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*REVIEW*

# Management of oligometastatic non-small cell lung cancer patients: Current controversies and future directions

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## Abstract

Oligometastatic non-small cell lung cancer (NSCLC) describes an intermediate stage of NSCLC between localized and widely-disseminated disease. This stage of NSCLC is characterized by a limited number of metastases and a more indolent tumor biology. Currently, the management of oligometastatic NSCLC involves radical treatment (radiotherapy or surgery) that targets the metastatic lesions and the primary tumor to achieve disease control. This approach offers the potential to achieve prolonged survival in patients who, in the past, would have only received palliative measures. The optimal therapeutic strategies for the

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different scenarios of oligometastatic disease (intracranial *vs* extracranial disease, synchronous *vs* metachronous) remain undefined. Given the lack of head-to-head studies comparing radiotherapy to surgery in these patients, the decision to apply surgery or radiotherapy (with or without systemic treatment) must be based on prognostic factors that allow us to classify patients. This classification will allow us to select the most appropriate therapeutic strategy on an individualized basis. In the future, the molecular or microRNA profiles will likely improve the treatment selection process. The objective of the present article is to review the most relevant scientific evidence on the management of patients with oligometastatic NSCLC, focusing on the role of radiotherapy and surgery. We also discuss areas of controversy and future directions.

**Key words:** Non-small cell lung cancer; Metastasectomy; Oligometastases; Stereotactic ablative radiotherapy; Stereotactic body radiation therapy; Radiosurgery



**Core tip:** In recent years, numerous studies, including two randomized phase II trials, have demonstrated that local treatment, either radiotherapy or surgery, of the primary tumor and metastases improves progression-free survival and overall survival in patients who present with oligometastatic non-small cell lung cancer at diagnosis and in those who respond to the initial systemic therapy. As we await the results of ongoing randomized phase III trials, the main international clinical guidelines recommend a multimodal strategy to manage this subgroup of oligometastatic patients. Current guidelines recommend systemic therapy combined with local treatment of the metastases and, if applicable, the primary tumor.

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## INTRODUCTION

Lung cancer is the second most common cancer in both men and women and the leading cause of cancer-related death worldwide. Approximately 80% of newly-diagnosed lung cancers in Europe are non-small cell lung cancer (NSCLC), and 60%-70% of these patients have advanced disease at diagnosis[1]. Traditionally, these patients have been managed exclusively with chemotherapy and palliative treatments aimed at relieving symptoms and improving quality of life. Previously, patients with advanced NSCLC were not considered candidates for curative-intent treatment due to their poor prognosis, with a median survival of 8-11 mo and a 5-year overall survival (OS) rate of only 4%-6%[2]. Today, however, the situation has changed significantly. In recent years, advances in diagnostic imaging techniques, including $^{18}$F-FDG-positron-emission tomography (PET)/computed tomography (CT) and brain magnetic resonance imaging (MRI), have substantially increased the tumor detection rate. These advances, together with the emergence of targeted therapies such as anti-epidermal growth factor receptor (EGFR)/anaplastic lymphoma kinase (ALK), have increased survival in patients with metastatic disease, leading to a growing number of patients characterized by a limited number of metastases at only a few sites. This newly-defined patient subgroup represents an intermediate stage of NSCLC between locally-advanced and widely-disseminated disease. Patients with oligometastatic disease have a better long-term prognosis than those with more advanced NSCLC and may benefit from systemic therapy combined with local treatment (mainly radiotherapy and/or surgery) directed at the metastatic lesions[2].

The 8$^{th}$ edition of the Tumor, Node, Metastasis published by the International Association for the Study of Lung Cancer includes, for the first time, oligometastatic disease. These patients are divided into three distinct categories according to their

prognosis: Stage M1a: Involvement of the lung alone; M1b: Single extrathoracic metastasis; and M1c: Multiple extrathoracic metastases in one or more organs[3]. In this context, the aim of this article is to review the most relevant scientific evidence for the management of patients with oligometastatic NSCLC, with a focus on the role of surgery and radiotherapy. We also discuss current controversies and future directions.

## DEFINITION OF THE OLIGOMETASTATIC STATE

The oligometastatic state was first described by Hellman and Weichselbaum[4] in an editorial published in 1995, in which the authors proposed their "step-wise" and "seed and soil" hypotheses. Oligometastasis refers to a clinical stage in which patients present a limited number of metastases to a few sites (a single organ or a few organs). These lesions may be more indolent than those typically observed in patients with multiple metastases, and thus these oligometastatic patients have a better prognosis. The incidence of oligometastatic NSCLC is estimated to range from 20%-50%[5] of patients with NSCLC, depending on the specific definition used to define oligometastatic disease (*i.e.* number of metastases: Three *vs* five and time of presentation: Synchronous *vs* metachronous). The most common metastatic site in NSCLC is the brain (60%), followed by multiorgan metastases to the contralateral lung, lymph nodes, liver (23%), and adrenal glands (10%)[6].

Data from observational studies suggest that the recurrence pattern in up to 60% of patients diagnosed with oligometastatic NSCLC treated with systemic therapy is mainly local, involving the same sites affected at the time of diagnosis[7]. This pattern of progression supports the application of local treatment to target the individual metastases and the primary tumor in order to improve local control and progression-free survival (PFS). Conceivably, an increase in PFS could improve OS by preventing the uncontrolled growth of the oligometastatic lesions, thus reducing or preventing the progressive dysfunction of the involved organ(s). In recent years, numerous studies, mostly retrospective, have evaluated the treatment of oligometastatic NSCLC. Most of those studies found that administering aggressive local treatment to all of the metastatic lesions improved both PFS and OS.

Oligometastatic disease can be subclassified according to the initial diagnosis and the systemic therapy. The term synchronous or *de novo* oligometastases refers to the presence at diagnosis of a limited number of metastases. By contrast, oligo-recurrence refers to the development of new, metachronous metastases after definitive treatment of the locoregional thoracic disease[8]. Two other terms, oligoprogression and oligo-resistance, are used to describe patients with disseminated disease at diagnosis that partially respond to systemic treatment (disease stabilization), except for the development of a limited number of metastases that progress (oligoprogression) or persist (oligo-resistance) after systemic chemotherapy. Oligoprogression and oligo-resistance are common in patients treated with targeted therapies (anti-EGFR/anti-ALK) due to acquired resistance after treatment with tyrosine kinase inhibitors (TKI).

To identify accurately oligometastatic patients, the use of modern imaging techniques, such as PET and brain MRI, is essential to detect the presence of occult metastases that are not visible with conventional imaging techniques. MRI is superior to CT in the detection of brain metastases, often detecting lesions that are not visible on CT. The use of PET/CT imaging is associated with better survival outcomes because metastases detected with PET/CT, which are not visible on standard CT, result in stage migration. Approximately 15% of patients with NSCLC[9,10] who are initially classified as stage I-III by CT will be upstaged to stage IV if PET/CT imaging is performed. These more advanced imaging tests can detect occult metastases in patients initially considered oligometastatic, thus obviating the application of aggressive local therapy in patients unlikely to benefit from treatment. In this regard, Tonnies *et al*[9] sought to determine whether the use of staging PET/CT in patients with NSCLC with a single surgically-resected metastasis had any influence on survival. Those authors compared patients who underwent surgery after preoperative staging with PET/CT ($n$ = 66) *vs* conventional CT ($n$ = 115). Five-year survival in the PET/CT group was 58% *vs* 33% in the conventional CT group ($P$ = 0.01). It is important to note that the vast majority of published reports about oligometastatic NSCLC were conducted prior to the PET/CT era.

## METASTASIS-DIRECTED LOCAL THERAPIES

Surgery has traditionally been the main treatment option in oligometastatic patients,

with approximately 55% of patients undergoing surgical resection[11]. However, the use of less invasive ablative techniques, principally stereotactic radiosurgery (SRS), has increased significantly in recent years. SRS, which was first used to treat brain metastases[5], involves the administration of ablative doses of radiation (delivered in one or more sessions) to the intracranial lesion. SRS is a highly precise technique that minimizes the dose to the surrounding healthy tissues. The application of SRS outside the brain is known as stereotactic ablative radiotherapy (SABR) or stereotactic body radiation therapy (SBRT). No studies have yet directly compared surgery to radiotherapy in oligometastatic disease. Moreover, many of the available studies have included patients who received both surgery and radiotherapy[5]. Although other ablative techniques, including radiofrequency ablation and cryoablation, have been used in oligometastatic patients, their role for this indication is limited and thus not discussed in the present review.

