respectively, and their characteristics at the time of diagnosis of BMBC are presented in Table 1. Patients with BMI ≥ 25 trended toward having slightly increased age at the time of diagnosis of BMBC, but this was not significant ($p = 0.061$). Fewer patients in the BMI < 25 kg/m² cohort had Type 2 diabetes mellitus at the time of diagnosis of BMBC ($p = 0.001$). Prognostic factors such as KPS ($p = 0.878$), receptor status ($p = 0.883$), breast-specific GPA ($p = 0.484$), and modified breast-GPA ($p = 0.141$) were similar between the two groups. No significant differences were detected in the stability of extra-cranial metastatic disease ($p = 0.43$), number of intracranial metastatic foci ($p = 0.737$), or intracranial disease burden assessed by the cumulative intracranial tumor volume ($p = 0.580$).

Univariate characteristics associated with survival

At the time of analysis, 81 survival events had occurred and median OS was 21.7 months (range 1.2–86.6 months). Factors hypothesized to be associated with OS were analyzed are shown in Table 2 [18, 19]. In support of our hypothesis that obesity and diabetes may worsen prognosis in patients with BMBC, both BMI ≥ 25 kg/m² (HR 2.42, $p < 0.001$) and a diagnosis of diabetes (HR 2.89, $p = 0.002$) significantly worsened survival. The number of lines of systemic therapy prior to BMBC diagnosis was not significantly associated with OS (HR 1.14, $p = 0.388$); however, patients who had stable systemic disease (HR 0.77, $p = 0.022$) and higher KPS (HR 0.98, $p = 0.013$) had significantly improved OS. While there was a numerical difference in OS between patients who underwent surgical resection vs. those who did not, it was statistically insignificant (HR 0.77, $p = 0.226$). When comparing receptor subtypes, patients with triple negative tumors had a worse prognosis (HR 2.21, $p = 0.001$) while survival was better for those who had HR + tumors, regardless of HER2 status (HR 0.61, $p = 0.012$).

Given that these findings could be confounded by obesity or diabetes-related comorbidities or toxicities, we assessed the incidence of pre-existing or development of peripheral neuropathy, chronic kidney disease (Stages III–V) [20], and cardiac morbidity, including acute coronary syndrome and left ventricular dysfunction [21] (Supplemental Data, Table 1). Overall, these toxicities and comorbidities were relatively uncommon.

Survival data: BMI and diabetes

BMI ≥ 25 kg/m² was associated with a significantly shorter median OS from the time of radiographic diagnosis of BMBC (13.7 months vs. 30.6 months; $p < 0.001$) and intracranial PFS (7.4 vs. 10.9 months; $p = 0.049$) as shown in the Kaplan–Meier curves Fig. 1a and b. A diagnosis of diabetes was also associated with decreased median OS (11.8 months vs. 26.2 months; $p < 0.001$) and intracranial PFS (4.5 months vs. 10.3 months; $p = 0.001$), as shown in Fig. 1c, d. Median OS ($p = 0.46$) and intracranial PFS ($p = 0.22$) times were similar between patients with insulin-dependent and non-insulin-dependent diabetes. Despite the association of obesity with diabetes, there is a significant separation of OS curves between non-diabetic and diabetic patients with elevated BMI ($p = 0.0497$) (Fig. 1e). However, trends toward decreased intracranial PFS in diabetic patients with BMI ≥ 25 kg/m² compared to non-diabetic patients with BMI ≥ 25 kg/m² did not reach statistical significance ($p = 0.18$) (Fig. 1f).

Furthermore, BMI ≥ 25 kg/m² was associated with decreased median OS in all three major molecular sub-types of breast cancer. OS in patients with BMI ≥ 25 kg/m² was significantly worse regardless of histologic sub-type; triple negative breast cancer (9.6 months vs. 21.6 months; $p = 0.009$), HR+ breast cancer (18.5 months vs. 35.0 months $p = 0.013$), (Fig. 2a, b), and HER2+ breast cancer (19.6 months vs. 36.5 months; $p = 0.045$) (Fig. 2c). Finally, we assessed the effects of BMI on OS as a continuous rather than a binary variable in the entire cohort. As shown in Fig. 3a, there was a non-zero ($p < 0.001$) inverse relationship between BMI and OS.

