Second Chance for Cure: Stereotactic Ablative Radiotherapy in Oligometastatic Disease

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ABSTRACT

PURPOSE Local ablative therapy, such as radiotherapy or surgery, plays a key role in treatment of patients with oligometastatic disease. Stereotactic ablative body radiotherapy (SABR) comes to the fore as a safe and effective treatment for patients with a limited number of metastases, even those located in hard-to-reach body sites. Many researchers have suggested that metastatsis-directed therapy could improve long-term progression-free survival (PFS) and overall survival (OS) in patients with oligometastases.

PATIENTS AND METHODS This was a retrospective, single-arm, observational study conducted between July 2015 and February 2022. In our institute, 60 patients with controlled primary tumors and one to five metastases were treated with SABR. Prescribed radiation doses ranged from 12 to 60 Gy administered in one to seven fractions. We aimed to determine whether metastatic-directed therapy using SABR for all oligometastases affects OS and PFS and whether the primary tumor or metastatic site influences OS/PFS.

RESULTS The most common primary malignancy types were prostate (n = 14), colorectal (n = 10), lung (n = 7), and breast cancers (n = 6). The median follow-up was 30 months, ranging from 9 to 79. The 1-, 3-, and 5-year PFS and OS rates were 54.9%, 37.0%, and 37.0% and 98.3%, 84.4%, and 73.8%, respectively, and the median time to first progression was 15 (range, 2-32) months. Twenty-four (40%) patients had no recurrence. In our analysis, primary tumor site was not an independent prognostic factor. The metastatic site may influence on patient outcome in cases of localized bone and liver metastases.

CONCLUSION In our retrospective analysis, SABR was associated with favorable levels of PFS and OS in patients with oligometastases. The limitations of our study were lacking high-level evidence, and randomized studies to compare SABR and palliative standard of care are mandatory.

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INTRODUCTION

In 1995, oligometastatic disease was described as an intermediate stage between localized and widespread cancers, characterized by the limited number and size of metastases.[1] In 2020, the European Society for Radiotherapy and Oncology, in conjunction with the American Society for Radiation Oncology (ASTRO), concluded that oligometastatic disease can be defined as one to five metastatic lesions, a controlled primary tumor being optional, but where all metastatic sites must be safely treatable.[2,3]

Systemic therapy is the standard of care for most patients with metastatic cancer, and although chemotherapy can improve survival in some cases, it never cures solid tumors.[4,5] Many patients develop subsequent disease progression and die as a result. The lack of effective alternatives to systemic therapy has led to the exploration of metastasis-directed ablative therapies. In 1996, Pastorino et al[6] introduced the results of metastasectomy in 5,206 patients. The actuarial survival after complete metastasectomy was 36% at 5 years, 26% at 10 years, and 22% at 15 years.[6] These results confirmed that metastasectomy is a safe and potentially curative procedure. However, surgical treatment is not a universal method because of (1) the frequent location of metastases in places inaccessible to surgery, (2) the number and size of metastases in one organ, and (3) patient performance status and other relative features specific for each individual case.

The improvement of radiation therapy techniques led to emergence of stereotactic radiosurgery (SRS) and stereotactic body radiotherapy, also known as stereotactic ablative

CONTEXT

Key Objective

Can stereotactic ablative body radiotherapy (SABR) revolutionize the treatment of oligometastatic disease, and what distinguishes this approach from other standard treatment methods?

Knowledge Generated

While we await the results of randomized control trials, our retrospective analysis demonstrates that SABR offers a groundbreaking approach, yielding improvements in both progression-free and overall survival rates among patients with oligometastatic disease, regardless of their primary tumor site.

Relevance

These findings underscore the potential of SABR as a game-changing therapeutic option and suggest its adoption as a valuable treatment strategy. Clinicians may consider SABR as a noninvasive, precise, and effective therapeutic method for managing oligometastatic disease, potentially improving patient outcomes and quality of life while delaying or altering their systemic therapy. Further exploration and integration of SABR in clinical settings are warranted to harness its full benefits for patients with this condition.

body radiotherapy (SABR). These modern techniques allow delivery of ablative doses of radiation to sites typically inaccessible for surgery. SABR is crucial in two cancer stages: early primary cancer and oligometastatic disease, with the goal of inducing complete cancer remission in both. In the context of oligometastatic cancer, SABR presents a novel opportunity for local therapy of precise tumor for some patients who retain the possibility of long-term disease control.

Encouraging results are presented in the SABR-COMET trial. Ninety-nine patients with a controlled primary solid tumor and one to five metastatic lesions were randomly allocated to receive standard-of-palliative care treatment alone or in addition to SABR delivered to all metastatic lesions. The results showed a 13-month increase in overall survival (OS) and a doubling of progression-free survival (PFS) in the SABR group.[7] The results of two other studies, SARON and CORE, which evaluate the effectiveness of SABR for patients with oligometastatic disease, are awaited. In another phase III, SARON trial, the authors are investigating the impact and feasibility of adding SABR/SRS and radical radiotherapy after standard chemotherapy on OS of patients with non–small cell lung cancer (NSCLC).[8] The CORE study will focus on patients with oligometastatic cancer from primary sites including breast, prostate, and NSCLC. Participants will be randomly assigned to receive either standard care or standard care in addition to SABR. The primary outcome measure for the trial will be PFS.[9]

In our study, we aimed to determine whether radiation therapy affects OS and PFS when all metastatic lesions are treated with SABR. We also investigated whether the primary tumor or metastatic site influences OS/PFS. The opportunity to prolong PFS and OS and improve the quality of life for patients with cancer with metastatic disease from any primary site prompted us to explore SABR for oligometastases. Undoubtedly, new data will refine or even upend our understanding of the definition and optimal management of oligometastatic disease. Randomized studies to compare SABR and palliative standard of care are mandatory.