Treatment selection (*i.e*. surgery or radiotherapy) for oligometastatic patients will depend on several variables: Age; performance status; comorbidities; time of appearance of the metastases relative to the primary tumor (metachronous metastases have a better prognosis); number of lesions (prognosis is better in patients with a single metastasis); localization of the metastases (prognosis is better for metastases located in the brain, lung, and adrenal glands); extension of the primary tumor; and mediastinal lymph node involvement (better prognosis in stage N0 disease)[5]. It is important to interpret cautiously the results of the studies that have compared metastasis-directed treatments given the potential for selection bias due to the better prognosis of these patients (good performance status, technically operable, *etc*).

### Surgery

Traditionally, surgical metastasectomy is the most common approach to oligometastatic NSCLC. The indication for surgery depends on various metastasis-related factors (size, number, and location of the metastases) and patient-specific factors (age, performance status, comorbidities, and prognosis). The strongest evidence supporting the benefits of surgical metastasectomy comes from studies involving patients with brain metastases. Patchell *et al*[12] randomized 48 patients (77% with NSCLC) with a single brain metastasis to receive either whole brain radiotherapy (WBRT) or surgical metastasectomy followed by WBRT. The results showed an increase in local control and OS in the surgically-treated group. Nevertheless, few studies have specifically evaluated the surgical resection of extracranial metastases in NSCLC. Of the studies that are available, most are retrospective and heterogenous, including patients treated a range of different radical intent approaches (surgery, SBRT, radiosurgery, or other ablative therapies)[11,13]. A study conducted in Germany[14] examined the role of surgery in NSCLC patients with synchronous, solitary metastatic lesions. At 5 years, OS was 38%; median survival was longer in patients without mediastinal lymph node involvement (50 mo *vs* 19 mo, $P$ = 0.015). OS rates were better in patients with localized lung metastases compared to those with extrathoracic lesions (5-year OS: 48.5% *vs* 23.6%). Johnson *et al*[15] reported a 5-year OS rate of 58% in 22 patients with synchronous oligometastatic NSCLC without mediastinal node involvement who underwent surgery or radiotherapy to the primary tumor and metastases.

### Radiotherapy

Several local ablative treatments, including radiotherapy, can be used to treat oligometastatic NSCLC. Technological advances of the last decade have made it possible to administer high ablative doses with great precision to various sites. Brain metastases are treated with SRS while SBRT is used for extracranial lesions. An important advantage of these high-dose treatments is that they require fewer fractions, and thus the treatment duration is shorter than with conventional fractionation schedules. SRS and SBRT are considered safe, with minimal treatment-related toxicity and only requiring a brief interruption of systemic therapy. In addition, ablative radiotherapy can be administered to all tumor sites throughout the body. Historically, surgical resection was the preferred local therapy for oligometastases in patients with NSCLC[16]. However, in many cases, these metastatic lesions are unresectable, or the patient is considered inoperable, or the long postoperative recovery period may require an unacceptable delay in the initiation of systemic therapy. As a result, less invasive treatments such as radiotherapy are often necessary. A recent survey (published in 2017) of more than 1000 radiation oncologists from 43 countries[17] found that the use of SBRT to treat oligometastatic NSCLC is growing. The most common pattern of recurrence in patients with oligometastatic NSCLC who undergo first-line systemic therapies is local recurrence alone[18]. This pattern of progression supports the application of aggressive local treatments to the primary tumor and the metastatic sites to increase PFS[19] and,

ultimately, OS. SBRT has proven beneficial in patients with a single metastasis as well as in those with multiple metastases[20], with local control rates ranging from 70%-90% and grade (G) ≥ 3 toxicity rates less than 10%[2]. Hasselle *et al*[21] investigated the role of SBRT in 25 patients with oligometastatic NSCLC (1-5 metastases). At a median follow-up of 14 mo, the median PFS and OS rates in that series were 7.6 and 22.7 mo, respectively. Several variables were associated with worse PFS: > two sites treated with SBRT; non-adenocarcinoma histology; prior systemic therapy; and progression after systemic therapy.

## PRINCIPAL STUDIES OF OLIGOMETASTATIC NSCLC

### *Retrospective studies*

One of the most important retrospective studies was carried out by López Guerra *et al*[22]. From January 2000 through June 2011, 78 consecutive patients with oligometastatic NSCLC (< 5 metastases) at diagnosis underwent definitive radiochemotherapy (≥ 45 Gy) to the primary tumor. Most of these patients (61/78; 78.2%) had only a single metastatic lesion, most (42%) located in the brain. The oligometastases were treated with local therapy in 44 patients (56%). The 2-year OS in the full cohort was 32%. Several variables were associated with improved OS: Tumor volume (gross tumor volume ≤ 124 $cm^3$), performance status, administration of ≥ 63 Gy to the primary tumor, and definitive local treatment of the oligometastases. Severe (grade ≥ 3) pulmonary and esophageal toxicity were observed in 6.4% and 19.4% of patients, respectively.

Another important retrospective study of oligometastatic NSCLC was performed by Mordant *et al*[23]. That study included 94 patients with NSCLC who had a solitary, extrathoracic synchronous metastasis. The primary tumor and metastases were treated surgically in all patients (69 of 94 metastases resected). The most common metastatic site was the brain ($n$ = 57), followed by bone ($n$ = 14), adrenal glands ($n$ = 12), liver ($n$ = 5), and skin ($n$ = 5). Mediastinal node status was distributed as follows: N0 ($n$ = 46), N1 ($n$ = 17), and N2 ($n$ = 32). The 5-year OS was 16% (median survival, 13 mo). Induction therapy, adenocarcinoma, N0 staging, and lobectomy were all associated with better prognosis, but surgical metastasectomy was not. These findings raise doubts about the superiority of surgical resection *versus* radiotherapy and/or chemotherapy as the treatment of choice for solitary synchronous M1b metastases.

During the 2006-2016 time period, several small (20 to 60 patients) retrospective studies[21-25] of oligometastatic NSCLC were published. In those studies, both the primary tumor and the metastases received radical treatment (either surgery or radiotherapy). The median survival in those studies ranged from 13-22 mo, and the incidence of grade ≥ 3 toxicity was low.

Merino-Lara *et al*[26] recently reported results of a Canadian study involving 108 patients with metastatic NSCLC treated with extracranial SBRT for oligometastasis ($n$ = 66), oligoprogression ($n$ = 20), and local control of dominant tumors ($n$ = 22). In the full cohort, median OS and PFS were, respectively, 27.3 and 4.4 mo. Patients treated with SBRT for oligometastasis presented longer OS and PFS (39.3 and 7.6 mo, respectively) than those treated for oligoprogression (21.1 and 3.3 mo, respectively) with better local control of dominant tumors (11.8 and 2.2 mo, respectively). The application of SBRT also delayed the time to starting/changing systemic therapy (SCST): Cumulative 1-year incidence = 21.5%. Predictors of time to SCST were: Tumor size ≤ 4 cm (1-year SCST: 11.3% *vs* 36.4% in tumors > 4 cm) and EGFR/ALK mutational status (1-year SCST in EGFR/ALK positive disease: 45.5% *vs* 16% in negative EGFR/ALK). The local failure rate at 1 year was 15.6%. Predictors of local failure at 1 year were tumor size (local failure: 7.7% in tumors ≤ 4 cm *vs* 26.6% in tumors > 4 cm) and treatment with previous systemic therapy (local failure without systemic therapy, 13.2% *vs* 17.7% with previous systemic therapy). Two patients developed grade ≥ 3 toxicity (respiratory events) and three patients developed radiation-induced bone fractures.

The Shanghai Pulmonary Hospital group[27] evaluated 145 patients with stage IV EGFR-mutant NSCLC and ≤ 5 metastases at diagnosis. Of these patients, 35.2% received consolidative local ablative therapy (LAT) to all metastases (all-LAT group), 37.9% received LAT to the primary tumor or to the oligometastases (part-LAT group), and 26.9% did not receive LAT (non-LAT group). All patients received first-line anti-EGFR therapy (TKI). Median OS in the all-LAT, part-LAT, and non-LAT groups was, respectively, 40.9, 34.1, and 30.0 mo ($P$ < 0.001). Median PFS was 20.6, 15.6, and 13.9 mo ($P$ < 0.001), respectively. There was a significant difference in OS between the all-LAT group and the other groups, but no difference between the part-LAT and the non-LAT groups. Adverse effects (grade ≥ 3) included pneumonitis (7.7%) and

esophagitis (16.9%).

