Increased risk of secondary sarcomas in women with breast cancer: a 40-year analysis with SEER data

Felipe E. M. Andrade, MD1; Danúbia A. Andrade, MD1; Sabrina Lima, MD1; Anna Paula Maia, MD2; Rebeca N. Heinzen, MD1; Larissa C. Marques, MD1; Alfredo C. S. de Barros, MD, PhD3; Katina B. Ribeiro, DDS, PhD2

Background
• Second malignancies can develop as a consequence of cancer treatment. Several studies have described an association between radiation exposure and the development of soft tissue sarcomas.
• The aim of this study was to identify factors associated with increasing risk of sarcomas in women with breast cancer, with a particular focus on radiation field.

Methods
• We identified 488,804 women diagnosed with primary breast cancer in the period 1973-2013 (SEER 9 registries database).
• The development of subsequent sarcoma in the cohort was identified by querying the SEER database for all microscopically confirmed tumors with ICD-O-3 codes 880 through 958 that occurred in women in the cohort during the study period.
• Women with a diagnosis of sarcoma within 6 months of diagnosis of their breast cancer (n=136) were excluded from further analyses, in order to avoid the inclusion of synchronous malignancies.
• Results were stratified by location of sarcoma into in-field and out-of-field. In-field sarcomas were defined as those occurring at sites that would be included in the RT field, i.e., thorax and ipsilateral upper extremity. Out-of-field sarcomas were those occurring at all other sites.
• Standardized incidence ratios (SIR) and corresponding 95% confidence intervals (95% CI) for secondary sarcomas were calculated using SEERstat 8.3.2.

Results
• 1,388 secondary sarcomas were identified (1,373 women) within a median latent period of 105 months after the diagnosis of breast cancer (range 7-471 months).
• The risk of developing secondary sarcomas was increased for both located in-field (SIR=2.01, 95% CI, 1.72-2.36) and out-of-field (SIR=1.35, 95% CI, 1.28-1.43).
• Overall, mullerian mixed tumors (n=274), carcinosarcomas (n=229), and leiomyosarcomas (n=154) were the most frequent histological types (Figure 1).
• Radiation therapy increased the risk of secondary sarcomas both in-field (SIR=3.22, 95% CI 2.63-3.91) and out-of-field (SIR=1.46, 95% CI 1.33-1.59), while women not submitted to RT only presented increased risk of secondary sarcomas out-of-field (SIR=1.28, 95% CI 1.19-1.38) (Figure 2).
• In the group of secondary sarcomas in-field, the most frequent secondary sarcomas were malignant fibrous histiocytoma (n=21), leiomyosarcomas (n=18), and dermatofibrosarcoma (n=16) (Figure 3).
• Risk of secondary sarcomas in-field for those women submitted to RT only started to increase significantly 5 years after the diagnosis of the first primary (6-11 months after first primary, SIR=0.61, 95% CI 0.02-3.41; 12-59 months, SIR=1.64, 95% CI 0.97-2.59, 60-119 months, SIR=4.72, 95% CI 3.43-6.34; 120 months and later, SIR=4.00, 95% CI 2.84-5.47) (Figure 4).

Conclusions
• An increased risk of secondary sarcomas was found for women with breast cancer submitted to RT, including tumors both inside and outside the radiation field. These findings can suggest the presence of cancer predisposition syndromes, with the RT possibly increasing even more the risk of sarcomas in this group of cancer-predisposed women.
• Our findings highlight the importance of the long-term follow-up of these patients in order to increase early detection of these secondary sarcomas, minimizing the consequent morbidity and mortality.