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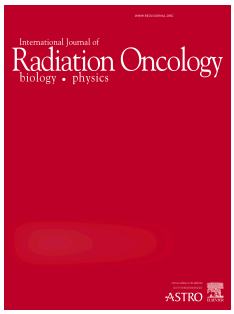

Definitive Management of Presumed Synchronous Early-Stage Non-Small Cell Lung Cancers: Outcomes and Utility of Stereotactic Ablative Radiotherapy

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PII: S0360-3016(20)30162-0

DOI: https://doi.org/10.1016/j.ijrobp.2020.02.001

Reference: ROB 26179

To appear in: *International Journal of Radiation Oncology • Biology • Physics*

Received Date: 2 October 2019

Revised Date: 30 January 2020

Accepted Date: 2 February 2020

Please cite this article as: Ayoub Z, Ning MS, Brooks ED, Kang J, Welsh JW, Chen A, Gandhi S, Heymach JV, Vaporciyan AA, Chang JY, Definitive Management of Presumed Synchronous Early-Stage Non-Small Cell Lung Cancers: Outcomes and Utility of Stereotactic Ablative Radiotherapy, *International Journal of Radiation Oncology • Biology • Physics* (2020), doi: https://doi.org/10.1016/j.ijrobp.2020.02.001.

Definitive Management of Presumed Synchronous Early-Stage Non-Small Cell Lung Cancers: Outcomes and Utility of Stereotactic Ablative Radiotherapy

Short Running Title: SABR in Synchronous Early-Stage NSCLC

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Conflict of Interest: The authors report no proprietary or commercial conflicts of interest with respect to any product mentioned or concept discussed in this article. Outside of the present submitted work, Dr. James Welsh reports research support from GlaxoSmithKline, Bristol Meyers Squibb, Merck, Nanobiotix, Mavu Pharma and Checkmate Pharmaceuticals. Dr. Welsh serves on the scientific advisory board for RefleXion Medical, MolecularMatch, OncoResponse, CheckMate, Mavu Pharmaceuticals, Alpine Immune Sciences. He is co-founder of Helios Oncology, MolecularMatch, and OncoResponse and serves as an advisor to Astra Zeneca, Merck, MolecularMatch, Incyte, Aileron and Nanobiotix. Dr. Welsh has the following patents: MP470 (amuvatinib), MRX34 regulation of PDL1, XRT technique to overcome immune resistance. MD Anderson Cancer Center has a trademark for RadScopal^{TM}. Dr. John Heymach reports royalties and licensing fees from Spectrum Pharmaceuticals and Biotree; research support from AstraZeneca, Bayer, GlaxoSmithKline and Spectrum Pharmaceuticals; and advisory Committee membership from AstraZeneca, Boehringer-Ingelheim, Exelixis, Genentech, GlaxoSmithKline, Guardant Health, Hengrui Therapeutics, Eli Lilly, Novartis, Spectrum Pharmaceuticals, EMD Serono and Synta Pharmaceuticals. Dr. Chang reports grants from BMS as well as personal fees from AstraZenaca and Varian, and is a shareholder in Global Oncology One, all outside of the submitted work.

Funding: This work was supported by the National Institutes of Health [grant number CA016672] and the Joan and Herb Kelleher Charitable Foundation. Dr. Kang's stipend was partly supported by the China Scholarship Council.

Data Sharing: Research data are not available at this time.

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ABSTRACT

Purpose: Management of synchronous early-stage non-small cell lung cancer (NSCLC) remains controversial, as resection is not always feasible. This study evaluates efficacy and patterns of failure following stereotactic ablative radiotherapy (SABR) for synchronous early-stage NSCLC.

Methods and Materials: From 2005-2015, patients presenting with ≥2 synchronous NSCLC tumors (T1a-T2b) and receiving SABR to ≥1 lesion were reviewed. The most common prescriptions were 50-Gy in 4 or 70-Gy in 10-fractions. Patients underwent multidisciplinary management with work-up including CT-Chest and PET/CT, plus brain imaging and EBUS for most patients to rule-out mediastinal and distant disease. Synchronous lesions were defined as multiple ipsilateral or contralateral intrapulmonary lesions diagnosed within 6 months.