PATIENTS AND METHODS

This was an open-label, one-arm retrospective treatment analysis. We enrolled 60 patients with a controlled primary tumor and one to five metastatic lesions (overall 215 metastatic lesions), who were treated at the Radiation Oncology Department of the European Medical Center (Moscow, Russia) between July 2015 and November 2021 and met the following criteria: (1) patients with one to five metastatic lesions in any organ from any primary tumor, (2) all metastases were treated with SABR (one to seven fractions, with a minimum dose of 8 Gy per fraction), (3) possibility of performing positron emission tomography/computed tomography (PET/CT) or CT with intravenous (IV) contrast or brain magnetic resonance imaging (MRI), (4) life expectancy of at least 6 months, and (5) Eastern Cooperative Oncology Group performance status 1-2. The excluding criteria were as follows: (1) patients with more than five metastases, (2) unknown primary tumor site, and (3) at least one or more metastases treated with a non-SABR technique. The median age was 60.4, ranging from 32.4 to 86.4 years, and 30 (50.0%) patients were female. We stratified patients by metastatic site lesion. Most metastases were located in bone, 51 (23.7%), and in lung, 51 (23.7%), followed by liver metastases, 41 (19.1%), and lymph nodes (LNs), 31 (14.4%), in third place. We did not exclude patients with intracranial lesions in cases when patients also had extracranial metastases. Overall, three (5%) patients had intracranial metastases. During the treatment, 43 (71.7%) patients had systemic or hormone therapy, whereas 17 (28.3%) did not

TABLE 1. Patient Characteristic

Characteristic	No. (%)
No. of patients	60
Male	30 (50.0)
Female	30 (50.0)
Primary tumor site	
Prostate cancer	14 (23.3)
Colorectal cancer	12 (20.0)
Lung cancer	7 (11.7)
Gynecologic cancer	6 (10.0)
Breast cancer	6 (10.0)
Melanoma	5 (8.3)
Other[a]	10 (16.7)
Metastatic lesion	215
Bone	51 (23.7)
Lung	51 (23.7)
Liver	41 (19.1)
Lymph nodes	31 (14.5)
CNS	16 (7.4)
Soft tissue	9 (4.2)
Other[b]	16 (7.4)
No. of primary metastases	
1	28 (46.7)
2	17 (28.3)
3	11 (18.3)
4	3 (5.0)
5	1 (1.7)
Any systemic therapy	
Received	43 (71.7)
Not received	17 (28. 3)

[a]Pancreatic cancer, kidney cancer, head and neck cancer, anal cancer.
[b]Implant, adrenal, ovary, spinal cord, prostate.

receive any systemic/hormone or maintenance therapy. Baseline characteristics are listed in Table 1.

Pre-enrollment imaging requirements included the following: (1) brain CT or MRI with IV contrast for tumors with a propensity for brain metastasis, (2) body imaging with either a PET/CT with 18 F-fluorodeoxyglucose (18FDG) or prostate-specific membrane antigen (PSMA), and (3) MRI of the spine for patients with vertebral metastases.

The final decision regarding the inclusion of a patient in the analysis was made by a multidisciplinary team and approved by the intrainstitutional ethics committee (European Medical Center Ethics Committee from April 6, 2015).

The study was conducted in accordance with the principles of the Declaration of Helsinki. Clinical outcomes and toxicity data were collected according to the Common Criteria for Terminology for Adverse Events (version 4.0).

SABR Technique

All patients underwent CT simulation using a Philips Brilliance CT big Bore X-ray tomography (Philips, Amsterdam, the Netherlands) with individual immobilization devices specific for different treatment sites. For head and neck area metastasis, Qfix Portrait with individual thermoplastic mask was used; for lung, LN, and bone metastasis, only individual vacuum cushions were used; for reducing respiratory motion in liver and abdominal metastasis abdominal compression with Qfix DoseMax, individual vacuum cushions were used. CT slice was 1 mm in size. For lung and liver tumors, four-dimensional CT was additionally conducted. CT simulation was fused with 18FDG/PSMA PET/CT or MRI with or without IV contrast scans for more precise delineation. Gross tumor volume (GTV), allowance for clinical target volume, and

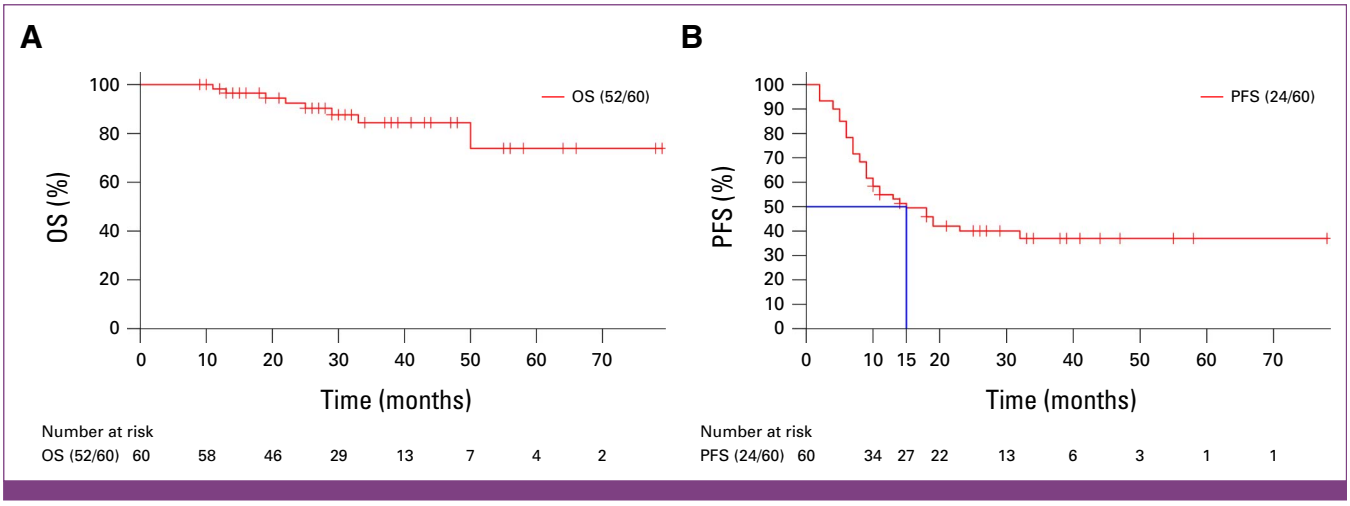

FIG 1. Kaplan-Meier curves of all patients with oligometastatic disease: (A) OS and (B) PFS. OS, overall survival; PFS, progression-free survival.