Another recent study conducted in Asia[28] evaluated 231 patients with oligometastatic, EGFR-mutant lung adenocarcinoma treated with TKI alone ($n$ = 88) or TKI plus local treatment of the metastases ($n$ = 143). PFS (15 mo *vs* 10 mo) and OS (34 mo *vs* 21 mo) were both significantly better in the local metastasis-directed treatment.

### Clinical trials

Several clinical trials, including two randomized phase II trials, have been conducted to evaluate the efficacy and safety of local ablative therapies (surgery or SBRT) in patients with oligometastatic NSCLC (Table 1).

A phase I/II trial[7] assessed the efficacy and tolerability of SBRT (36 Gy in phase I and 60 Gy in phase II, delivered in 3 fractions) in 47 cancer patients (21.3% with lung cancer) who presented 1-3 liver metastases (63 lesions in total). Most (69%) of the patients had received at least one (range, 0 to 5) previous systemic treatments for metastatic disease, and 45% had extrahepatic disease at study inclusion. Median follow-up was 16 mo. Only one patient (2%) developed toxicity ≥ grade 3. One- and 2-year local control rates after SBRT were 95% and 92%, respectively. The 2-year local control rate was 100% in patients with lesions ≤ 3 cm in diameter. Median OS was 20.5 mo.

In 2012, Salama *et al*[29] reported the results of a dose escalation (SBRT) trial involving 61 patients with one to five metastases (total: 113 metastatic lesions). Only 11 patients in that study had NSCLC. Median follow-up was 20.9 mo. Treatment tolerance was good. At 2 years, PFS and OS rates were, respectively, 22% and 56.7%. In the patients whose tumors progressed, most (72%) were oligoprogression (one to three metastases). Two-year OS was 60.3% in patients with metastases *versus* 21.9% in patients with four to five metastases.

A prospective, single-arm, phase II trial[13,30] evaluated the role of SBRT in 39 patients with oligometastatic NSCLC (≤ metastases). Most (74%) of the patients had local stage III disease, and 87% had a single metastasis, most commonly in the brain (44%). In 95% of the patients, the primary treatment included chemotherapy. Median OS and PFS were, respectively, 13.5 and 12.1 mo. At 3, 5, and 6 years, OS rates were 10.3%, 7.7%, and 5.1%, respectively; the corresponding values for PFS were 7.7%, 7.7%, and 2.5%. Only three patients (7.7%) developed local recurrence. The treatment was well-tolerated, with no cases of grade ≥ 3 toxicity

Iyengar *et al*[31] conducted a phase II randomized clinical trial involving 29 patients with oligometastatic NSCLC, without EGFR or ALK mutations, who achieved partial response or stable disease after chemotherapy. Patients were randomized to maintenance chemotherapy alone ($n$ = 15) or SBRT followed by maintenance chemotherapy ($n$ = 14). The trial was closed prematurely after the interim analysis revealed a significant increase in PFS in the SBRT group (9.7 mo *vs* 3.5 mo) *versus* the chemotherapy alone group ($P$ = 0.01). Toxicity was similar in both arms. There were fewer recurrences overall in the SBRT group.

In 2016, Gómez *et al*[32] reported the results of a prospective, multicenter, randomized phase 2 study involving 74 patients with oligometastatic NSCLC (≤ 3 metastases). All patients received standard first-line systemic therapy consisting of chemotherapy and EGFR or ALK inhibitors. Patients with ≤ 3 metastases after systemic therapy were randomized to receive either local consolidation therapy (LCT) with surgery +/- radiotherapy to the primary tumor and metastases, with or without maintenance treatment or maintenance treatment (including observation, at the clinician's discretion) alone. The patient groups were comparable with regards to lymph node involvement, EGFR/ALK status, response to first-line systemic therapy, brain metastases, and number of metastases. The study was closed after the first interim analysis (49 patients recruited) due to the treatment efficacy observed in the experimental arm. At a median follow-up of 12.39 mo, the study achieved the main objective: A statistically significant increase in PFS in the 25 patients who received LCT (11.9 mo) *versus* the 24 patients in the non-LCT group (3.9 mo, $P$ = 0.0054). In addition, time to the appearance of a new lesion was longer in the LCT arm (11.9 mo *vs* 5.7 mo, $P$ = 0.0497), suggesting that LCT may have altered the natural course of the disease, either by limiting the potential for subsequent dissemination or by altering systemic anticancer immune responses to facilitate longer control of subclinical disease. Adverse events were similar in the two groups, with no treatment-related grade 4 adverse events or deaths. The lead author of that study presented updated results at the American Society for Radiation Oncology congress in 2018[33]. At a median follow-up of 38.8 mo, the PFS benefit was durable, with a median PFS of 14.2 mo in the LCT arm *versus* 4.4 mo in the maintenance therapy/observation arm ($P$ = 0.014). The extended follow up also demonstrated that LCT improved OS, with a median OS of 41.2 mo in the treatment arm *versus* 17.0 mo in the control arm ($P$ =

**Table 1 Prospective trials of local treatment in oligometastatic disease**

| Author | *n* | Primary site, *n* | Treatment groups | Type of treatment | Endpoints | Toxicity |
|---|---|---|---|---|---|---|
| Rusthoven *et al*[7], 2009 | 47 | CRC: 15; Lung: 10; breast: 4; other: 10 | SBRT | Phase I: 36-60 Gy in 3 fx; Phase II: 60 Gy in 3 fx. | LC 2 yr: 92%; OS 2 yr: 30% | G3: 2%; No RILD |
| Salama *et al*[29], 2011 | 61 | NSCLC: 11; SCLC: 5; H&N: 5. Other: 40 | SBRT | 3 fx: 8 Gy 3 fx: 20 Gy | MFu: 20.9 mo; PFS 2 yr: 22%; OS 2 yr: 56.7% | G3 ($n$ = 2) |
| Iyengar *et al*[88], 2014 | 24 | NSCLC | SBRT: 1 fx: 19-24 Gy; 3 fx: 27-33 Gy; 5 fx: 35-40 Gy | SBRT + erlotinib | MFU: 11.6 mo; PFS: 14.7 mo;; OS: 20.4 mo | G3 ($n$ = 2); G4 ($n$ = 1); G5 ($n$ = 1) (after SBRT to three sites) |
| Collen *et al*[104], 2014 | 26 | NSCLC | SBRT after primary treatment | 50 Gy in 10 fx | MFu: 16.4 mo; PFS 1 yr: 45%, median 11.2 mo; OS 1 yr: 67% | G2: 15% G3: 8% ($n$ = 2) |
| Gomez *et al*[33], 2018 | 49 | NSCLC | LCT (CRT/Surgery of all lesions) *vs* maintenance therapy/obs. | SBRT $n$ = 5; Surgery $n$ = 3; pemetrexed $n$ = 16, erlotinib $n$ = 2; afatinib $n$ = 1, bevacizumab | Median PFS: 14.2 mo/4.4 mo ($P$ < 0.05) Median OS: 41.2 mo/17.0 mo ($P$ < 0.05) | Similar, G3 |
| Iyengar *et al*[31], 2018 | 29 | NSCLC | Maintenance Ct alone *vs* SBRT followed by maintenance Ct | Ct: carboplatin + pemetrexed; SBRT: 1, 3 and 5 fractions with 21-27 Gy, 26.5-33 GY and 30-37.5 Gy respectively | MFu: 9.6 mo Median PFS: -Ct: 3.5 mo - SBRT: 9.7 mo ($P$ < 0.05); Median OS: - no difference | G3 $n$: 4 *vs* 2; G4 $n$: 1 (ct only); G5 $n$: 3 *vs* 6. No grade 3 or higher toxicity attributable to SBRT |
| De Ruysscher *et al*[30], 2018 | 40 | NSCLC | Primary: RT or CRT, LCT (surgery, SBRT) | SBRT: 54 Gy of bone metastases. CNS: 1 fx: 8-20 Gy single or 24 Gy × 3 fx. PORT: 60 Gy | Median OS: 13.5 mo; 2-6 yr OS: 23.3%-10.3% Median PFS: 12.1 mo; 2-6 yr PFS: 51.3%-2.5% | G3 esophagitis: 15%; > G4: 0% |

CRC: Colorectal cancer; NSCLC: Non-small cell lung cancer; SCLC: Small cell lung cancer; CNS: Central nervous system; ECOG: Eastern Cooperative Oncology Group; PORT: Postoperative radiotherapy; PFS: Progression-free survival; MFU: Median follow up; OS: Overall survival; LCT: Local consolidative therapy; Ct: Chemotherapy; RT: Radiotherapy; fx: Fraction; CRT: Chemoradiotherapy; SBRT: Stereotactic body radiotherapy; LC: Local control; RILD: Radiation-induced liver disease; H&N: Head and neck.