Multivariate analysis

All factors associated with OS to a level of $p < 0.10$ were incorporated into a multivariate model for overall survival. These included age, BMI, diabetes, KPS, stability of extra-cranial disease, ER+, or triple negative cancers. A backwards elimination model selection procedure was implemented to sequentially remove other predictors until all predictors were $p < 0.05$. Despite the insignificance of age ($p = 0.167$), this variable was retained in the multivariate model. The variable of ER+ breast cancer was dropped from the model, and hazard ratios for the remaining variables are shown in Table 2.

Discussion

BMBC portends a poor prognosis despite advances in radiation therapy [2, 18, 22, 23]. Obesity has been implicated as a risk factor for metastases and overall poor prognoses and its resultant metabolic dysregulation may promote radioresistance [24, 25]. We hypothesized that obesity and diabetes may be drivers of survival in patients with BMBC treated with intracranial radiotherapy. Indeed, BMI ≥ 25 kg/m² was correlated with decreased OS ($p < 0.001$) and intracranial PFS ($p = 0.049$), and we identified a linear, inverse relationship between BMI and OS. Similarly, diabetes was associated with decreased OS ($p = 0.002$). On multivariate analysis, both BMI and diabetes were independent risk factors for death. As expected, triple negative breast cancer patients overall had a worse prognosis, which has been corroborated in previous data [2, 4, 18]. Further, BMI was negatively correlated with OS in all three molecular subtypes of breast cancer: triple negative ($p = 0.009$), HR+ ($p = 0.013$), and HER2+ ($p = 0.045$). While both obesity and BMI have been associated with poor OS in patients with metastatic breast cancer, our finding of reduced local control of irradiated BMBC in these patients appears to represent a novel finding.

In support of this, preclinical studies have shown that obesity, increased caloric intake, and states of insulin resistance enhance cancer cell proliferation, evasion of anti-tumor immunity, and radioresistance [16, 26, 27]. The availability of glucose within the CNS, however, bestows a metabolic advantage upon breast cancer, as it is conducive to the War-burg-like metabolic reprogramming from oxidative phosphorylation toward a glycolytic metabolic preference [15, 28]. IGF-1 availability is also increased in states of obesity and insulin resistance [29], and activation of the IGF-1R axis has been implicated as a key mediator of breast cancer radioresistance [30]. Thus, “metabolic syndromes” characterized by elevated BMI, diabetes, increased IGF-1 and insulin resistance may account for the poor prognosis we observed in patients with BMI ≥ 25 kg/m² and/or diabetes.

The possibility also remains that these OS survival outcomes were influenced by an obesity-related or diabetes-related potentiation of toxicity. In early-stage breast cancer, for example, obesity exacerbates skin toxicity [31]. Within the CNS, radiographic white matter changes, a marker of neurocognitive decline, are prevalent in patients with BMBC treated with WBRT [32, 33] and even more common in patients with hyperglycemia and hypertension [34]. Neurocognitive decline can be a significant contributor to a patient’s eligibility for additional systemic therapy and therefore if obese patients experience increased toxicity and therefore neurocognitive decline, it is possible that they receive fewer lines of systemic therapy than those patients who are not obese [35–37]. The insulin resistance inherent to obesity and

diabetes diabetic also undoubtedly complicates best supportive care with glucocorticoids in managing cerebral edema [38]. Aside from this, obese and diabetic patients are at greater risk of peripheral neurological, cardiac, and renal toxicity, all of which may limit systemic therapy options and confound survival data. Notably, in our cohort, these toxicities were relatively uncommon (Supplemental Data).