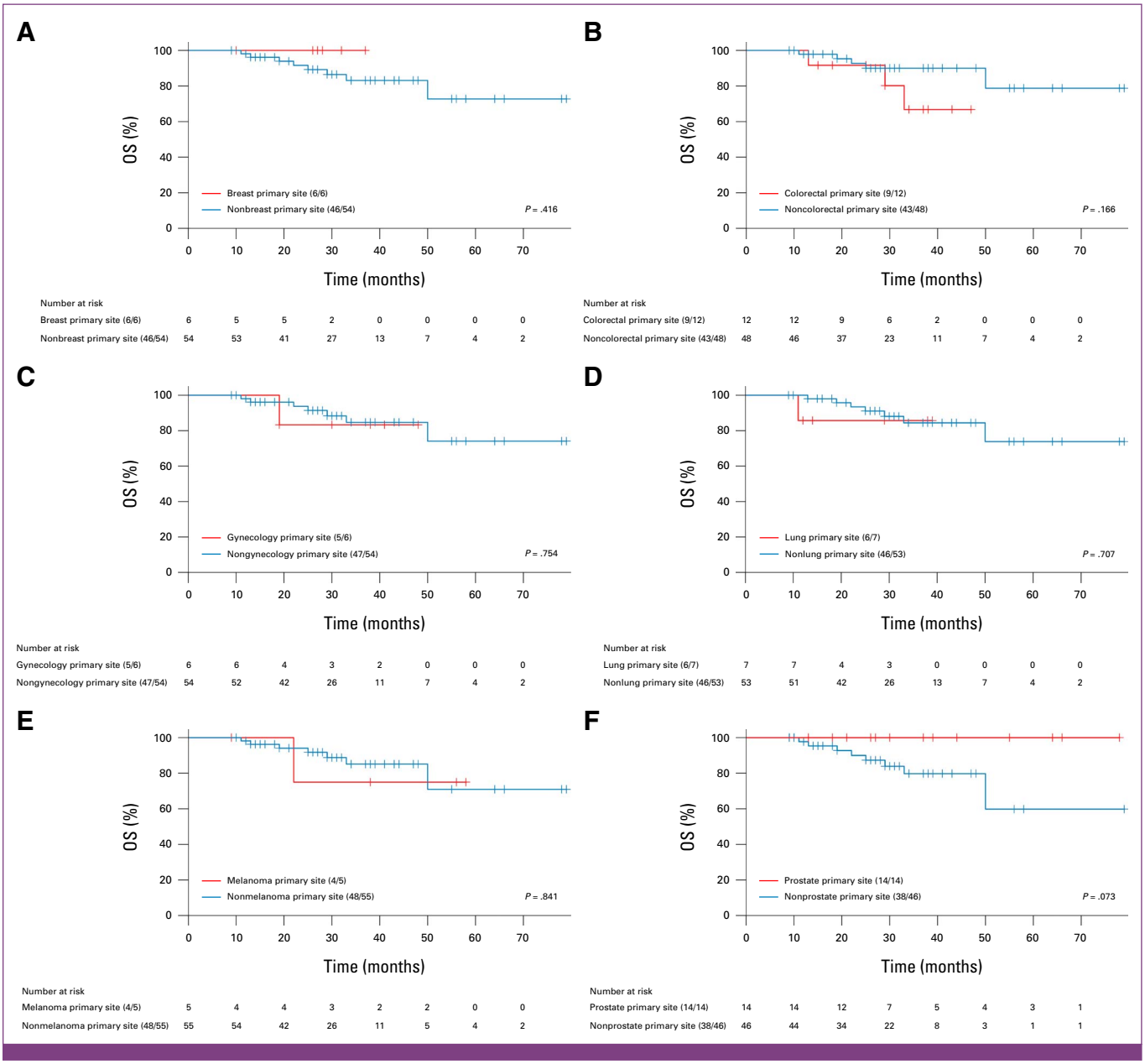

FIG 2. Kaplan-Meier OS curves stratified by primary tumor site. Pairwise comparison between primary and nonprimary in (A) breast cancer, (B) colorectal cancer, (C) gynecologic cancer, (D) lung cancer, (E) melanoma, and (F) prostate cancer. (G) Survival curve comparison of all primary tumor sites. OS, overall survival. (continued on following page)

planning target volume (PTV) were determined individually in each case. Organs at risk (OARs) were delineated in each patient, taking into account the location of the GTV according to Radiation Therapy Oncology Group (RTOG) protocols and International guidelines for each metastatic site separately.

From 2015 to 2019, a total of 215 VMAT treatment plans were optimized using Eclipse version 15.6 and implemented on Varian TrueBeam and EDGE (Varian Medical Systems, Palo Alto, CA) linear accelerators with appropriate multileaf collimator. Post-2019 treatments shifted exclusively to the Varian EDGE. The Acuros XB algorithm (Acuros XB, ver. 15.6.06, Varian Medical Systems) with varying grid sizes was used for dose calculation on the basis of PTV volume. Treatment customization took into account individual patient anatomy, with arc field arrangements ensuring target coverage and OAR dose minimization as per the institutional protocol; 99% of the PTV received at least 95% of the prescribed dose. Isocenter placement was carefully chosen to prevent gantry collisions. Depending on lesion size and location, either 10 megavoltage flattening filter free (MV FFF) or six MV FFF beams were selected. Plans ranged from two to five arcs, adjusted for target positioning, with quality assurance conducted using SNC125 and SRS Mapcheck (Sun Nuclear Corporation, Melbourne, FL), achieving over 95%

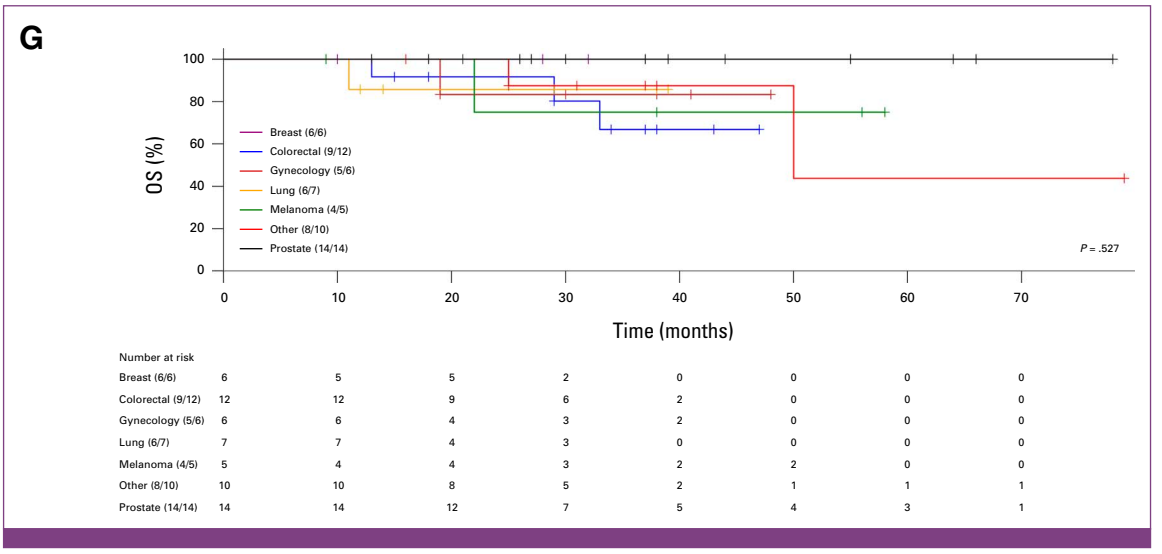

FIG 2. (Continued).

gamma pass rates. PTV coverage and doses to OARs in all plans were evaluated by a medical physicist and radiation therapist in accordance with the TG-101 protocol. Final treatment verification involved on-board imaging and cone beam computed tomography (CBCT) for precise patient alignment.