0.017). No additional grade 3 or higher toxicities were observed in either arm. This was the first randomized clinical trial to demonstrate an increase in OS in patients with oligometastatic NSCLC. The main limitations of the study were the limited sample size, molecular heterogeneity (including EGFR and ALK patients), and the definition of oligometastatic disease (which was defined after systemic therapy).

In the American Society for Radiation Oncology 2018 congress, Palma *et al*[34] presented results of the international (Australia, Canada, Scotland, and Netherlands) SABR-COMET trial that included 99 patients with oligometastatic cancer treated from 2012 to 2016. All of the patients had good performance status (Eastern Cooperative Oncology Group (ECOG) 0-1). The most common primary tumor types were breast ($n$ = 18), lung ($n$ = 18), colorectal ($n$ = 18), and prostate ($n$ = 16) cancer. The inclusion criteria allowed for up to 5 metastatic lesions, although 93% had only 1-3 lesions. Median age was 68 years, and 59% of the patients were men. Patients were randomized 2:1 to SABR plus standard palliative care (treatment group) or palliative care alone (control arm). The baseline characteristics of the two groups were comparable. Some of the patients who developed new metastatic lesions during the trial were successfully treated with additional ablation therapy. At a median follow-up of 27 mo, median PFS was 12 mo in the treatment group *versus* 6 mo in the control arm ($P$ = 0.001). At 5 years, 46% of patients in the SABR arm remained alive *versus* only 24% in the control arm. The median OS was numerically better in the SABR group: 41 mo [95% confidence interval (CI), 26 mo to "not reached"] *versus* 28 mo (95%CI: 19-33 mo) in the control group ($P$ = 0.09). Adverse events (AEs) ≥ grade 2 were more common in the SABR group (30% *vs* 9%). The most common AEs were fatigue, dyspnea, and pain (muscle, joint, bone, or other types). Three AE-related deaths occurred in the investigational arm. No differences in quality of life were observed. At 6 mo post-treatment, overall scores on the Functional Assessment of Cancer Therapy General questionnaire were high in both the SABR and control arms: 82.5 *versus* 82.6, respectively ($P$ = 0.992).No significant between-group differences were observed on the functional, emotional, physical, and social subscales of the Functional Assessment of Cancer Therapy General. A follow-up phase III study (SABR-COMET-3) will evaluate this treatment approach in patients with up to three

metastatic lesions. The phase III SABR-COMET-10 will evaluate the same treatment approach but with lower doses of radiation in patients with up to 10 lesions.

A recent multicentric phase 2 trial[35] evaluated 147 patients with oligometastatic cancer (≤ 5 metastases), 21.8% of whom had lung cancer. All patients received SBRT. At a median follow-up of 41.3 mo [interquartile range: 14.6-59], median OS was 42.3 mo and 5-year OS was 43%. Local and metastatic PFS rates were 74% and 17%, respectively. Late toxicity ≥ 3 was 1.4%. There was a significant improvement in patient-reported quality of life at months 6 and 12.

Petty *et al*[36] conducted a phase II trial involving 27 patients with oligometastatic NSCLC (≤ 5 metastases) who had responded to three to six cycles of platinum-based chemotherapy. All patients received radiochemotherapy to the primary tumor and the metastases. Although the study closed prematurely due to poor recruitment, the study endpoint (PFS > 6 mo) was met ($P < 0.0001$). Median PFS and OS were, respectively, 11.2 and 28.4 mo. OS and PFS in patients with brain metastases or lymph node involvement did not differ significantly from the overall results.

## PROGNOSTIC FACTORS FOR OLIGOMETASTATIC NSCLC

One of the keys to treatment selection in oligometastatic NSCLC is to identify patients likely to benefit from aggressive metastasis-directed therapies. However, only a relatively small percentage (15%-25%) of oligometastatic patients will have an extended disease-free interval (DFI) following ablative treatment of the metastatic lesions. The prognostic factors associated with survival include the following: Number of metastases; mediastinal node involvement; time until onset of metastases (DFI > 6 mo); histology; age; performance status; diagnosis-specific graded prognostic assessment (DS-GPA classification)[5] in patients with brain metastasis; pathological T-staging; the metastatic location (brain or adrenal glands *versus* other locations); treatment of the primary tumor (the type of surgical resection, intrathoracic small radiotherapy treatment volumes); and the molecular profile.

Although nearly all of the studies to date have included patients with up to five metastases, most of those patients had three or fewer metastases. Moreover, half of the patients in the meta-analysis by Ashworth *et al*[6] had only a single metastasis. In general, prognosis is better in patients with few metastases *versus* those with multiple metastases, regardless of whether metastasis-directed therapy is administered or not[37]. In this regard, the study by Albain *et al*[38] is worth highlighting. They evaluated 2531 patients with disseminated NSCLC, finding better OS in patients with a single metastasis (8.7 mo) *versus* those with multiple metastases in a single organ (6.2 mo) *versus* patients with multiple metastases in multiple organs (5.1 mo). Similar results were obtained by the International Association for the Study of Lung Cancer [3] in a validation study conducted in the context of preparing the 8$^{th}$ edition of the American Joint Committee on Cancer staging manual. In that study, OS was longer (median, 17.8 mo) in patients with a single extrathoracic metastasis than in those with multiple metastases (13.6 mo, $P < 0.001$).

Mediastinal node involvement is an important adverse prognostic factor for OS in patients with oligometastatic NSCLC. In this regard, a study of 39731 patients with M1a NSCLC included in the Surveillance, Epidemiology, and End Results database demonstrated that patients without lymph node involvement had the best cancer-specific survival, followed by patients with N1 disease; there were no differences in cancer-specific survival between patients with N2 or N3 disease[39].

The timing of the appearance of metastases is another important prognostic factor evaluated in the meta-analysis by Ashworth *et al*[6], which included a total of 757 patients with oligometastatic (one to five metastases) NSCLC. The metastases were synchronous in 75.5% of patients and metachronous in the other 24.5%. Treatment consisted of ablative therapy (mainly surgery) plus curative-intent treatment of the primary tumor. The median patient age was 61.1 years. Most patients had good performance status. The majority of patients (96.5%) had only one or two metastases. Median OS was 26 mo. The following factors were associated with worse OS: Synchronous metastasis, N-stage, and a non-adenocarcinoma histology. Patients were stratified into three prognostic groups based on an analysis of the study data: Low-risk: Metachronous metastases (5-year OS, 47.8%); intermediate risk: Synchronous metastases and N0 disease (5-year OS, 36.2%); and high risk: Synchronous metastases and N1/N2 disease (5-year OS, 13.8%).

In patients with brain metastases, predictors of survival include performance status, extent of extracranial disease, patient age, and number of brain metastases. This is known as the diagnosis-specific graded prognostic assessment (DS-GPA). Median survival according to DS-GPA values are as follows: 0-1: 3 mo; 1.5-2: 5.5 mo;

2.5-3: 9.4 mo; and 3.5-4: 14 mo[40].

In a retrospective study of 168 patients with oligometastatic NSCLC (≤ 5 lesions), Parikh *et al*[37] assessed the role of performance status and histology on outcomes, finding that N2-3 nodal status was an unfavorable prognostic factor. In that study, ECOG performance status ≥ 2, squamous cell histology, and metastases to multiple organs were all associated with a greater risk of death. By contrast, definitive local therapy to the primary tumor was associated with prolonged OS.

The role of pathologic T-stage on treatment outcomes was evaluated in a retrospective study of 29 patients with synchronous, single-organ metastatic NSCLC treated by lung resection and metastasis-directed therapy. Median survival was 20.5 mo, with a 5-year OS of 36%. Pathologic T stage was a predictor of survival. Median survival was significantly longer in patients with pT1-2 disease (26 mo) *versus* those with pT3-4 disease (8 mo, $P = 0.007$)[41].

The site of the metastatic lesion is another important prognostic factor. Lung, brain, and adrenal gland metastases appear to be associated with better survival than bone or liver metastases[42]. Griffoen *et al*[25] retrospectively evaluated 61 patients with one to three synchronous metastases treated with radical intent. Those authors found that the factors associated with improved survival after first progression were: Surgical excision of the primary lung tumor, presence of brain metastases (13.0 mo *vs* 3.3 mo, $P = 0.002$), and absence of bone metastases (11.9 mo *vs* 3.3 mo, $P = 0.004$). The study conducted to validate externally the prognostic value of the newly-proposed M staging classification system included a total of 1024 patients with stage IV NSCLC, showing that patients with lung metastases (M1a) had a better prognosis than those with extrathoracic metastases (M1a: 22.5 mo *vs* M1b: 17.8 mo *vs* M1c: 13.6 mo, $P < 0.001$).