Results: Of 912 patients treated with SABR for early-stage NSCLC at our institution, 82 (9%) presented with synchronous disease, with a total of 169 lesions. SABR was delivered to 142 lesions (84%), with 57 patients (69.5%) receiving SABR for all sites. Median overall survival (OS) and progression-free survival (PFS) was 5.1 and 2.7 years. At a median follow-up of 58 months, OS was 67% and 52% at 3- and 5-years; and corresponding PFS was 47% and 29%. Thirty-nine patients (48%) had progression, with 21 (26%) experiencing distant failure, while intra-lobar recurrence was among the first failure for 15 patients (18%). Of the 142 SABR-treated sites, these included 6 in-field (4%) and 4 marginal (3%) recurrences. There were no Grade≥3 adverse events. Among patients receiving SABR for all sites, there were no differences in OS (p=.946), PFS (p=.980), local control (p=.683), regional and distant control (p=.656), or toxicity

(p=.791). On multivariable analysis, ipsilateral synchronous disease was associated with greater regional and distant failure (HR 2.691; p=0.025).

Conclusion: Synchronous NSCLC can be managed with definitive local therapy. With high control rates and favorable outcomes, SABR is an effective and feasible treatment for synchronous early-stage NSCLC.

INTRODUCTION

Stereotactic ablative radiotherapy (SABR), also known as stereotactic body radiation therapy (SBRT), has gained worldwide acceptance as the standard treatment for medically non-operable patients with early stage non-small cell lung cancer (NSCLC) [1, 2]. Up to 10% of patients with NSCLC may develop multiple lung lesions [3]; however, it is often difficult to determine if these lesions represent distinct primary cancers or intrapulmonary metastases, which in turn impacts their treatment approach. Multiple primary lung cancers (MPLCs) have historically been treated with surgery when feasible [4-7]; however, a significant proportion of patients presenting with multiple lung primaries are not ideal surgical candidates due to limited cardiopulmonary reserve, the need for extensive functional lung resections (e.g. multiple lobectomies), or the presence of comorbidities [8].

Emerging data suggest that SABR is a safe and effective local treatment alternative to surgery, but the majority of studies examining MPLC have included both synchronous MPLC and metachronous MPLC (diagnosed more than 6 months apart) [9-15]. Therefore, larger studies are warranted which specifically evaluate patients with synchronous lung primaries treated with SABR. To address this knowledge gap, we retrospectively analyzed the characteristics and clinical outcomes of patients with synchronous lung lesions treated with SABR at our institution. We aimed to report the different management strategies, determine predictors of outcomes, and assess patterns of treatment failure for this patient population.

METHODS AND MATERIALS

Subjects

Records of patients who presented with synchronous early-stage NSCLC between 2005 and 2015 and received SABR at the Radiation Oncology Department at our institution were reviewed. This is a retrospective cohort study of a prospectively-registered patient database, approved by our institutional review board (IRB).

Selection Criteria

Patients were eligible if they had a *de novo* diagnosis of NSCLC, presenting with at least 2 synchronous intrapulmonary lung lesions, stage T1a-T2b N0 M0 each, of which both or at least one was biopsied and proven to be invasive NSCLC. The first biopsy-proven lesion was denoted the "index" tumor. We used criteria modified from Martini and Melamed to define synchronous lung tumors [16]. A synchronous lung tumor was defined as a separate lung mass arising from the same lobe, a different ipsilateral lobe, or the contralateral lung, and diagnosed within 6 months of the primary lung cancer diagnosis. We also included patients with a synchronous lesion diagnosed more than 6 months after the initial diagnosis, if in retrospect the second lesion had been present on imaging at the time of diagnosis of the index lesion. This 6-month interval represents a realistic and generalizable timeframe to account for delays in confirmation of synchronous lesions (despite their simultaneous presentation), either due to an interval period between biopsies of separate lesions or the need for serial imaging to detect interval growth.

Patients had to be treated with SABR to at least one of the synchronous intrapulmonary

lesions. Patients with suspicious hilar, mediastinal or metastatic disease at diagnosis, and patients who developed a biopsy-proven hilar or mediastinal lymph node recurrence on follow-up (if present in retrospect on the initial diagnostic images) were excluded. We also excluded patients with clinically lymph node negative disease at diagnosis who underwent SABR to one lesion and surgery with mediastinal lymph node dissection or sampling to another lesion detecting hilar and/or mediastinal disease on pathology. Patients with small cell lung cancer were also excluded.