All patients received from one to seven fractions for each metastatic lesion administered once daily, excluding weekends. All treatment protocols in our study are based on National Comprehensive Cancer Network Guidelines and RTOG and ASTRO protocols for metastatic disease. The minimum prescribed dose per fraction was 8.0 Gy, and the maximum was 24.0 Gy. The minimum total dose was 12.0 Gy (12.0 Gy in one fraction), and the maximum total dose was 60.0 Gy (20.0 Gy in three fractions). The most common treatment regimens were 50.0 Gy for lung metastases in five fractions, 35.0 Gy for metastatic LNs in seven fractions, 24.0 Gy in three fractions and 16.0 Gy in one fraction for any bone metastases, and 50.0 Gy in five fractions for liver metastases.

Statistical Analysis

The toxicity events were tabulated by grade and frequency. The feasibility rate and response rate were estimated with an exact 95% CI. Time-to-event end points were described using the Kaplan-Meier method. Estimates at key time points were provided with 95% CI. The log-rank test was used for paired group comparison. $P < .05$ denoted statistical significance.

Follow-Up

18FDG or PSMA PET/CT, CT with IV contrast, or MRI was performed every 3-6 months. Complete response was defined as the disappearance of lesions on imaging. On 18FDG/PSMA PET/CT, changes were assessed on the basis of a decrease in the standardized uptake value (SUV) before and after treatment. No change was considered as stabilization; any growing SUV not associated with fibrosis was recorded as disease progression.

Ethics Approval

Ethics approval for the study was obtained from the Local Research Ethics Committee (European Medical Center Ethics Committee) dated April 21, 2015. Informed consent was obtained from the patients. Written consent was obtained from the patients for publication of this article, including all images.

RESULTS

A total of 60 patients were included in the current analysis, and all of them are presented with oligometastatic disease (one to five metastatic lesions). Thirty (50.0%) patients were female, and the median age of all patients at the time of treatment was 60.4 years. The median follow-up was 30 months (from 9 to 79 months). The primary outcome event, death as a result of any cause, occurred in five (8.3%) patients. The status of three patients is unknown, and so we considered them dead. The median time to first progression was 15 months, ranging from 2 to 32 months. The 1-, 3-, and 5-year PFS and OS rates were 54.9%, 37.0%, and 37.0% and 98.3%, 84.4%, and 73.8%, respectively. OS and PFS are shown in Figure 1. Twenty-four (40%) patients have no recurrence. Two of three patients with intracranial metastases were alive at the end of the study. There were no grade 2-5 adverse events.

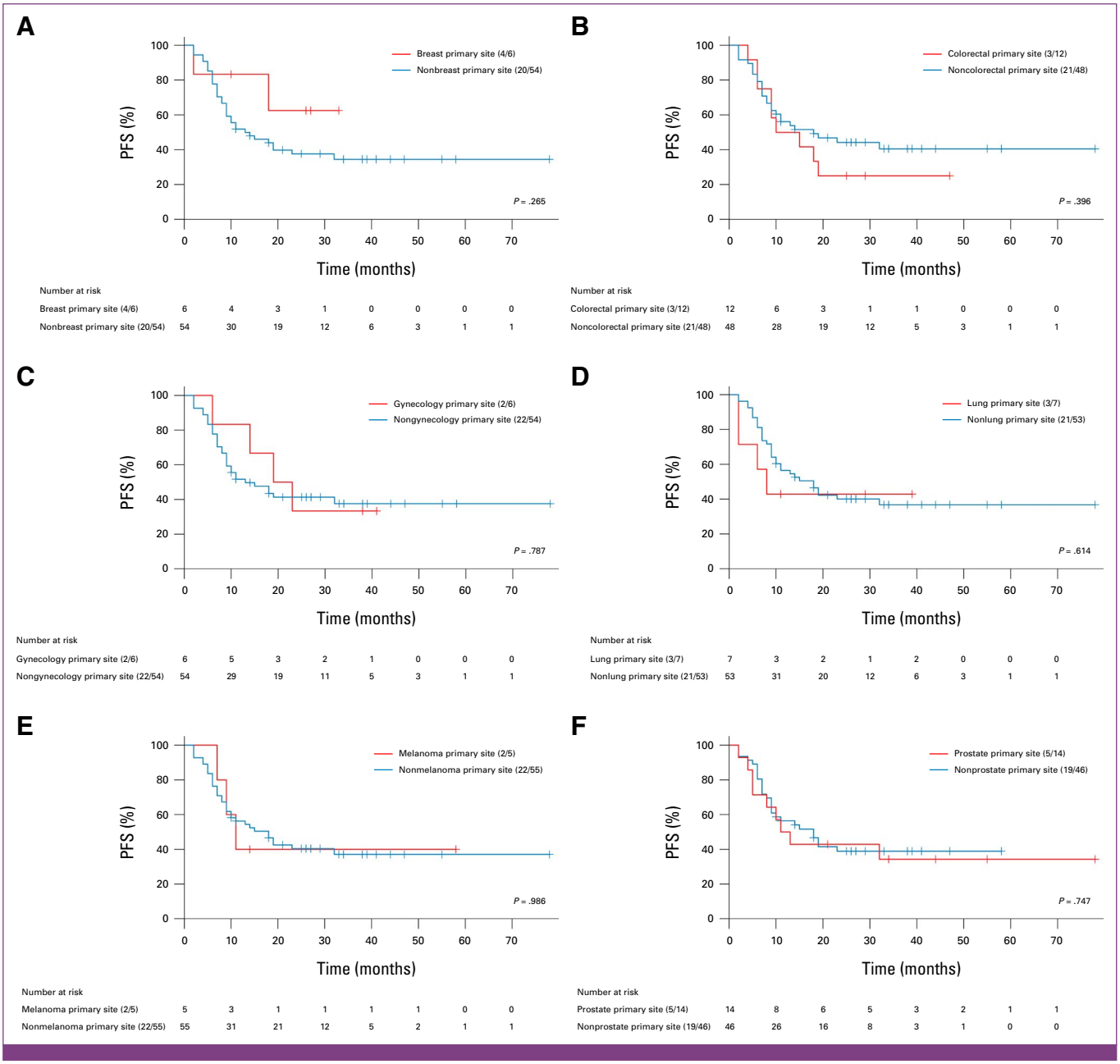

FIG 3. Kaplan-Meier PFS curves stratified by primary tumor site. Pairwise comparison between primary and nonprimary in (A) breast cancer, (B) colorectal cancer, (C) gynecologic cancer, (D) lung cancer, (E) melanoma, and (F) prostate cancer. (G) Survival curve comparison of all primary tumor sites. PFS, progression-free survival. (continued on following page)

In addition, we analyzed the relationship between the primary tumor site and OS/PFS (Figs 2 and 3). There was no correlation observed in a pairwise comparison of all primary tumor sites (the *P* value was >.05). The smaller number of patients in our cohort might also have influenced this outcome. We have noted some differences in OS in patients with prostate cancer ($P = .073$), which had a 100% OS rate. We suppose that this is primarily because the prostate cancers in our study had only bone metastases because of early detection of metastases. We assume that if we had more patients with prostate cancer with metastases to other sites, the OS rates would be worse.