Franceschini *et al*[43] recently evaluated patient-, treatment-, and disease-related variables that could potentially predict response to SBRT and survival. That study included 358 oligometastatic patients (≤ 5 lesions to three or fewer sites) from different primary tumors (23.7% NSCLC). At a median follow-up of 31.8 mo, 6- and 24-mo local control rates were, respectively, 94.6% and 78.9%; the corresponding PFS rates were 66.1% and 18.4%. Median OS was 34.7 mo (95%CI: 29.6-43.8), and 6- and 24-mo OS rates were 96% and 63.5%, respectively. On the multivariate analysis, pulmonary and nodal metastases were both associated with longer OS. Local response was also associated with OS. By contrast, primary lung cancer, older age, and metastases in locations other than those irradiated were all independent predictors of shorter OS.

Frost *et al*[44] conducted a retrospective propensity score analysis of 180 patients with synchronous oligometastatic (≤ 4 metastases) lung cancer (including NSCLC and neuroendocrine lung cancer) who received local treatment (surgery or SBRT) to all metastatic sites (experimental group) or standard chemotherapy combined, if needed, palliative-intent local treatment (control group). The experimental group had significantly better PFS (25.1 mo *vs* 8.2 mo, hazard ratio (HR) = 0.30, 95%CI: 0.21-0.43, $P < 0.001$) and OS (60.4 mo *vs* 22.5 mo, HR = 0.42, 95%CI: 0.28-0.62, $P < 0.001$). The most important prognostic factor was local treatment of the metastases. Several variables were associated with better PFS: adenocarcinoma histology, stage T1a, lymph node stage (N0-2 *vs* 3), and single *versus* multiple metastases. Performance status (ECOG 0-1 *vs* 2) was associated with better OS.

The meta-analysis conducted by Li *et al*[45] examined 24 studies (clinical trials and comparative retrospective studies) to identify prognostic factors in oligometastatic NSCLC. A total of 1935 patients were included. On the univariate analysis, neither age, nor smoking status, nor type of metastasis had any influence on OS. By contrast, several variables were significant prognostic factors for OS: Female sex (HR = 1.21, 95%CI: 1.02-1.45, $P = 0.03$), stage pN0 (HR = 1.82, 95%CI: 1.40-2.36, $P < 0.00001$), and adenocarcinoma (HR = 1.44, 95%CI: 1.10-1.88, $P = 0.008$). On the multivariate analysis, stage pN0 disease was associated with significantly better OS compared to stage pN1 disease (HR = 1.63, 95%CI: 1.27-2.10, $P = 0.001$) but not when compared to stage pN2 (HR = 2.01, 95%CI: 0.80-5.03, $P = 0.14$). In the subgroup analyses, none of the following variables had a significant impact on OS: thoracic stage, primary tumor, tumor histology, or number of oligometastases. However, patients who received aggressive/radical local treatment of the primary tumor had better OS (HR = 0.56, 95%CI: 0.37-0.83, $P = 0.001$), as did patients who received aggressive/radical local treatment of the oligometastases (HR = 0.54, 95%CI: 0.36-0.82, $P < 0.00001$).

The molecular profile of the patients also appears to be a prognostic factor associated with survival. Lussier *et al*[46] identified a specific microRNA expression that identified the patients most likely to remain oligometastatic after metastasis-directed treatment and therefore associated with a better prognosis.

## SPECIFIC SITUATIONS

### *Brain oligometastases*

Lung cancer is the main source of brain metastases, and 25%-30% of lung cancer patients present brain metastases at diagnosis. In certain cases, radical management of these metastases is associated with better outcomes: Limited number of metastases, good performance status, and favorable histology[47,48]. The main treatment approaches for this indication are surgery, WBRT, and SRS (Figure 1).

Data from retrospective case series show that patients with NSCLC with a single synchronous brain metastasis who undergo radical treatment of the primary tumor and the brain metastasis have better OS (7%-24% at 5 years)[49,50]. One of the first and most important studies was conducted by Patchell *et al*[12], who carried out a prospective randomized trial involving patients (77% with NSCLC) with a single brain metastasis treated by surgery or surgery-WBRT. The surgery-WBRT arm had a better OS with a lower rate of recurrence (18% *vs* 70%).

SRS is another treatment option in this postoperative scenario. In 2017, Lamba *et al*[51] carried out a meta-analysis of retrospective studies, finding that SRS of the surgical cavity appears to yield survival outcomes and local and distant control rates that are comparable to WBRT. In a recent phase III trial, Mahajan *et al*[52] randomized patients ($n$ = 128) who had undergone complete resection of one to three brain metastases to either observation or SRS. Those authors observed no local recurrences in 72% of the SRS group *versus* 43% of the observation group. This finding supports the use of SRS as an alternative to postoperative WBRT in this patient profile. In non-surgical patients, the RTOG 9508 phase III clinical trial evaluated 331 patients with one to three brain metastases from different primary tumors (64% lung cancer). The patients were randomized to receive either WBRT or WBRT plus an SRS boost to all lesions. On the univariate analysis, there was a survival benefit for the SRS boost only in the patients with a single brain metastasis (mean survival, 6.5 mo *vs* 4.9 mo, $P$ = 0.0393)[53].

An important consideration in the treatment of brain oligometastases is the need to avoid the neurocognitive morbidity associated with WBRT. A randomized trial of 132 patients with up to four brain metastases (maximum diameter, 3 cm), compared SRS alone to SRS-WBRT and reported similar survival outcomes (8 mo *vs* 7.5 mo), indicating that patients with brain oligometastases could be treated with SRS alone[54]. Bhatnagar *et al*[55] evaluated the results of SRS alone in 205 patients (42% with NSCLC) with four to fifteen brain metastases. The 1-year local control rate was 71%, with a mean OS of 8 mo. The total treatment volume was a better predictor of survival than the number of metastases, a finding that raised the possibility that the concept of brain oligometastasis may be more closely associated with tumor volume than with the number of lesions. The recent meta-analysis by Tsao *et al*[56] compared WBRT to WBRT-SRS and SRS to WBRT-SRS, finding that combined treatment offers no OS benefit compared to SRS alone. While WBRT improved local control, toxicity with SRS was much lower[56].

There are no randomized trials comparing surgery-WBRT to SRS-WBRT, although one phase III trial compared surgery-WBRT to SRS for the treatment of single brain metastasis (≤ 3 cm in diameter). Although that study was closed early due to low recruitment, there were no significant survival differences between the two groups (64 patients)[57].

There is some controversy surrounding the optimal management of NSCLC patients with brain metastases who present an actionable oncogenic driver mutation (*e.g.*, EGFR or ALK). Different phase III trials with third-generation anti-EGFR/ALK TKI, with ability to cross the blood-brain barrier, have shown CNS (central nervous system) response rates of up to 80% and an increase in OS[58,59]. The greater efficacy to treat CNS diseases raises the option of treating these patients with TKI alone, thus allowing for a delay in radiotherapy until progression is detected. However, there are still no randomized studies comparing these strategies directly and prospectively. On the other hand, Magnuson *et al*[61] reported results of a multi-institutional analysis of 351 patients treated with SRS followed by EGFR-TKI or WBRT followed by EGFR-TKI, or EGFR-TKI followed by SRS or WBRT upon intracranial progression. There were significant differences among the three groups in median OS: 46, 30, and 25 mo, respectively ($P$ < 0.001), showing better results with the early local treatment.