Evaluations and Interventions

Diagnostic work-up included a computed tomography (CT) scan of the chest and a positron emission tomography/computerized tomography (PET/CT) scan. Staging was done according to the seventh edition of the American Joint Committee on Cancer TNM staging system. Initial work-up for the majority of patients also entailed contrast-enhanced brain imaging and mediastinal evaluation via endoscopic bronchial ultrasound (EBUS), driven by multidisciplinary case review and clinical suspicion for high-risk factors (e.g. central tumors, larger lesions, suspicious nodes on imaging, ipsilateral synchronous lesions) in this historical cohort; although our current institutional practice now consistently includes these tests for all such cases, as recommended by current NCCN guidelines for the setting of multiple pulmonary lesions suspicious for lung cancer.

At least one of the synchronous intrapulmonary lesions for each patient was treated using SABR, which delivers a biologically effective dose, assuming $\alpha/\beta=10$ (BED_{10}), of >100 Gy to the tumor via hypo-fractionation (≤10 fractions). Other treatments included fractionated RT (>10 fractions), surgical resection of the lesion,

systemic therapy, radiofrequency ablation, and observation. Fractionated RT prescriptions ranged from 45-87.5 Gy in 15-37 daily fractions (median BED_{10} = 80.5 Gy). Details of SABR planning and treatment delivery have been previously described [11]. For multiple treated lesions, a single isocenter technique was used if inter-lesion distance was within a few centimeters, at discretion of the physician and physicist, whereas multiple isocenters were commonly employed for most patients. An internal gross tumor volume (iGTV) was created, based on the maximum intensity projection (MIP) image from the 4D-CT scan, accounting for motion throughout the entire respiratory cycle. The planning target volume (PTV) was then created by adding a 5 millimeter uniform expansion margin to the iGTV.

Most lesions were treated to a total dose of 50 Gy in 4 fractions (BED_{10} = 112.5 Gy) or 70 Gy in 10 fractions (BED_{10} = 119 Gy), or less commonly 63 Gy in 9 fractions (BED_{10} = 107 Gy). Treatment plans were typically normalized to 80% (range: 60-90%) of the maximum dose for heterogeneity, with iGTV optimized to 10-30% higher than prescription isodose and fall-off to <50% of prescription isodose at 2-cm beyond the PTV. For each fraction, patient set-up was performed using daily kV-IGRT to bone, then by cone-beam CT to soft tissue and tumor, followed by a final MV port film immediately before treatment initiation to ensure match with digitally reconstructed radiographs as a final real-time quality assurance practice.

Outcome Measures

Follow-up consisted of physical examination and CT scan of the chest every 3 months for the first 2 years, then every 6 months for 3 years, then yearly thereafter. Any suspicious finding on CT scan was further evaluated with a PET/CT scan; and when

lesions were suspicious or equivocal for recurrence, a biopsy was performed for confirmation when feasible. All cases with suspected disease recurrence were discussed in a multidisciplinary tumor board where a consensus was reached regarding the optimal management.

Overall survival (OS) and progression-free survival (PFS) times were calculated from the date of diagnosis, defined as the date of biopsy of the index lesion. Local recurrence (LR) was defined as the progression of a treated lung lesion or the appearance of a new lung lesion within the same lobe that then corresponded to areas avid on PET or positive biopsy findings. Regional recurrence (RR) was defined as the development of hilar and/or mediastinal LN disease. Recurrence in previously uninvolved lobes or outside the thorax was defined as distant failure. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

Statistical Methods

Statistical analyses were performed using SPSS 23.0 (SPSS inc., Chicago, IL, USA). Actuarial rates of survival and progression outcomes were calculated using Kaplan-Meier method and compared using the log-rank test. For OS, patients were censored at last follow-up; and for PFS, death and disease progression were scored as events. For local control, only LR was scored as an event, with patients otherwise censored at last follow-up or death. Likewise, for combined regional and distant control, only RR and distant progression were scored as events, with patients otherwise censored at last follow-up or death. Associations with outcomes were analyzed using Cox proportional hazards modeling, while associations with toxicities were analyzed via logistic

regression. Patient demographic and clinical characteristics were compared among groups by use of the Mann–Whitney U test for continuous variables and $\chi 2$ test for categorical variables. For all analyses, a p-value <0.05 was considered statistically significant.