We explored the relationship between metastatic sites and OS/PFS (Figs 4 and 5). We grouped patients on the basis of the site of metastases, regardless of their number at the start of the treatment. Patients with localized bone metastases had a 100% OS versus 68.7% no bone metastasis ($P = .039$), which is barely significant, and a better PFS rate of 53.7% versus 29.4% ($P = .01$). Patients with localized liver

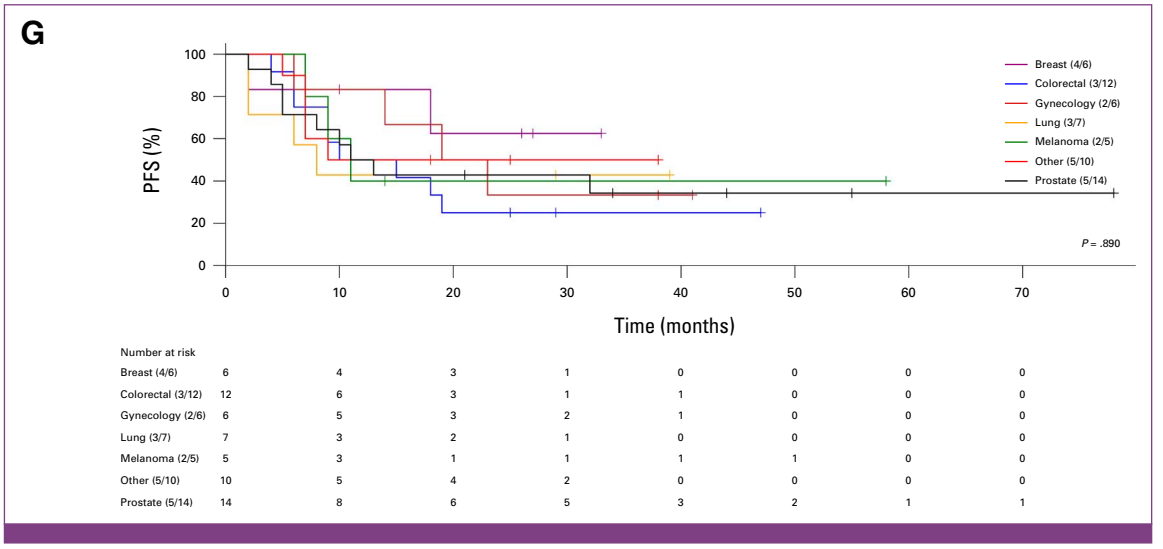

FIG 3. (Continued).

metastases had a worse PFS rate of 13.9% versus 39.0% (P = .003) compared with others, but this did not influence the OS rates.

We also analyzed this relationship in a group of patients with a single site of metastases (Figs 6 and 7). From the patients with multiple-site metastases, we identified a subgroup with single-site metastases at the start of the treatment. Patients with bone metastases had a better OS of 100% versus 59.3% no bone metastasis (P = .049) and a PFS of 62.0% versus 31.3% (P = .004). In a pairwise comparison, we observed significant differences in PFS between bone (62.0%) versus lung (34.3%; P = .014) and bone versus liver (15.9%; P = .001).

Safety and Tolerability

Treatment-related adverse events were observed in six patients (7%). All of them had evidence of general toxicity (nausea, weakness, fatigue). Patients with liver metastases (n = 4) had worse toxicity rates than patients with metastases to other organs. There were no grade 3 or 4 toxicities.

DISCUSSION

Metastatic disease constitutes the primary cause of death for >90% of patients with cancer.[10,11] The rapid evolution of diagnostic imaging in modern oncology practice and easy access of patients to these new visualization modalities have been associated with the rising number of patients diagnosed with a small number of metastatic lesions. Previously, the standard to treat patients with metastatic cancer was systemic palliative therapy, whereas radiation therapy was mainly used for symptom relief and local control. In 1995, Hellman S. and Weichselbaum R. published a new concept of oligometastatic disease as an intermediate stage between localized and widespread diseases. They suggested that tumors early in their progression should be amenable to localized therapy. Patients with oligometastases, either de novo or after systemic treatment, can be cured by ablation of these lesions.[1] Early experiences primarily focused on surgical resection or metastasectomy of solitary or a few secondary lesions.[12,13] In the United States from 2000 to 2011, surgical resection increased substantially across common cancer types, such as colorectal, lung, and breast cancers and melanoma.[14] However, as mentioned above, surgery is not the only treatment method for oligometastases.

Considering recent radiotherapy advances, and especially SRS success in the treatment of intracranial metastases, SABR for extracranial lesions has arisen as a particularly attractive noninvasive strategy for the management of oligometastases.[15] SABR differs from other radiation techniques in several important aspects, including the use of highly precise radiotherapy setup techniques, taking into account tumor motion, and the availability of contemporary planning algorithms. These advanced features allow for large doses of radiotherapy to be delivered in a small number of treatment fractions. The clinical efficacy of SABR explained by radiobiology, where daily high-dose radiotherapy induces the radiobiologic alteration including vascular endothelial injury and the immune activation, which has been indicated in the literature, is reported to play a crucial role in tumor control.[16-18] Other advantages of SABR include a favorable overall toxicity profile and short recovery period.[19-22] To maximize the benefits of SABR and minimize side effects or treatment-related failures, a practice guideline for the performance of SABR was published in 2011.[23]

To determine which patients with oligometastatic disease are eligible for metastatic-directed therapy (MDT), beyond the number of metastases, other prognostic factors should be considered. Broadly, these factors were highlighted by many researchers and may include, but are not limited to,

