We thank Berry et al. [1] for their interest in our work. As we have mentioned in our manuscript [2], lack of radiotherapy services or multidisciplinary discussions in some centers participating in our study could partly explain the discordance between the high pathologic complete response (pCR) rates observed and the higher rates of breast conserving surgery (BCS) [3]. We also recognize that a multidisciplinary approach may be conducted differently in different countries, although the difference might be minor for patients within clinical trials. Unfortunately, besides observing these data, it is not possible—to date—to prove the reasons that might have influenced surgeons when deciding on the type of surgery. Hence, we thank Berry et al. for their speculations regarding such reasons.

We completely agree with Berry et al. on the potential causes they stated regarding the discordance between high pCR rates and low BCS rates including the presence of residual ductal carcinoma in situ (DCIS) component, presence of microcalcifications, and lobular component with multifocal/multicentric tumors. The authors also referred to the lack of MRI access as baseline staging as a reason for low BCS rates. However, we highlight the evidence supporting that the use of preoperative MRI has resulted in increasing mastectomy rates [4–7]. So, we are not sure that implementing routine MRI in our study would have resulted in increased breast conservation.

Another important issue is the lack of data on patients’ preference regarding surgical extent that was not prospectively collected within the NeoALTTO trial. This is indeed a limitation and since breast conserving rates are among the secondary end points of the study, prospective collection of patient choices should have been considered. With the advances in breast reconstruction evolving role of prophylactic mastectomies, capturing patients’ preferences could have refined our understanding to the factors associated with surgical management in our study.

Regarding the use of oncoplastic techniques that could eventually increase the BCS rates after neoadjuvant treatments, no data were gathered on what type of BCS was carried out and if oncoplastic procedures were done. Patients who do not respond to neoadjuvant treatments or have T3 tumors after neoadjuvant therapy have an increased risk of local recurrence (LR) [8], so even with the use of oncoplastic techniques, we consider that the main problem is the assessment and the correlation between the pre- and post-treatment in the surgical decision-making after neoadjuvant treatment.

Finally, Berry et al. stated on how the surgeon perception of historical data regarding the high rate of local recurrence in patients with ER+ HER2—play a vital role in their decision. This represents the core of the message that we convey which is the importance of discussions between different disciplines and clarification on how advances in systemic therapy have improved treatment outcome. This would call for revisiting the indications of mastectomy in these patients.

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references
Are male gender and non-adenocarcinoma histology valid prognostic factors for breast cancer?

We read with great interest the article published by de Vin et al. [1]. The authors identified male gender and non-adenocarcinoma histology among independent predictors of impaired OS. Patients with breast cancer constitute 11% of the whole population analysed. We claim that inclusion of patients with breast cancer may confound the results due to several reasons. First, metastatic breast cancer histology itself confers better prognosis than many other solid tumours. This inherent better prognosis may influence the results of treatment in oligometastatic setting. In Milano et al.’s series, breast cancer patients with oligometastatic disease was found to have better OS at 6 years, better PFS at 2 years and better local control than other patients with non-breast primaries [2]. Second, more than 90% of primary breast cancers are histologically adenocarcinomas. The presence of breast carcinomas may favour adenocarcinoma histology as a better prognostic group than non-adenocarcinoma histology in the oligometastatic setting. Third, breast cancer incidence is much higher in women than men. We learn whether male gender and non-adenocarcinoma histology are still valid prognostic factors after excluding patients with breast cancer from analyses.

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Reply to the letter to the editor ‘Are male gender and nonadenocarcinoma histology valid prognostic factors for breast cancer?’ by Eren et al.

We acknowledge that the extraction of prognostic factors from our study may be confounded by patient’s heterogeneity as oligometastases from various primary tumors were included. Breast cancers are indeed predominantly adenocarcinomas, affecting females, and are considered a favorable origin in case of metastatic disease [1]. Nevertheless, male gender (P = 0.036) and nonadenocarcinoma histology (P < 0.001) were still associated with significantly impaired overall survival (OS) on additional multivariate analysis (MVA) after exclusion of all breast cancer patients (n = 33). In the remaining population (n = 276) consisting of patients with non-small-cell lung cancer (NSCLC; n = 89), colorectal cancer (CRC; n = 101) and other primary tumors (n = 86) such as small-cell lung cancer, prostate, renal cancer and melanoma, MVA revealed that women with NSCLC (n = 28) experienced a significantly longer median survival time (MST of 15 months) than men with NSCLC (MST of 11 months, P = 0.018). Furthermore, adenocarcinoma histology also remained a favorable survival determinant among the NSCLC oligometastatic patients (MVA, P = 0.004). These two factors have been frequently associated with favorable prognosis in all stages of NSCLC and possibly related to female hormones, smoking history, sex-influenced biologic mechanisms and responsiveness to targeted drugs [2, 3]. In oligometastatic CRC patients (n = 101), no significant survival difference was observed between men and women (MST of 27 versus 24 months, P = 0.633), which is in concordance with the results of one of the largest datasets available on gender disparities in metastatic CRC survival [4]. However, when age was accounted for in the latter study, younger women with metastatic CRC were found to live longer than younger men [4]. Since there were only 10 men and 10 women <55 years of age among the oligometastatic CRC patients in the current study, with a MST of 31 and 37 months, respectively, a potential benefit for younger women in terms of OS could not be demonstrated (P = 0.429). There was also no significant interaction on MVA between sex and OS in the remaining 86 oligometastatic patients with other primary tumors (MST of 15 months for males versus MST of 27 months for females, P = 0.982), whereas there was a benefit for adenocarcinoma histology (MST of 33 versus 12 months for nonadenocarcinoma, P < 0.001). In conclusion, histology and gender remained as a significant prognostic factor on MVA after exclusion of breast cancer patients. Concerning sex, the benefit to women appeared to extend only in the subgroup of patients with NSCLC.

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