RESULTS

Patient and Tumor Characteristics

A total of 912 patients were treated with SABR for NSCLC between 2005 and 2015, of whom 82 patients presented with synchronous lung disease, with a total of 169 lesions. This represents 9% of patients receiving SABR as part of their initial treatment strategy for NSCLC at our institution. The patient and tumor baseline characteristics are summarized in **Table 1**.

Of the patients with synchronous lung tumors, the median age at diagnosis was 70 years, 34 patients (41.5%) were males, and the median Eastern Cooperative Oncology Group performance status (ECOG PS) score was 1. The median forced expiratory volume in 1 second (FEV1), diffusing capacity of the lungs for carbon monoxide (DLCO), and body mass index (BMI) were 63%, 59% and 26.1 kg/m^2, respectively. A total of 36 patients (43.9%) were current smokers, and 42 patients (51.2%) were former smokers, with a combined median pack-year history of 50 (IQR 34-64 years). Regarding tumor characteristics, the median diameter of the index lesion was 2.1 cm (IQR 1.6-3 cm), and the median diameter of the second lesion was 1.5 cm (IQR 1.1-2.2 cm). The most common pathology was adenocarcinoma (representing 55% and 54% of index and biopsied second lesions, respectively), followed by

squamous cell carcinoma (comprising 32.9% and 32.8% of index and biopsied second lesions, respectively).

While all patients had a biopsy of their index lesion (which marked the date of diagnosis), 61 (74.4%) had a biopsy of their second lesions as well. The median time between biopsies of synchronous lesions was 36 days (IQR 18-58 days). Of those, 39 patients (64%) had the same pathology findings among their synchronous tumors. A minority of patients (25.6%) did not undergo sequential biopsy of their synchronous lesion due to precarious location or significant medical comorbidities. In these cases, diagnosis was established through multidisciplinary discussion between the treating physician and a board-certified diagnostic radiologist, incorporating axial imaging findings such as suspicious appearance, serial enlargement on CT scans, and/or FDG-avidity on PET/CT. With regard to presentation patterns, 21 patients (25.6%) presented with ipsilateral synchronous tumors, and 6 patients (7.3%) had lesions within the same lobe. Three patients (3.7%) had more than 2 synchronous lesions. Work-up included evaluation of the mediastinum via EBUS in 44 patients (54%) and contrast-enhanced imaging of the brain in 73 patients (89%).

Treatment Overview

Table 2 shows the local management patterns of all synchronous tumors. Of the 169 synchronous tumors, treatment entailed RT for 149 (SABR for 142), surgery for 17, and observation for 3 lesions. Sixteen patients (19.5%) underwent surgery, with 1 patient undergoing resection for 2 sites; and 13 received mediastinal lymph node dissections (following initial EBUS) without evidence of regional disease. Sixty-four patients (78%) received RT for all sites, including 57 (69.5%) treated with SABR to all tumors. The

most commonly used fractionation regimens for SABR in peripheral and central lesions were 50 Gy in 4 fractions and 70 Gy in 10 fractions, with a median PTV mean dose of 56.2 Gy (IQR 54.9-58.6 Gy) and 74 Gy (IQR 68.7-77.1 Gy), respectively. For patients receiving SABR to both their index and second sites, the median time interval between these courses was 0 days (IQR: 0-14), with 42% treated to both sites simultaneously.

Eighteen patients (22%) received chemotherapy as part of their initial management: 15 in the neoadjuvant setting and 3 in the adjuvant setting. These patients had clinical factors similar to the overarching study population: median diameter of 2.4-cm and 1.6-cm for index and second lesions, respectively; half (50%) with adenocarcinoma histology of the index lesion; and only 4 (22%) had multiple synchronous lesions in the same lung. None of these factors differed significantly among patients who did and did not receive chemotherapy (P >.143 for all). In addition, none of these patients had >2 synchronous lesions, and none had tumors within the same lobe.