Our findings are subject to inherent limitations, the first being its small, retrospective nature of this study. To determine whether the association of BMI with decreased OS was confounded by another prognostic variable, we compared the validated breast-specific GPA and modified-breast specific GPA indexes between the two BMI cohorts [4, 18], both of which were similar between the two groups. The relatively low number of diabetic patients ($n = 17$) prevents an assessment of the impact of diabetes among different receptor subtypes as well as the relationship between OS and diabetes-related toxicities and comorbidities. Undoubtedly, the relevance of diabetes and obesity as they pertain to intracranial control and OS will need to be prospectively validated on a larger scale. Second, given the retrospective nature of this study and delivery of care in a tertiary setting, we are unable to report cancer-specific mortality. Increased mortality among over-weight, obese, and diabetic patients is a competing risk for death and this is not accounted for in our model OS [39]. However, the inverse relationship between intracranial PFS following radiotherapy is consistent with our hypothesis that metabolic dysfunction can mitigate treatment efficacy.

Regardless of these limitations, these data support the core goal of the American Society of Clinical Oncology to develop therapeutic metabolic interventions in breast cancer [26], several of which have already been proposed. For example, a secondary analysis of the ALLTO trial suggested a potential benefit and detriment of metformin and insulin, respectively, in diabetic patients with HER2+ cancer [40]. Observational studies have found a decreased risk of breast cancer death associated with statin-use [41, 42], although no definitive cause-effect relationships have been reported. Pre-clinical research has demonstrated anti-breast cancer activity in either caloric restriction or intermittent fasting [43–46], and we have demonstrated therapeutic synergy between caloric restriction and radiotherapy in animal models [11, 27]. A fundamental concern with the clinical translation of therapeutic caloric restriction, however, is adherence. In 2013, we launched the CaReFOR trial, a pilot study assessing the feasibility of caloric restriction in addition to surgery and radiation in patients with early-stage breast cancer [47]. Given the association of elevated BMI and diabetes with poor OS and local control, we speculate that caloric restriction may benefit patients with BMBC and encourage its incorporation into future trial design.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Fox BD, Cheung VJ, Patel AJ et al. (2011) Epidemiology of meta-static brain tumors. *Neurosurg Clin N Am* 22:1–6. 10.1016/j.nec.2010.08.007 [PubMed: 21109143]
2. Rostami R, Mittal S, Rostami P et al. (2016) Brain metastasis in breast cancer: a comprehensive literature review. *J Neurooncol* 127:407–414. 10.1007/s11060-016-2075-3 [PubMed: 26909695]
3. Park YH, Park MJ, Ji SH et al. (2009) Trastuzumab treatment improves brain metastasis outcomes through control and durable prolongation of systemic extracranial disease in HER2-overexpressing breast cancer patients. *Br J Cancer* 100:894–900. 10.1038/sj.bjc.6604941 [PubMed: 19240719]
4. Sperduto PW, Kased N, Roberge D et al. (2012) Effect of tumor subtype on survival and the graded prognostic assessment for patients with breast cancer and brain metastases. *Int J Radiat Oncol Biol Phys* 82:2111–2117. 10.1016/j.ijrobp.2011.02.027 [PubMed: 21497451]
5. Patchell RA, Tibbs PA, Regine WF et al. (1998) Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA* 280:1485–1489 [PubMed: 9809728]
6. Brown PD, Ballman KV, Cerhan JH et al. (2017) Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC-3): a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol* 18:1049–1060. 10.1016/S1470-2045(17)30441-2 [PubMed: 28687377]
7. Nam B-H, Kim SY, Han H-S et al. (2008) Breast cancer subtypes and survival in patients with brain metastases. *Breast Cancer Res* 10:R20 10.1186/bcr1870 [PubMed: 18307763]
8. Dawood S, Broglio K, Esteva FJ et al. (2009) Survival among women with triple receptor-negative breast cancer and brain metastases. *Ann Oncol* 20:621–627. 10.1093/annonc/mdn682 [PubMed: 19150943]
9. Carmichael AR (2006) Obesity as a risk factor for development and poor prognosis of breast cancer. *BJOG* 113:1160–1166. 10.1111/j.1471-0528.2006.01021.x [PubMed: 16945118]
10. Pajares B, Pollán M, Martín M et al. (2013) Obesity and survival in operable breast cancer patients treated with adjuvant anthracyclines and taxanes according to pathological subtypes: a pooled analysis. *Breast Cancer Res* 15:R105 10.1186/bcr3572 [PubMed: 24192331]
11. Simone BA, Dan T, Palagani A et al. (2016) Caloric restriction coupled with radiation decreases metastatic burden in triple negative breast cancer. *Cell Cycle* 15:2265–2274. 10.1080/15384101.2016.1160982 [PubMed: 27027731]
12. Arendt LM, McCready J, Keller PJ et al. (2013) Obesity promotes breast cancer by CCL2-mediated macrophage recruitment and angiogenesis. *Cancer Res* 73:6080–6093. 10.1158/0008-5472.CAN-13-0926 [PubMed: 23959857]
13. Jiang S, Wang R, Yan H et al. (2016) MicroRNA-21 modulates radiation resistance through upregulation of hypoxia-inducible factor-1 α -promoted glycolysis in non-small cell lung cancer cells. *Mol Med Report* 13:4101–4107. 10.3892/mmr.2016.5010
14. Han T, Kang D, Ji D et al. (2013) How does cancer cell metabolism affect tumor migration and invasion? *Cell Adhes Migr* 7:395–403. 10.4161/cam.26345
15. Chen EI, Hewel J, Krueger JS et al. (2007) Adaptation of energy metabolism in breast cancer brain metastases. *Cancer Res* 67:1472–1486. 10.1158/0008-5472.CAN-06-3137 [PubMed: 17308085]
16. Saleh AD, Simone BA, Palazzo J et al. (2013) Caloric restriction augments radiation efficacy in breast cancer. *Cell Cycle* 12:1955–1963. 10.4161/cc.25016 [PubMed: 23708519]
17. Witkiewicz AK, Dasgupta A, Sammons S et al. (2010) Loss of stromal caveolin-1 expression predicts poor clinical outcome in triple negative and basal-like breast cancers. *Cancer Biol Ther* 10:135–143 [PubMed: 20431349]
18. Subbiah IM, Lei X, Weinberg JS et al. (2015) Validation and development of a modified breast graded prognostic assessment as a tool for survival in patients with breast cancer and brain metastases. *J Clin Oncol* 33:2239–2245. 10.1200/JCO.2014.58.8517 [PubMed: 25987700]
19. Ahn HK, Lee S, Sohn JH et al. (2011) Prognostic index for patients with brain metastases from breast cancer: a validation and refinement of the breast-specific graded prognostic assessment (GPA) index. *J Clin Oncol* 29:1097 10.1200/jco.2011.29.15_suppl.1097