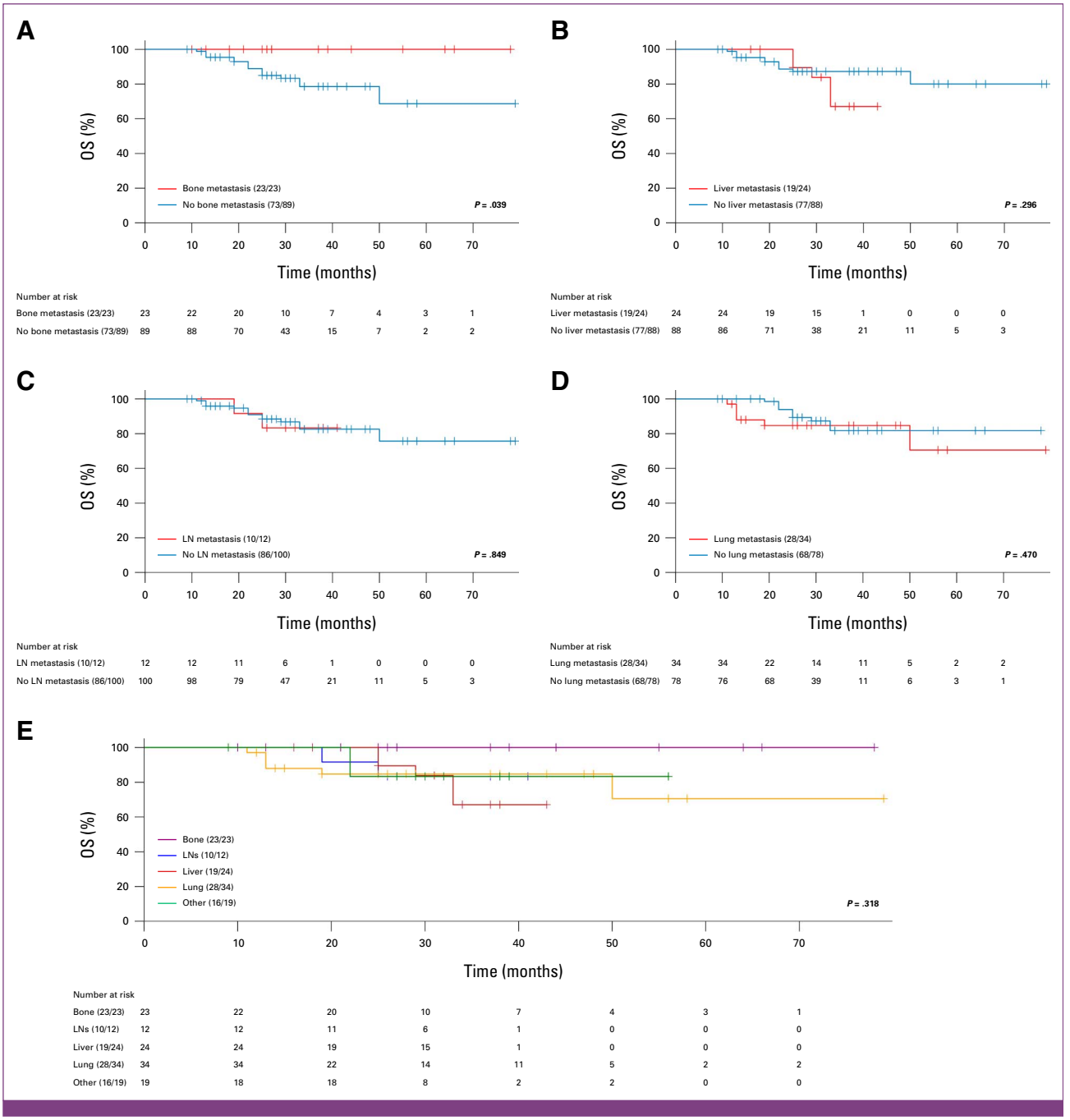

FIG 4. Kaplan-Meier OS curves. Pairwise comparison between metastases and nonmetastases in (A) bone cancer, (B) liver cancer, (C) lymph node cancer, and (D) lung cancer; (E) Kaplan-Meier OS curves of all metastatic sites. LNs, lymph nodes; OS, overall survival.

age/performance status, the disease site/histology, the size/location of lesions, the kinetics of disease progression, and the development of distal metastasis.

In 2004, Singh et al[24] revealed that patients with controlled prostate cancer with five or less metastases had significantly better survival rates than patients with >five lesions. They suggested that early detection and aggressive treatment of patients with a small number of metastatic lesions is worth testing as a new approach to improve long-term survival.[24] Zumsteg et al[25] suggested that the atypical location of metastasis for each specific disease, compared with the classic distribution routes, has the worst prognosis. For example, prostate cancer most often metastasizes to the bones or to the pelvic and retroperitoneal LNs, whereas the detection of visceral involvement to the lungs, liver, or other organs is associated with the worst forecast of survival.[25] Ho et al[26] hypothesized that patients with oligometastatic disease of the spine have a more favorable chance of survival compared with patients with synchronous metastatic disease into other