Disease and Survival Outcomes

At a median follow-up time of 58 months, the median PFS and OS for the entire cohort were 32 months (95% CI: 19.5-44.5) and 61 months (95% CI: 38.7-83.3), respectively. The estimated 1-, 3-, and 5-year PFS rates were 85.4%, 47.3%, and 28.5%, respectively; the corresponding OS rates were 95.1%, 66.9%, and 52.4%, respectively (**Figure 1**). Patterns of failure and treatment following recurrence are shown in **Table 3**. Among all 82 patients, 39 patients (48%) had disease progression, with 18 patients (22%) developing locoregional recurrence as the first site of failure and 21 patients (26%) developing distant progression (**Table 3**).

There were 15 local recurrences out of all 169 treated sites (9%): 6 were in-field following SBRT and 5 were marginal recurrences, at the edge (but outside) of the high-dose SBRT region (n=4) or at the edge of resection (n=1), while the remaining 4 were intra-lobar recurrences elsewhere, out of proximity. The 1-, 3-, and 5-year actuarial local control rates by patient (n=82) were 97.5%, 82.8%, and 75.6%, respectively; and the corresponding combined regional and distant control rates were 91.4%, 72.0%, and 64.0%.

Looking specifically at the sub-group of 57 patients who received SABR to all sites of disease, outcomes remained favorable. The median PFS and OS were 35 months (95% CI: 19.0-51.0) and 61 months (95% CI: 36.5-85.5), respectively, for this particular population. The 1-, 3-, and 5-year PFS rates were 89.5%, 47.0%, and 28.7%, respectively; and the corresponding OS rates were 94.7%, 68.2%, and 51.0%, respectively. There were no significant differences with respect to OS (p=.946), PFS (p=.980), local control (p=.683), or combined regional and distant control (p=.656) among these 57 patients versus the 25 with mixed treatment.

The 3 patients with >2 synchronous lesions (total 11 sites) survived 15-75 months, with 1 progressing locally at 75 months, and 1 progressing distantly at 6 months. Outcomes remained similar when these 3 patients were excluded, with median PFS and OS of 32 months (95% CI: 19.8-44.2) and 61 months (95% CI: 51.0-83.0). For these 79 patients (with 158 synchronous lesions), the estimated 1-, 3-, and 5-year PFS rates were 86.1%, 46.6%, and 30%, respectively; while the corresponding OS rates were 94.9%, 66.9%, and 50.3%.

Factors Associated with Outcomes

On univariate analysis, factors associated with improved PFS were: adenocarcinoma histology of the index lesion (HR 0.388; p-value=0.001), higher FEV1 (HR 0.457; p=0.018), and a >30-day interval between biopsies of synchronous lesions (HR 0.414; p-value=0.006). Factors associated with worse PFS were: ECOG PS score >1 (HR 2.154; p-value=0.006), and having all synchronous lesions within the ipsilateral lung (HR 2.551; p-value=0.001). On multivariable analysis, the index lesion pathology (HR 0.488; p-value=0.014) remained significant for PFS (**Supplemental Table A**).

On univariate analysis for OS, factors associated with improved survival were again: adenocarcinoma histology of the index lesion (HR 0.310; p-value<0.001), and a >30 day interval between biopsies of synchronous lesions (HR 0.488; p-value 0.042). Factors associated with worse OS were: ECOG PS >1 (HR 3.055; p-value <0.001), and having all synchronous lesions within the same lung (HR 2.365; 95% CI 1.277-4.380; p-value 0.006). On multivariable analysis, only ECOG PS (HR 2.301; p-value=0.010) and adenocarcinoma histology (HR 0.404; p=0.006) maintained significance (**Supplemental Table B**).

With respect to local control, adenocarcinoma histology of the index lesion was associated with decreased local failure (HR 0.087; p=0.001), while size of the second lesion was associated with increased local failure (HR 18.264; p<0.001) on multivariable analysis (**Supplemental Table C**). When evaluating combined regional and distant control, univariate analysis determined smoking history (HR 3.130; p=0.011) and ipsilateral tumor location (HR 2.664; p=0.016) to be significantly associated with combined regional and distant failures, while longer inter-biopsy interval (HR 0.345; p=0.020) portended a decreased combined regional and distant failure rate. On

multivariable analysis, both smoking history (HR 3.217; p=0.011) and ipsilateral location of synchronous tumors (HR 2.691; p=0.025) remained associated with higher combined regional and distant failure rates (**Supplemental Table D**).