20. Vassalotti JA, Centor R, Turner BJ et al. (2016) Practical approach to detection and management of chronic kidney disease for the primary care clinician. *Am J Med* 129:153–162.e7. 10.1016/j.amjmed.2015.08.025 [PubMed: 26391748]
21. Florido R, Smith KL, Cuomo KK, Russell SD (2017) Cardio-toxicity from human epidermal growth factor receptor-2 (HER2) targeted therapies. *J Am Heart Assoc.* 10.1161/JAHA.117.006915
22. Gorovets D, Rava P, Ebner DK et al. (2015) Predictors for long-term survival free from whole brain radiation therapy in patients treated with radiosurgery for limited brain metastases. *Front Oncol* 5:110 10.3389/fonc.2015.00110 [PubMed: 26029666]
23. Kodack DP, Askoxylakis V, Ferraro GB et al. (2015) Emerging strategies for treating brain metastases from breast cancer. *Cancer Cell* 27:163–175. 10.1016/j.ccell.2015.01.001 [PubMed: 25670078]
24. Mazzarella L, Disalvatore D, Bagnardi V et al. (2013) Obesity increases the incidence of distant metastases in oestrogen receptor-negative human epidermal growth factor receptor 2-positive breast cancer patients. *Eur J Cancer* 49:3588–3597. 10.1016/j.ejca.2013.07.016 [PubMed: 23953055]
25. Widschwendter P, Friedl TW, Schwentner L et al. (2015) The influence of obesity on survival in early, high-risk breast cancer: results from the randomized SUCCESS A trial. *Breast Cancer Res* 17:129 10.1186/s13058-015-0639-3 [PubMed: 26385214]
26. Wright C, Simone NL (2016) Obesity and tumor growth: inflammation, immunity, and the role of a ketogenic diet. *Curr Opin Clin Nutr Metab Care* 19:294–299. 10.1097/MCO.0000000000000286 [PubMed: 27168354]
27. Champ CE, Baserga R, Mishra MV et al. (2013) Nutrient restriction and radiation therapy for cancer treatment: when less is more. *Oncologist* 18:97–103. 10.1634/theoncologist.2012-0164 [PubMed: 23299773]
28. Ciminera AK, Jandial R, Termini J (2017) Metabolic advantages and vulnerabilities in brain metastases. *Clin Exp Metastasis.* 10.1007/s10585-017-9864-8
29. Mauro L, Naimo GD, Ricchio E et al. (2015) Cross-talk between adiponectin and IGF-IR in breast cancer. *Front Oncol* 5:157 10.3389/fonc.2015.00157 [PubMed: 26236690]
30. Li P, Veldwijk MR, Zhang Q et al. (2013) Co-inhibition of epidermal growth factor receptor and insulin-like growth factor receptor 1 enhances radiosensitivity in human breast cancer cells. *BMC Cancer* 13:297 10.1186/1471-2407-13-297 [PubMed: 23777562]
31. Effect of elevated BMI on radiation toxicity in early stage breast cancer patients. 2016 ASCO Annual Meeting|Abstracts|Meeting Library. <http://meetinglibrary.asco.org/content/165881-176>. Accessed 16 May 2017
32. Stokes TB, Niranjana A, Kano H et al. (2015) White matter changes in breast cancer brain metastases patients who undergo radiosurgery alone compared to whole brain radiation therapy plus radio-surgery. *J Neurooncol* 121:583–590. 10.1007/s11060-014-1670-4 [PubMed: 25445836]
33. Kullmann S, Callaghan MF, Heni M et al. (2016) Specific white matter tissue microstructure changes associated with obesity. *Neuroimage* 125:36–44. 10.1016/j.neuroimage.2015.10.006 [PubMed: 26458514]
34. Szerlip N, Rutter C, Ram N et al. (2011) Factors impacting volumetric white matter changes following whole brain radiation therapy. *J Neurooncol* 103:111–119. 10.1007/s11060-010-0358-7 [PubMed: 20725847]
35. Chang EL, Wefel JS, Hess KR et al. (2009) Neurocognition in patients with brain metastases treated with radiosurgery or radio-surgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol* 10:1037–1044. 10.1016/S1470-2045(09)70263-3 [PubMed: 19801201]
36. Tsao M, Xu W, Sahgal A (2012) A meta-analysis evaluating stereotactic radiosurgery, whole-brain radiotherapy, or both for patients presenting with a limited number of brain metastases. *Cancer* 118:2486–2493. 10.1002/cncr.26515 [PubMed: 21887683]
37. Soliman H, Das S, Larson DA, Sahgal A (2016) Stereotactic radio-surgery (SRS) in the modern management of patients with brain metastases. *Oncotarget* 7:12318–12330. 10.18632/oncotarget.7131 [PubMed: 26848525]