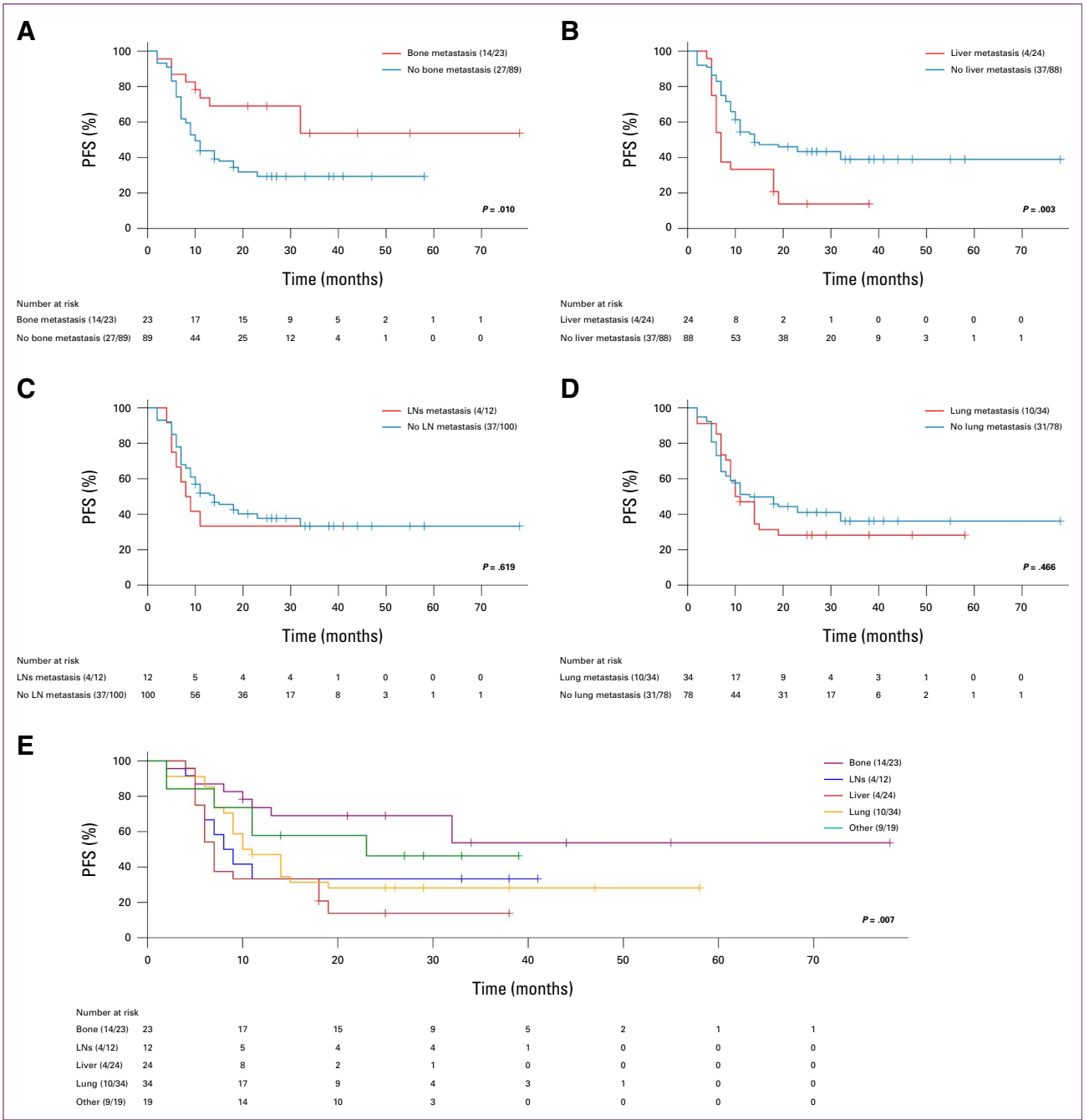

FIG 5. Kaplan-Meier PFS curves. Pairwise comparison between metastases and nonmetastases in (A) bone cancer, (B) liver cancer, (C) lymph node cancer, and (D) lung cancer; (E) Kaplan-Meier PFS curves of all metastatic sites. LNs, lymph nodes; PFS, progression-free survival.

sites and thus are believed to benefit from more aggressive treatments, such as an ablative rather than a palliative dose of radiotherapy. A retrospective analysis by Petrelli et al,[27] which included 18 studies and a total of 656 patients, explored SABR as a primary modality treatment for patients with liver oligometastases. The median PFS and OS were 11.5 and 31.5 months, respectively. SABR can be used to deliver high doses of irradiation to any metastatic lesion, which is located in different hard-to-reach body sites.

Kinj et al[28] stated in their study that the primary tumor location is one of the most important factors influencing patient outcomes. In our study, we could not confirm this fact. In our analysis, the primary tumor site was among other important factors that may influence patient outcomes and not an independent prognostic factor, whereas the metastatic site may influence patient outcome in some cases as described in the Results section. Nevertheless, when selecting a patient with oligometastatic disease, this

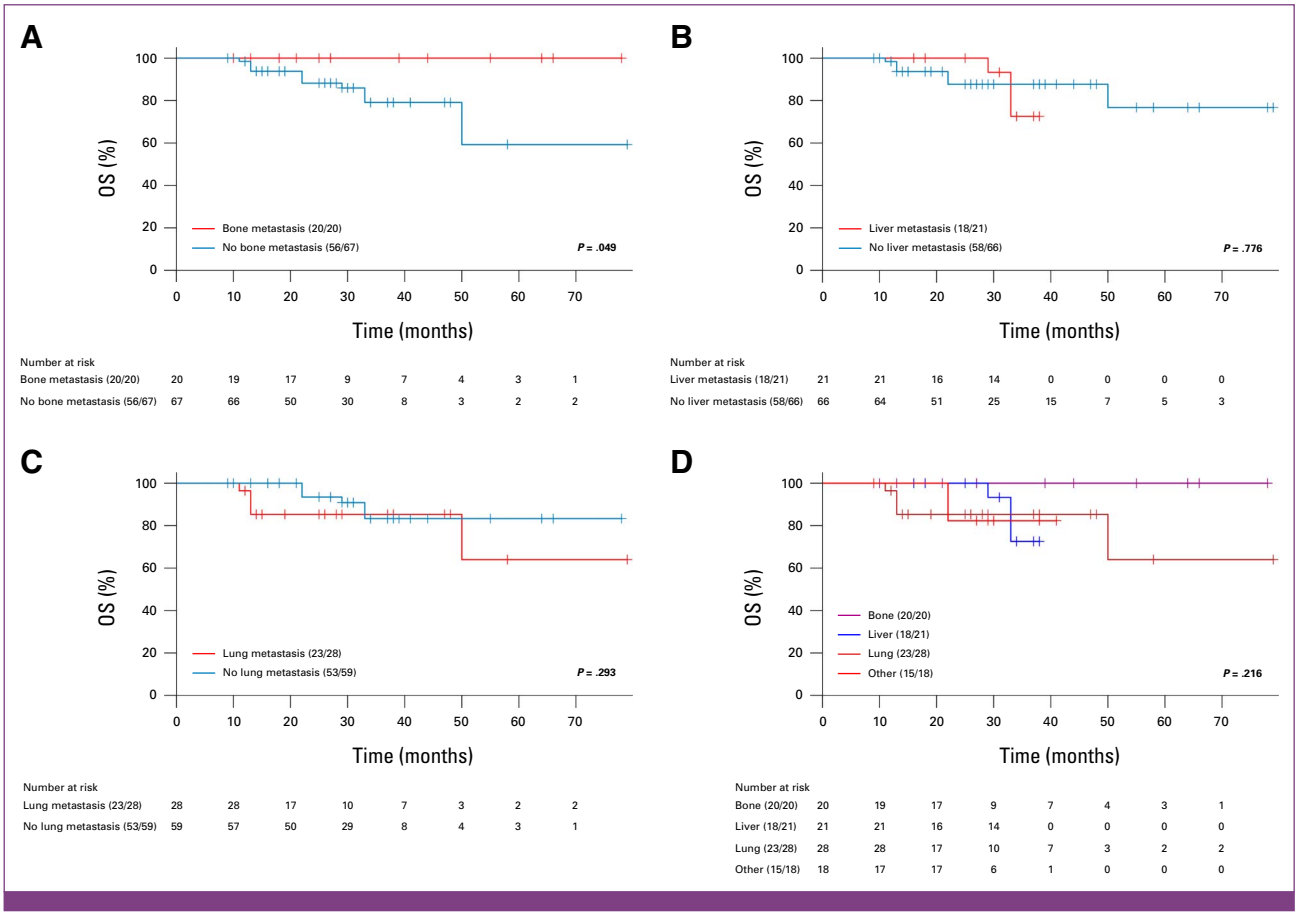

FIG 6. Kaplan-Meier OS curves. Pairwise comparison in the patient cohort with single metastatic site between metastases and non-metastases in (A) bone cancer, (B) liver cancer, and (C) lung cancer. (D) Kaplan-Meier OS curves of all metastatic sites. OS, overall survival.

factor should be taken into consideration and must be discussed in multidisciplinary tumor boards for the possibility of MDT.