Notably, no associations were found between the use of chemotherapy as part of initial management and survival outcomes. Similarly, no difference in outcomes was observed whether all lesions were treated with SABR, as compared to mixed management with SABR and other modalities. Surgical resection (of ≥1 sites) was also not associated with improvements in disease-related or survival endpoints.

Toxicities

Finally, we evaluated the incidence of acute and late toxicities, including radiation pneumonitis, chest wall pain, skin toxicities, esophagitis, brachial plexopathy, and lung collapse. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events [version 3.0]. No patients experienced Grade ≥3 treatment-related adverse events. Fifteen patients (18%) experienced any Grade 2 toxicity. Specifically, there were 12 acute Grade 2 toxicities among 11 patients (13%): pneumonitis (n=7), dermatitis (n=3), chest wall pain (n=1), and pleural effusion (n=1). There were also 9 Grade 2 late toxicities among 8 patients (10%): fibrosis (n=5), chest wall pain (n=2), rib fracture (n=1), and pleural effusion (n=1).

The incidence of any Grade 2 toxicity was not increased among patients undergoing surgical resection (OR 1.04, p=.958), receiving chemotherapy (OR .25, p=.192), or with ipsilateral synchronous disease (OR 2.42, p=.335); nor was Grade 2 toxicity increased among the 57 patients treated with SABR to all sites, versus the 25

patients with mixed management (OR .85, p=.791). Interestingly, for patients receiving SABR to index and second lesions, Grade 2 toxicity was actually lower among those treated to both sites simultaneously, versus sequentially (OR .10, p=.006).

DISCUSSION

The management of synchronous early-stage NSCLC lesions remains controversial, and it is often unclear whether multiple lesions represent distinct NSCLC primary tumors as opposed to advanced-stage disease. Surgical resection is often recommended for patients with multiple lung primaries when feasible [5-7, 17]. Yet to date, the literature on the optimal treatment of synchronous lung lesions has been scarce, with many of the available studies combining synchronous with metachronous lesions under the MPLC spectrum [5-7,9,11,15].

The available literature suggests that metachronous tumors may yield better outcomes as compared to synchronous lesions. An earlier analysis of MPLC included 39 patients with synchronous and 62 with metachronous tumors and found that the latter had better OS and PFS [12]. Creach et al reported similar findings, demonstrating poor OS in patients with synchronous disease, suggesting that many of these patients likely represent early metastatic disease and thus require systemic therapy [18]. On the other hand, a surgical series by Rosengart et al. found no significant difference in outcomes between patients with synchronous and metachronous lung cancers, although some patients in the metachronous group had stage IV disease at the time of diagnosis [5]. However, these studies included relatively small patient numbers, limiting the generalizability of their findings.

To the best of our knowledge, the present study represents the largest cohort composed specifically of patients with synchronous NSCLC. Here we demonstrate that offering local treatment to synchronous NSCLC lesions (with SABR to one or more lesions) can yield durable outcomes, with a median PFS over 2.5 years and a median OS over 5 years, alongside low rates of LR by site (<10% for all 169 sites). These favorable results persist even among the 69.5% of our study cohort receiving SABR to all synchronous sites, and survival outcomes are comparable to those series of single lung lesions treated with SABR [2, 19-22]. Of patients who did progress, the majority recurred distantly, consistent with published data on patterns of failure after SABR for early-stage NSCLC [2, 23, 24].

Taken together, these data indicate that synchronous NSCLC lesions can be approached as separate primaries and thus managed with definitive local therapy for curative intent. Among patients receiving SABR as part of their initial treatment for NSCLC at our institution, 9% presented with synchronous lung tumors. While it is unclear whether this rate can be generalized to all newly diagnosed lung cancer patients, this figure may actually represent an underestimate of true prevalence, since we did not capture patients treated with surgery alone for all synchronous sites. It is worthy to note that patients in the current study underwent thorough assessment of mediastinal lymph nodes and distant metastases using contrast-enhanced Chest CT and PET/CT scans for every patient, as well as brain imaging in nearly all cases. The majority also received EBUS for pathologic mediastinal staging. Evaluation of mediastinal and distant metastasis status is necessary prior to labeling patients as having synchronous disease and managing them as such; invasive staging methods

may be warranted for certain scenarios [25], such as central tumors, larger lesions, suspicious nodes on imaging, or even ipsilateral synchronous lesions [11].