38. Richardson LC, Pollack LA (2005) Therapy insight: influence of type 2 diabetes on the development, treatment and outcomes of cancer. *Nat Clin Pract Oncol* 2:48–53. 10.1038/nponc0062 [PubMed: 16264856]
39. GBD (2015) Collaborators O, Afshin A, Forouzanfar MH et al. (2017) Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med* 377:13–27. 10.1056/NEJMoa1614362 [PubMed: 28604169]
40. Sonnenblick A, Agbor-Tarh D, Bradbury I et al. (2017) Impact of diabetes, insulin, and metformin use on the outcome of patients with human epidermal growth factor receptor 2-positive primary breast cancer: analysis from the ALTTO phase III randomized trial. *J Clin Oncol* 35:1421–1429. 10.1200/JCO.2016.69.7722 [PubMed: 28375706]
41. Bjarnadottir O, Romero Q, Bendahl P-O et al. (2013) Targeting HMG-CoA reductase with statins in a window-of-opportunity breast cancer trial. *Breast Cancer Res Treat* 138:499–508. 10.1007/s10549-013-2473-6 [PubMed: 23471651]
42. Ahern TP, Lash TL, Damkier P et al. (2014) Statins and breast cancer prognosis: evidence and opportunities. *Lancet Oncol* 15:e461–e468. 10.1016/S1470-2045(14)70119-6 [PubMed: 25186049]
43. Lv M, Zhu X, Wang H et al. (2014) Roles of caloric restriction, ketogenic diet and intermittent fasting during initiation, progression and metastasis of cancer in animal models: a systematic review and meta-analysis. *PLoS ONE* 9:e115147 10.1371/journal.pone.0115147 [PubMed: 25502434]
44. Cleary MP, Grossmann ME (2011) The manner in which calories are restricted impacts mammary tumor cancer prevention. *J Car-cinog* 10:21 10.4103/1477-3163.85181
45. Chen Y, Ling L, Su G et al. (2016) Effect of intermittent versus chronic calorie restriction on tumor incidence: a systematic review and meta-analysis of animal studies. *Sci Rep* 6:33739 10.1038/srep33739 [PubMed: 27653140]
46. Longo VD, Fontana L (2010) Calorie restriction and cancer prevention: metabolic and molecular mechanisms. *Trends Pharmacol Sci* 31:89–98. 10.1016/j.tips.2009.11.004 [PubMed: 20097433]
47. Thomas Jefferson University Hospitals (2016) Caloric restriction in treating patients with stage 0–I breast cancer undergoing surgery and radiation therapy (CAREFOR). In: Clinical Trials.Gov. <https://clinicaltrials.gov/ct2/show/NCT01819233>. Accessed 15 May 2017