### *Adrenal oligometastasis*

The lung is the main site of origin for most adrenal gland metastases[5]. The incidence of these lesions has increased in recent years due to the increasing use of PET-CT and MRI. Unilateral involvement is more common when no other metastases are present (50% of cases); however, if metastatic involvement is present in other sites, unilateral adrenal involvement is only observed in 25% of cases[62]. Traditionally, adrenalectomy

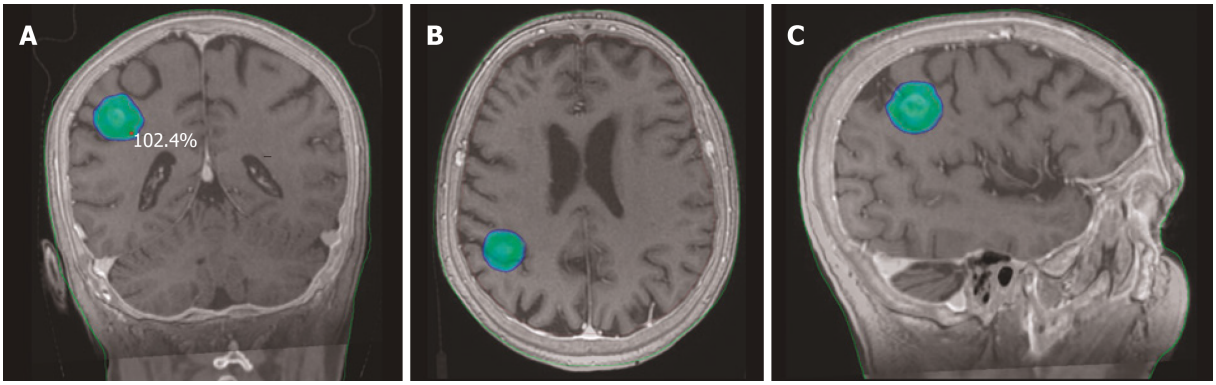


**Figure 1 Stereotactic body radiation therapy dose distribution for a single brain metastasis from non-small cell lung cancer.** Planning computed tomography fused with magnetic resonance images. A: Coronal view; B: Axial view; C: Sagittal view.

has been the treatment of choice in selected patients[63]. The results of laparoscopic surgery are equivalent to open surgery, with less morbidity[64].

Recently, SBRT has become an excellent alternative to surgery for the treatment of adrenal oligometastasis[65] (Figure 2). Published case series, most with > 12 mo of follow-up, suggest that toxicity ≥ G2 is practically nonexistent. Moreover, the excellent local control rates (> 90%) are highly promising. Probably the most notable case series published to date is the 34 patient series reported by Scorsetti *et al*[66]. This study has the longest median follow-up to date (41 mo), with excellent local control rates (93%).

Holy *et al*[67] reported a median OS of 23 mo, comparable to surgical series, in patients with NSCLC with a single adrenal metastasis treated with SBRT (40 Gy in five fractions). Casamassima *et al*[68] reported results from a series of patients with adrenal metastases from different primary tumors (including NSCLC). Those patients received SBRT (36 Gy in three fractions), obtaining a 2-year local control rate of 90%. To date, a range of different fractionation schedules and doses have been used to treat adrenal gland metastases. Some authors, such as Li *et al*[69], have proposed a biologically-effective dose (BED) 10 > 100 Gy (as in other metastatic sites), suggesting that this BED provides greater local control.

The ideal candidate for radical intent local treatment to the adrenal metastasis remains to be defined. Similarly, we still need to define the optimal treatment, either surgery or SBRT. Given the lack of comparative studies, current evidence suggests that SBRT yields comparable local control rates to surgery, with less morbidity and lower mortality rates. Moreover, SBRT is easier to combine with systemic treatment.

### *Liver oligometastases*

While liver metastasis is less common than in other locations in patients with NSCLC, the presence of such lesions is an unfavorable prognostic factor[5]. Although surgery remains the treatment of choice for these lesions, estimates suggest that only 10%-20% of patients are eligible for surgery[70]. Several different ablative techniques have been investigated, with reported local control rates as high as 90%[71,72]. However, these ablative treatments are limited by the patient's reserve of healthy liver tissue, the risks of bleeding, lesion size, and the presence of nearby vascular structures[73]. SBRT has become a non-surgical option in these patients (Figure 3).

Numerous retrospective and prospective studies have evaluated SBRT for liver oligometastases, all of which have included patients with liver metastases from different primary tumors (Table 2). Of these, the recent study carried out by Mahadevan *et al*[70] stands out. They evaluated 427 patients with a total of 568 liver metastases (12% secondary to lung cancer) treated with SBRT. OS was longer (25 mo *vs* 15 mo) in small volume metastatic lesions (< 40 $cm^3$) and in lesions that received a BED 10 ≥ 100 Gy (27 mo *vs* 15 mo), which also yielded better local control (77.2% *vs* 59.6%). Tumor histology had no impact on local control rates. While we await the results of ongoing prospective studies, the available evidence indicates that the high local control rates obtained with SBRT appear to be similar to those achieved with other local treatments, with a good toxicity profile.

### *Lung oligometastases*

Surgical resection of lung metastases has a long history. The influential "Analysis of the International Registry of Pulmonary Metastases" was published in 1997[82]. In that study, 5206 cases of pulmonary metastases (of various different histologies) were

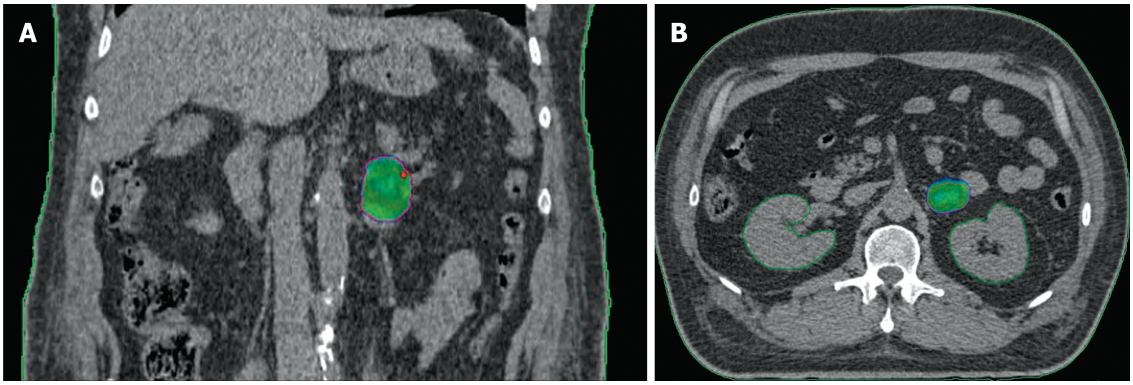


**Figure 2 Example of stereotactic body radiation therapy plan for adrenal gland metastases from non-small cell lung cancer with 95% isodose highlighted in dose heatmap.** A: Coronal view; B: Axial view.

evaluated, showing 5- and 15-year OS rates of 36% and 22%, respectively. The following were independent prognostic factors: Number of metastases, complete resection, and long DFI. Pulmonary metastases secondary to lung cancer are one of the most common metastatic locations. However, only a minority of patients are candidates for surgery. Local control rates range from 85%-95% after lobectomy and from 50%-70% after wedge resections[83,84].

A meta-analysis of 757 patients with oligometastatic NSCLC found that, among patients who underwent radical-intent local treatment, survival was better in those who had metachronous *versus* synchronous disease ($P < 0.001$)[6]. Various series have shown that survival rates achieved with lobectomy or pneumonectomy are comparable to sublobar resection but with greater morbidity[85,86].

In recent years, SBRT has become an excellent alternative to surgery for this indication (Figure 4). Rusthoven *et al*[7] carried out a phase I/II trial to evaluate the efficacy and tolerability of SBRT in patients with one to three lung metastases (≤ 7 cm in diameter). Radiotherapy was delivered in three fractions, and the dose was safely escalated from 48 to 60 Gy in phase I. The study included 38 patients (13.2% with primary NSCLC) and 63 metastatic lesions. Most (71%) of the patients received systemic treatment. The incidence of G3 toxicity was 8%, with no cases of G4 toxicity. Local control rates at 1 and 2 years were 100% and 96%, respectively. In the Mayo Clinic study carried out by Milano *et al*[87], 121 patients with ≤ 5 metastases of differing histologies (including NSCLC) received SBRT to all metastatic lesions. At 2 years, local control was 74% in patients with non-breast cancer tumor histologies, and mean survival was 18 mo. OS was longer in patients with a clinical response or stable disease after systemic treatment administered prior to SBRT. Iyengar *et al*[88] performed a randomized trial to assess SBRT in patients with oligometastatic NSCLC. SBRT was administered in one (19-24 Gy), three (27-33 Gy), or five sessions (35-40 Gy). All metastases (up to six extracranial lesions) were irradiated and patients received concurrent erlotinib after progression following first-line chemotherapy. PFS and OS were, respectively, 14.7 and 20.4 mo, which was higher than that from previous reports in patients who developed progression to first-line treatment without SBRT. A retrospective analysis at the University of Chicago included 25 patients (62 lesions) diagnosed with oligometastatic NSCLC (one to five lesions). At a mean follow-up of 14 mo, DFS and OS were, respectively, 7.6 and 22.7 mo[21]. The aforementioned study by Gomez *et al*[32] and Gómez *et al*[33] are among the most important conducted to date in oligometastatic NSCLC. Of the 25 patients who received local consolidative therapy after systemic treatment, 23 cases involved the lung, which is therefore the most important site in this study.