Furthermore, our data demonstrate low toxicity with this treatment approach, suggesting that SABR is both a safe and effective treatment for synchronous early lung malignancies. While surgery remains the standard of care in treating medically operable patients with early-stage NSCLC [26, 27], caution should be taken in the setting of multiple synchronous lung tumors, particularly when considering the potential for increased surgical morbidity and increased costs of multiple lung resections [28, 29]. SABR thus offers a safe and feasible alternative to simultaneously address two or more synchronous lesions within a condensed timeframe.

Finally, while the addition of systemic therapy in Stage Ib and above NSCLC has been considered to improve survival outcomes [30], our data did not reflect an impact on survival outcomes with the addition of chemotherapy, whether in the neoadjuvant or adjuvant setting. These findings perhaps further support the notion that synchronous tumors behave more as distinct simultaneous primaries rather than advanced metastatic disease. However, while tumor size has been established as a significant independent predictor of distant failure [31-34], it should be noted that our institution historically followed a uniform approach regarding lesion size, whereby the majority of lung lesions treated with SABR were ≤3 cm; thus only 25% of the patients in our cohort had a tumor size >3 cm (although our institution has expanded this cut-off in recent years). Therefore, our findings are merely consistent with the data showing the lack of a role for systemic therapy in early-stage, low-risk NSCLC lesions <4 cm in size [27, 35, 36].

Notably, our analysis identified ipsilateral location of synchronous tumors (within the same lung) to be associated with higher combined regional and distant failure rates. These patients could represent a higher-risk group (e.g. intrapulmonary metastases) who may potentially benefit from systemic therapy, in contrast to those patients presenting with contralateral tumors (in different lungs). Regarding other clinical associations with outcomes, adenocarcinoma histology was associated with improved PFS on multivariable analysis, as consistent with previous reports [37].

The primary limitation of this investigation is its single-institution retrospective nature with inherent biases in patient selection (e.g. surgical candidacy), intermittent follow-up off prospective protocol, and the use of multiple comparisons to evaluate for associations with clinical factors, all of which may affect interpretation of outcomes; although these concerns represent unavoidable limitations shared by the vast majority of retrospective series evaluating SABR for NSCLC. Furthermore, while the Martini and Melamed method is commonly used [16], this definition for synchronous disease is admittedly dated and fails to incorporate emerging radiographic and histopathologic work-up standards that can help differentiate among different subtypes of patients with multiple pulmonary sites of lung cancer. Indeed, as these patients were diagnosed prior to the era of routine testing and targeted treatment of mutations, our study lacks molecular characterizations of lesions and other tools that can help confirm if such lesions truly represent separate synchronous early-stage primaries. Liquid biopsy and next-generation sequencing, for example, can help distinguish between separate early-stage primaries versus multifocal/metastatic disease. As compared to standard histopathologic approach alone, comprehensive NGS in particular can permit the

unambiguous delineation of clonal relationships among separate lesions, and may contribute towards the robust identification of separate synchronous early-stage lesions in future clinical practice [38].

However, despite these limitations and in the absence of prospective data, our study represents the largest series of patients presenting with synchronous NSCLC, demonstrating excellent and durable outcomes following curative treatment. Accordingly, SABR is an effective and safe local treatment option for this patient population and should be considered in the definitive management of patients presenting with synchronous NSCLC.

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FIGURE LEGENDS

Figure 1. Overall and progression-free survival outcomes following definitive management of synchronous early-stage non-small cell lung primaries (n=82).

TABLES

Table 1. Patient and tumor characteristics (n=82)

Table 2. Local management of all synchronous lesions (n=169).