Fig. 1.

The effect of BMI and diabetes on overall survival and intracranial progression-free survival (PFS) among all patients. Kaplan–Meier OS curves for the entire cohort are shown according to BMI (a). Kaplan–Meier Intracranial PFS curves are shown for the entire cohort according to BMI (b). Kaplan–Meier OS curves for the entire cohort are shown according to diabetes (c). Kaplan–Meier intracranial PFS curves are shown for the entire cohort according to diabetes (d). The impact of diabetes on OS (e) and intracranial PFS (f) is depicted in the

Kaplan–Meier curve among patients with BMI 25. Differences in curves were assessed by the log-rank test

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Fig. 2.

The effect of BMI on survival according to receptor status. **a–c** A Kaplan–Meier curve presents OS in patients with **a** triple negative, **b** HR+, and **c** HER2 + breast cancer, according to BMI. Differences in curves were assessed by the log-rank test

Fig. 3.

The linear relationship between obesity and overall survival. **a** The linear, inverse relationship is graphed, showing a $p < 0.001$ that the slope is non-zero

Table 1

General characteristics of the study population

Characteristic	N (%)	BMI < 25 (n = 39)	BMI ≥ 25 (n = 45)	p value
Age (years) at diagnosis of BMBC				0.061
< 50	32 (38.1%)	20 (51.3%)	12 (26.7%)	
50–65	35 (41.7%)	12 (30.8%)	23 (51.1%)	
65	17 (20.2%)	7 (17.9%)	10 (22.2%)	
Diabetes	17 (20.2%)	2 (11.8%)	15 (33.3%)	0.001
Insulin-dependent	7 (8.3%)	0 (0.0%)	7 (15.5%)	
Non-insulin-dependent	10 (11.9%)	2 (11.8%)	8 (17.8%)	
KPS				0.878
70	16 (19.0%)	8 (20.5%)	8 (17.8%)	
80	29 (34.5%)	13 (33.3%)	16 (35.6%)	
90	24 (28.6%)	12 (30.7%)	12 (26.7%)	
100	15 (17.9%)	6 (15.4%)	9 (20.0%)	
Histology				0.982
Ductal carcinoma	67 (79.8%)	31 (79.5%)	36 (80.0%)	
Lobular carcinoma	6 (7.1%)	3 (7.7%)	3 (6.7%)	
Inflammatory carcinoma	11 (13.1%)	5 (12.8%)	6 (13.3%)	
Histologic grade				0.439
Grade 2	20 (23.8%)	7 (17.9%)	13 (28.9%)	
Grade 3	40 (47.6%)	19 (48.7%)	21 (46.7%)	
Unknown	24 (28.6%)	13 (33.3%)	11 (24.4%)	
Receptors				0.883
Triple negative	30 (35.7%)	12 (35.9%)	18 (40.0%)	
HR+/HER2–	14 (16.7%)	7 (18.0%)	7 (15.5%)	
HR–/HER2+	23 (27.4%)	11 (28.2%)	12 (26.7%)	
HR+/HER2+	16 (19.0%)	8 (18.0%)	8 (17.8%)	
No. intracranial metastatic lesions				0.737
1	38 (45.2%)	16 (41.0%)	22 (48.9%)	
2–3	21 (25.0%)	11 (28.2%)	10 (22.2%)	