Among others, the addition of SABR to systemic therapy will mostly benefit some patients with oligometastatic disease. In a retrospective study by Deek et al,[29] adding SABR to systemic therapy was associated with favorable outcomes and improved cancer control when compared with the change in systemic treatment alone in patients with oligoprogressive castrate-resistant prostate cancer. Gomez et al[30] conducted a multicenter randomized trial, where patients with oligometastatic disease with stage IV NSCLC were randomly allocated to receive either MDT (surgery or SABR) in conjunction with systemic therapy or systemic treatment alone. The trial was terminated at the interim analysis. The results showed that MDT plus maintenance therapy improved PFS compared with maintenance therapy alone. The median PFS was 11.9 months versus 3.9 months, respectively.[30]

In an article on metastasis, Fares et al[31] concluded that metastatic disease is a complex challenge that requires more than one therapeutic agent for effective treatment. Therefore, embracing the combination therapy model and targeting multiple pathways simultaneously seem to be key to countering the significant genomic and phenotypic alterations presented by metastatic cancer cells.[31]

Moreover, for patients with metastases on systemic treatment, SABR allows them to remain on the same line of treatment that they received before the oligoprogression.

Currently, there is no consensus on how to define the oligometastatic state and the current TNM staging does not reflect the oligometastases in most cancer types. We think that this subject should be proposed for the future TNM editions. This will also affect socioeconomical and treatment guidelines aspects.

In conclusion, in our retrospective analysis, patients with an oligometastatic state and who received SABR demonstrated long-term disease control. There was no observed statistical correlation between primary tumor site and OS/

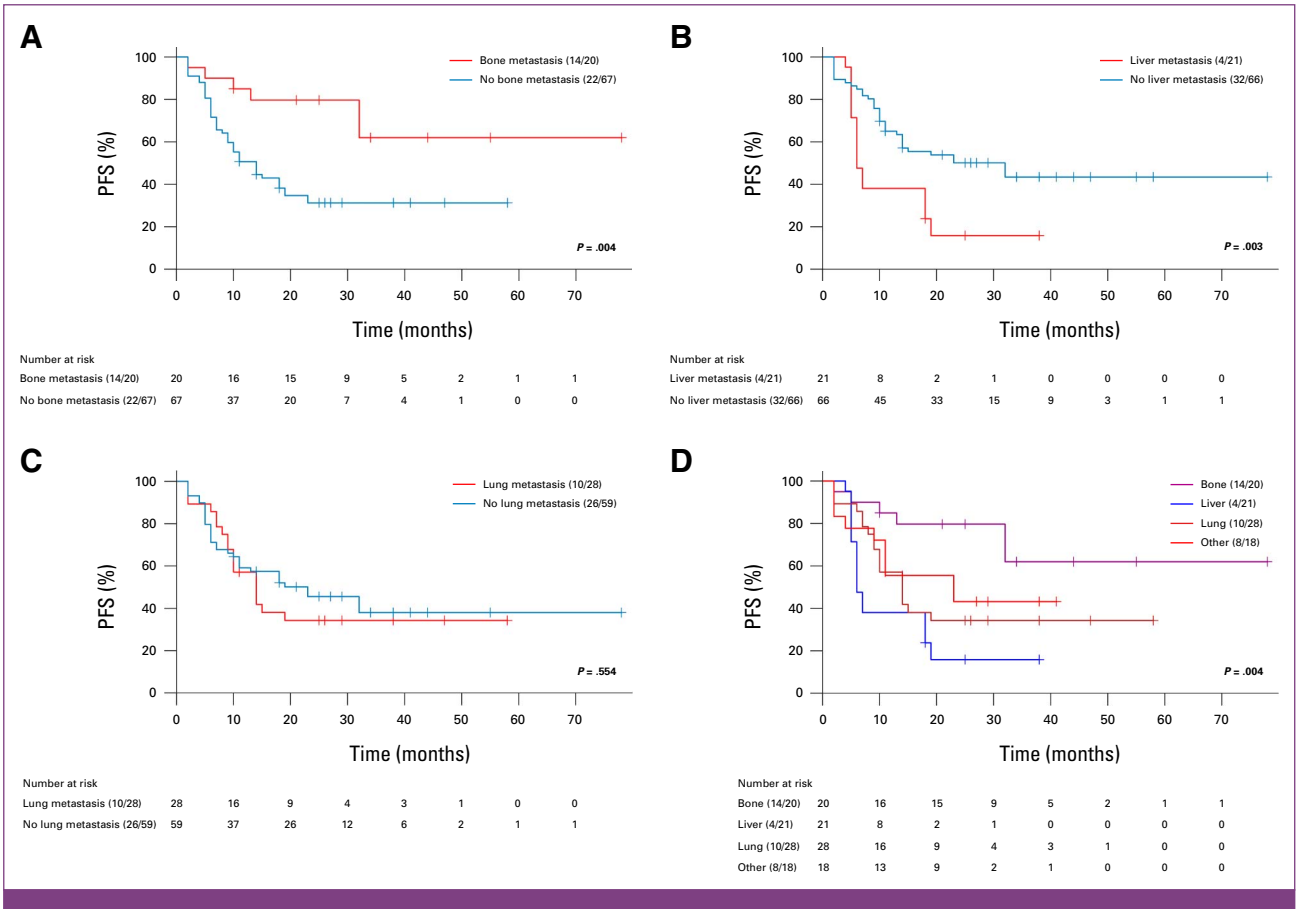

FIG 7. Kaplan-Meier PFS curves. Pairwise comparison in the patient cohort with single metastatic site between metastases and non-metastases in (A) bone cancer, (B) liver cancer, and (C) lung cancer. (D) Kaplan-Meier PFS curves of all metastatic sites. PFS, progression-free survival.

PFS, whereas the metastatic site may influence patient outcomes in some cases. Proper selection of patients with oligometastatic disease may influence treatment decisions, and their survival chances could be improved. Randomized studies to compare SABR and palliative standard of care are mandatory.

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DATA SHARING STATEMENT

Available upon request.

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Data analysis and interpretation: Nidal Salim, Alexey Popodko
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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I = Immediate Family Member, Inst = My Institution. Relationships may

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

No potential conflicts of interest were reported.

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