Table 3. Patterns of failure and salvage management of recurrences among all patients (n=82)

SUPPLEMENTARY TABLES

Supplemental Tables. Univariate and multivariable analysis of patient and tumor characteristics and their associations with **(A)** PFS; **(B)** OS; **(C)** Local Failures; and **(D)** Combined Regional and Distant Progression

Table 1. Patient and tumor characteristics (n=82)

Characteristics	N *(%)*
Age (*years*)	
Median (*IQR*)	70 (*67-77*)
Gender	
Males	34 (*41*)
Females	48 (*59*)
ECOG performance status	
0	7 (*8.5*)
1	50 (*61*)
2	22 (*26.8*)
3	3 (*3.7*)
Smoking Status	
Never	4 (*5*)
Current	36 (*44*)
Former	42 (*51*)
FEV1 *(%)*	
Median (*IQR*)	63 (*41-83*)
DLCO *(%)*	
Median (*IQR*)	59 (*43-74*)
Body Mass Index	
Median (*IQR*)	26.1 (*22.8-30.0*)
Total number of lesions	
2	79 (*96.3*)
3	1 (*1.2*)
4	2 (*2.5*)
Lesion Size (*cm*)	
Index lesion – Median (*IQR*)	2.1 (*1.6-3*)
Second lesion – Median (*IQR*)	1.5 (*1.1-2.2*)

Stage	
Index lesion	
T1a-b	63 (*77*)
T2a-b	19 (*23*)
Second lesion	
T1a-b	77 (*94*)
T2a-b	5 (*6*)
PET SUV	
Index lesion – Median (*IQR*)	7.1 (*3.7-11.3*)
Second lesion – Median (*IQR*)	5.0 (*1.9-8.6*)
Location	
Index lesion	
Central	9 (*11*)
Peripheral	73 (*89*)
Second lesion	
Central	5 (*6*)
Peripheral	77 (*94*)
Pathology	
Index lesion	
Adenocarcinoma	45 (*55*)
Squamous cell carcinoma	27 (*33*)
Other	10 (*12*)
Second lesion	
Adenocarcinoma	33 (40)
Squamous cell carcinoma	20 (*24*)
Other	8 (*10*)
Unknown (no biopsy)	21 (*26*)

Relative location of lesions	
All lesions within the same lung	
Yes	21 (*26*)
No	61 (*74*)
All lesions within the same lobe	
Yes	6 (*7*)
No	76 (*93*)
Mediastinal evaluation	
Yes	44 (54)
No	38 (46)
Contrast-enhanced brain imaging	
Yes	73 (89)
No	9 (11)
Chemotherapy as part of the initial management	
None	64 (78)
Neoadjuvant	15 (18)
Adjuvant	3 (4)

Abbreviations: N, number of patients; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; FEV1, forced expiratory volume-one second; DLCO, diffusing capacity of lung for carbon monoxide; cm, centimeters; PET SUV, positron emission tomography standardized uptake value

Table 2. Local management of all synchronous lesions (n=169).

Treatment	Number of Pts (Index lesion)	Number of Pts (Second lesion)	Number of Pts (Third lesion)	Number of Pts (Fourth lesion)
Observation	**0**	**1**	**1**	**1**
Surgery	**8**	**7**	**1**	**1**
Wedge resection	1	3	0	1
Segmentectomy	1	1	0	0
Lobectomy	6	3	1	0
Radiation Therapy	**74**	**74**	**1**	**0**
SABR 50 Gy/4 fxs	51	60	1	0
SABR 70 Gy/10 fxs	16	13	0	0
SABR 63 Gy/9 fxs	0	1	0	0
Fractionated RT*	7	0	0	0

Abbreviations: SABR, stereotactic ablative radiotherapy; Gy, gray; fxs, fractions; RT, radiotherapy

*Fractionated RT prescriptions ranged from 45-87.5 Gy in 15-37 daily fractions (median BED_{10} = 80.5 Gy).

Table 3. Patterns of failure and salvage management of recurrences among all patients (n=82)

Type of first recurrence	N *(%)*	Management of recurrence (*N*)
Local intralobar recurrence	15 (*18*)	Chemotherapy (*5*), RFA (*3*), radiation therapy (*3*), surgical resection (*2*), and observation (*2*)
Isolated local recurrence	13 (*16*)	
Combined local and regional	2 (*2*)	
Isolated regional recurrence	3 (*4*)	Concurrent chemoradiation
Distant failure	21 (*26*)	Systemic Therapy, Hospice, Palliative Care (including RT), Consolidative RT
Non-locoregional intrathoracic	10 (12)	
Extra-thoracic recurrence	11 (13)	

Abbreviations: RFA, radiofrequency ablation

Figure 1. Progression-free survival (A) and Overall survival (B).