Characteristic	N (%)	BMI < 25 (n = 39)	BMI ≥ 25 (n = 45)	p value
4	25 (29.8%)	12 (30.7%)	13 (28.9%)	
Median cumulative intracranial tumor volume (cc)	3.3 (0.13–9.0)	3.1 (0.13–9.0)	3.3 (0.89–8.0)	0.580
Stable systemic disease	34 (40.5%)	14 (35.9%)	20 (44.4%)	0.430
Median prior lines of systemic therapy	1 (0–4)	1 (0–4)	1 (0–4)	0.659
Median breast-specific GPA	2.75 (1.0–4.0)	3.0 (1.0–4.0)	2.5 (1.5–4.0)	0.484
Median modified breast-specific GPA	2.75 (1.0–4.5)	3.0 (1.0–4.0)	2.5 (1.0–4.5)	0.131
Resection of brain metastases	45 (54.0%)	19 (48.7%)	26 (57.8%)	0.473
Radiation modality				
SRS alone	18 (21.4%)	8 (20.5%)	10 (22.2%)	0.999
WBRT±SRS	66 (78.6%)	31 (79.5%)	35 (77.8%)	

Medians are presented as: median (range)

N number of subjects (percentage of total population), BMI body mass index in kg/m², No number, KPS Karnofsky performance status, HER2 human epidermal growth factor receptor-2, HR hormone receptor, SRS stereotactic radiosurgery, WBRT whole brain radiotherapy

Table 2

Univariate and multivariate predictors of survival

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Age at diagnosis of BMBC	1.02 (1.00–1.04)	0.018	1.02 (0.99–1.04)	0.167
Grade	1.23 (0.68–2.34)	0.454	-	-
BMI 25 kg/m ²	2.42 (1.52–3.85)	< 0.001	2.35 (1.39–3.98)	0.002
Diabetes	2.89 (1.49–5.60)	0.002	2.77 (1.45–5.27)	0.002
Time to BMBC	0.99 (0.993–1.01)	0.172	-	-
Time from initial diagnosis of breast cancer to distant progression	0.99 (0.99–1.01)	0.159	-	-
Time from distant metastasis to BMBC	0.99 (0.99–1.02)	0.169	-	-
No. of intracranial metastatic lesions	1.03 (0.93–1.15)	0.544	-	-
Year of BMBC diagnosis	0.96 (0.90–1.06)	0.151	-	-
No. of prior lines of systemic therapy	1.14 (0.85–1.52)	0.388	-	-
Stable systemic disease	0.77 (0.61–0.96)	0.022	0.57 (0.34–0.92)	0.021
Cumulative intracranial tumor volume (cc)	1.05 (0.95–1.16)	0.230	-	-
KPS	0.98 (0.96–0.99)	0.013	0.97 (0.95–0.99)	0.004
Triple negative breast cancer	2.21 (1.39–3.54)	0.001	1.97 (1.21–3.23)	0.007
HER2+ breast cancer	0.78 (0.50–1.20)	0.122	-	-
HR+ breast cancer	0.54 (0.33–0.87)	0.012	-	-
HR+/HER2– breast cancer	0.42 (0.16–1.11)	0.090	-	-
Resection	0.77 (0.50–1.18)	0.226	-	-
SRS without WBRT	1.18 (0.68–2.05)	0.554	-	-

BMBC brain metastases from breast cancer, BMI body mass index, No number, KPS Karnofsky performance status, HER2 human epidermal growth factor receptor-2, HR hormone receptor, SRS stereotactic radiosurgery, WBRT whole brain radiotherapy