To date, no randomized trials have directly compared SBRT to surgery in the treatment of lung metastases. However, based on the currently available results of both treatments, SBRT seems to be the better option due to greater patient tolerability and because it is easier to combine with systemic treatment. Pending comparative results, the two treatments appear to provide similar local control.

### *Oligometastases in other localizations*

The use of local treatment is growing as is the number of oligometastatic possible sites[5]. Local therapy is now used to treat oligometastatic lesions in the bones, the spinal cord, and lymph nodes. Surgery has long been the treatment of choice for bone metastases in selected patients. However, due to the significant morbidity and mortality associated with surgery, the indications for this approach in bone

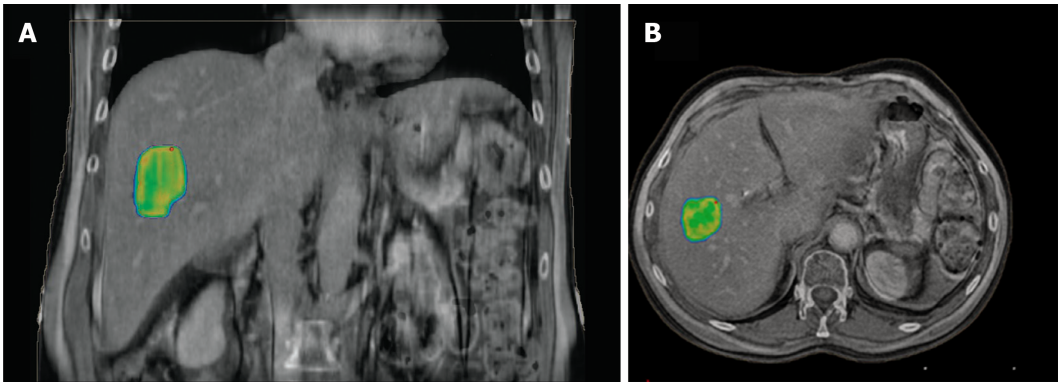


**Figure 3 Image capture from stereotactic body radiation therapy planning session showing concentration of radiation dose to the liver metastases.** Planning computed tomography fused with magnetic resonance images. A: Coronal view; B: Axial view.

metastases are limited[89]. The evidence base to support spinal cord or lymph node surgery in oligometastatic NSCLC is limited, which is why surgery is only indicated in cases in which a consensus decision by a multidisciplinary team has been reached after evaluating other therapeutic options.

The growing and increasingly effective use of local treatment of oligometastatic lesions is primarily due to the emergence of SBRT. Several recent reviews have evaluated the available body of evidence, mainly case series, for SBRT in these three metastatic sites (2, 3, and 4)[90-92]. Most of the studies published to date share several characteristics. For example, they all include patients with metastases to various sites, with differing histologies, treatment schemes, and a good tolerance profile (with exceptionally low rates of G3-4 toxicity). Moreover, in most published series, local control rates generally range from 80%-85% (or higher). Pending the publication of prospective studies, the decision to administer local treatment to these sites must be based on a consensus agreement among specialists after a thorough evaluation of the patient and careful consideration of the optimal local treatment.

## MANAGMENT OF THE PRIMARY TUMOR IN OLIGOMETASTASIC NSCLC

Management of the primary tumor in patients with oligometastatic NSCLC should be evaluated individually and based on the available evidence. Currently, as we can see in previous sections, the most robust evidence is for patients diagnosed with synchronous intracranial metastases (one to three lesions). There is some evidence suggesting that treatment of the primary thoracic tumor and mediastinal lymph nodes in oligometastatic patients is associated with better survival, as shown in the studies discussed previously[6,37,38,41]. Li *et al*[93] performed a meta-analysis of seven retrospective, observational cohort studies involving 668 synchronous oligometastatic NSCLC patients. Of those 668 patients, 227 (34.0%) received aggressive thoracic therapy (surgery and/or radiotherapy, total dose > 40 Gy). Aggressive thoracic therapy was associated with a significant improvement in OS in the full cohort (HR = 0.48, $P < 0.00001$) and in three subgroups: Patients with metastases to a single organ (HR = 0.42), those with a solitary brain metastasis (HR = 0.49), and patients with stage I-II thoracic disease (HR = 0.38). In addition, 4-year OS rates were significantly higher in patients who received aggressive thoracic therapy (12.6% *vs* 2.0%). Several studies have shown that definitive treatment of the primary tumor is a favorable prognostic factor for survival in NSCLC, as reflected in the results of the meta-analysis conducted by Ashworth and colleagues[6]. The main treatments for the primary tumor are surgery, primarily lobectomy, and radiotherapy, with or without chemotherapy (depending on the disease stage). Radiotherapy can be normofractionated or hypofractionated (SBRT) in patients with negative node disease, which is a favorable prognostic factor.

In their case series, López Guerra *et al*[22] evaluated prognostic factors in oligometastatic lung cancer, finding that small tumor volumes, radiotherapy doses > 63 Gy, and good functional status were all associated with better survival. Similarly, Griffoen *et al*[25] retrospectively analyzed 61 patients, finding that small radiation volumes and surgical treatment of the primary tumor were both prognostic factors for better survival.

**Table 2 Publishes results for stereotactic body radiation therapy-treated liver metastases**

| Study | Number of lesions | Patients, *n* | Primary tumor | Dose/fractions | Toxicity | Mean follow-up, mo | Control, local | Survival |
|---|---|---|---|---|---|---|---|---|
| Blomgren *et al*[74] | Variable | 31 | Various | 8-66 Gy/1-4 | 2 Hemorrhagic gastritis | 1.5-3.8 | 80% | Not reported |
| Hoyer *et al*[75] | 1-6 (< 6 cm) | 44 | Various | 45 Gy/3 | 1 liver failure 2 severe GI toxicity | 52 | 2-yr: 86% | 1-yr: 67% 2-yr: 38% |
| Mendez Romero *et al*[76] | 1-3 (< 7 cm) | 25 | Various | 37.5 Gy/3 | 4 acute grade ≥ 3 1 late grade 3 | 12.9 | 2-yr: 86% | 1-yr: 85% 2-yr: 62% |
| Rusthoven *et al*[7] | 1-3 (< 6 cm) | 47 | Various | 60 Gy/3 | < 2% late | 16 | 2-yr: 92% < 3 cm: 100% | mean, 17.6 mo |
| Lee *et al*[77] | Variable | 68 | Various | 28-60 Gy/3 | Acute: 8 GIII, 1 GIV | 10.8 | 1-yr: 71% | 18 m: 47% |
| Ambrosino *et al*[78] | 1-3 (< 6 cm) | 27 | Various | 25-60 Gy/3 | Not reported | 13 | 74% | Not reported |
| Goodman *et al*[79] | 1-5 (< 5 cm) | 26 | Various | 18-30 Gy/1 | Late: 4 GII | 17.3 | 1-yr: 77% | 1-yr: 62% 2-yr: 49% |
| Rule *et al*[80] | 1-5 | 27 | Various | 30 Gy/3 50-60 Gy/5 | No ≥ G2 | 20 | 30 Gy: 56% 50 Gy: 89%60 Gy: 100% | 30 Gy: 56% at 2-yr 50 Gy: 67% at 2-yr 60 Gy: 50% at 2-yr |
| Scorsetti *et al*[81] | 1-3 (< 6 cm) | 61 | Various | 52.5-75/3 | No ≥ G3 | 24 | 91% | 1-yr: 80%2-yr: 70% |
| Mahadevan *et al*[70] | Variable | 427 | Various | 45 (12-60) / 3 (1-5) | Not reported | 14 (1-91) | Median: 52 mo 1-yr: 84%2-yr: 72% | Mean: 22 mo 1-yr: 74% 2-yr: 49% |

GI: Gastrointestinal.

Recently, two interesting studies have been published to evaluate the role of irradiating the primary tumor in oligometastatic NSCLC. In the first one, Petrelli *et al*[94] conducted a systematic review and meta-analysis of all published prospective trials and retrospective studies (up to July 2018) that compared radiotherapy *versus* no radiotherapy to the primary lung tumor in patients with synchronous oligometastatic NSCLC. A total of 924 patients from 21 studies were included. Patients who received thoracic irradiation of the primary tumor had significantly better OS (HR = 0.44, 95%CI: 0.32-0.6, $P < 0.001$) and PFS (HR = 0.42, 95%CI: 0.33-0.55, $P < 0.001$). The second study conducted by Arrieta *et al*[95] is a phase II prospective trial to evaluate patients ($n = 37$) diagnosed with stage IV NSCLC with ≤ 5 synchronous metastases at any location, including the CNS. All patients received four cycles of systemic treatment. The metastases and primary tumor were both irradiated in patients who responded (stable disease or partial response) to systemic therapy. Nineteen patients (51.4%) showed a complete response (CR) to radiotherapy on PET-CT imaging. The PFS for the full cohort was 23.5 mo (95%CI: 13.6-33.3). OS was better in the patients with CR on PET-CT, leading the authors to conclude that CR is an important prognostic factor.

## LOCAL TREATMENT COMBINED WITH SYSTEMIC THERAPY

Although nowadays treatment of oligometastatic NSCLC with a radical intention is a routine practice, the optimal treatment sequence remains controversial because the data to support this recommendation come mostly from retrospective or small prospective studies. Therefore an individualized assessment of every patient is necessary to develop a radical-intent treatment plan and should always be determined by a multidisciplinary team. Several factors must be considered, including: Local extension of primary tumor, the tumor type (presence or absence of target mutations); the number, size and location of the metastases; the time of diagnosis (*i.e.* synchronous *vs* metachronous), and other patient-related factors such as the presence or absence of symptoms secondary to the disease, performance status, and comorbidities. Importantly, there are no clear criteria available to guide patient

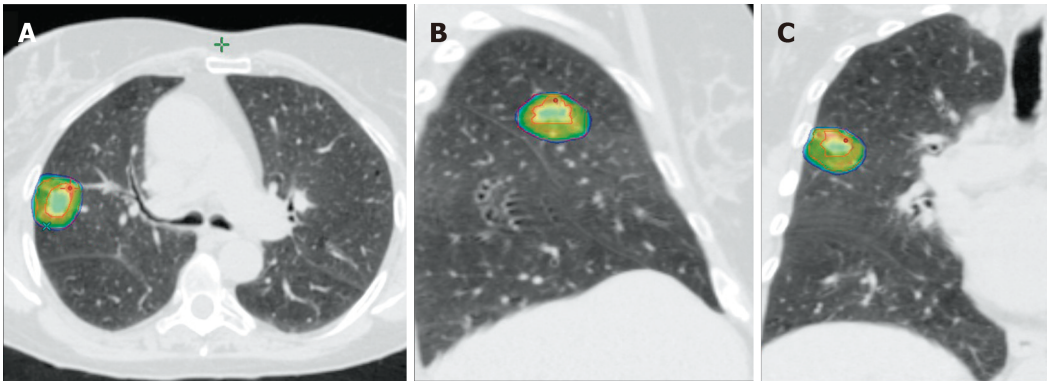


**Figure 4 Example of stereotactic body radiation therapy planning using 4D-computed tomography for a patient with right lung metastases from non-small cell lung cancer.** A: Isodose distribution in the axial plane; B: Isodose distribution in the sagittal plane; C: Isodose distribution in the coronal plane.

selection nor is there an standard strategy to combine ablative local treatment with systemic therapy in this patient profile.

In patients who present with synchronous metastases at diagnosis, an accepted strategy is to initiate systemic treatment and then re-stage the patient to confirm disease response (*i.e*. absence of progression) before administering radical treatment to the primary tumor and metastases. This was the strategy used in the two phase II randomized trials, both of which found better PFS and OS in patients who received radical local therapy[31,33].

A second strategy could be radical treatment of all metastatic lesions followed by systemic consolidation treatment. This approach was used by De Ruysscher *et al*[30] in a phase II prospective trial with 39 patients. The results were poor, with a 5-year PFS of only 8%, probably because this strategy does not include an option to select patients who respond to systemic therapy.

The use of more effective and less toxic treatments such as immunotherapy and targeted therapies has brought about a change in the natural history of NSCLC. There is a new subset of patients who present with oligoprogression during systemic treatment. In those patients, the local therapy of the progressive metastases is also associated with a longer PFS and OS while allowing continuation with the same systemic treatment[96,97].

With regard to the treatment strategy in patients with metastatic involvement limited to the CNS, there is a stronger consensus in favor of initiating treatment with SRS or surgical resection. In the subgroup of patients with activating mutations (EGFR or ALK) with asymptomatic lesions, it is considered reasonable to initiate targeted therapy before radiotherapy[98-100]. However, SRS follow ed by EGFR-TKI, an approach used in the study by Magnuson *et al*[61], is an alternative option to consider in these patients.

## RECOMENDATIONS IN CLINICAL GUIDELINES

The oligometastatic state is based on the concept of long-term disease control, which is achieved through the aggressive local treatment of metastases. For this reason, clinical guidelines have already begun to incorporate local treatment techniques such as SBRT.

### *Spanish Society of Medical Oncology*

The Spanish Society of Medical Oncology guidelines recommend local treatment (SBRT or surgery) in oligometastatic patients with up to five metastases, provided that all of lesions are susceptible to radical treatment[98].

The guidelines define four different clinical scenarios eligible for local treatment: (1) Metastases limited in number and location at the time of diagnosis. These metastases and the primary tumor must be susceptible to local treatment; (2) Limited number of metastases after primary treatment. All lesions must be susceptible to radical treatment; (3) Limited number of metastases that progress after systemic treatment; primary tumor and the other metastases remained controlled; and (4) Oligo-recurrence in patients who received radical-intent treatment, with one to five metachronous metastases susceptible to radical treatment.

The guidelines recommend that patients with oligometastatic disease at diagnosis receive radical treatment with systemic therapy plus local treatment to the primary

tumor and metastases. This recommendation is based on two phase II studies showing that local treatment after systemic treatment improves PFS.

These guidelines also note that NSCLC patients who receive targeted therapy and develop progression can be treated with SBRT in order to continue receiving the targeted treatment. In patients with asymptomatic brain metastases susceptible to treatment with TKIs, the guidelines recommend starting with TKI therapy and postponing local treatment (surgery or radiosurgery).

### *National Comprehensive Cancer Network*

The National Comprehensive Cancer Network guidelines include local treatment (SBRT or surgery) of metastases in well-selected patients with good ECOG performance status who have received radical treatment to the intrathoracic disease[101].

In patients with limited brain metastases, the guidelines recommend local treatment of these lesions (by surgery or radiosurgery). In patients with asymptomatic brain metastases with mutations, it is acceptable to continue with TKI, only administering local treatment if the lesions become symptomatic.

SBRT or surgery to the oligometastatic lesions (one to five metastases) is recommended provided that all sites can be safely treated. In patients who develop disease progression in a limited number of sites following systemic treatment, the use of SBRT may extend the duration of the benefit from that line of systemic treatment. These recommendations also apply to patients with driver mutations that progress to targeted therapy in some locations. In these cases, SBRT can be applied to allow the patient to continue with the same treatment. If SBRT is not feasible at the oligoprogression sites, the guidelines recommend using other hypofractionated treatments.

### *European Society for Medical Oncology*

The European Society for Medical Oncology guidelines[99] recommend local treatment with SBRT or surgery in the following situations: (1) Patients with a limited number of brain metastases who fulfil criteria for class I-II recursive partitioning analysis (RPA). WBRT can be obviated if the patient is closely monitored using brain MRI after local treatment; (2) In patients with mutations (EGFR, ALK, *etc*) and asymptomatic brain metastases, TKI can be started and radiosurgery delayed; (3) Stage IV patients with extracranial oligometastases and one to three synchronous metastases. In this case, DFS may improve if systemic treatment is combined with local treatment (SBRT). The guidelines recommend presenting these cases to a multidisciplinary tumor board due to the current lack of evidence; (4) In patients with mutations who develop oligoprogression. SBRT or surgery should be considered to prolong DFS and to continue with systemic therapy; and (5) In single contralateral pulmonary lesions that would be considered as a second synchronous tumor and would be treated with curative intent if possible.

## FUTURE DIRECTIONS AND CLINICAL TRIALS CURRENTLY UNDERWAY

Based on the current evidence, local treatment-either surgery or SBRT-of patients with oligometastatic NSCLC is associated with good survival rates with acceptable toxicity[33,34,102]. Numerous prospective studies are currently underway to corroborate these results. The following table summarizes the relevant trials that are currently registered in clinicaltrials.gov (Table 3)[103].

## CONCLUSION

Oligometastatic NSCLC is a heterogeneous disease. These patients may present brain and body metastases, which can be synchronous or metachronous. Most studies performed to date have limited the number of metastases to no more than five lesions, thus limiting our ability to extrapolate results from those studies to patients with more widely disseminated disease. Nevertheless, due to the technological advances and improvements in the therapeutic strategy in recent years, this an exciting time for specialists who manage oligometastatic NSCLC. In recent years, numerous studies, including two randomized phase II trials, have demonstrated that local treatment, either radiotherapy or surgery, of the primary tumor and metastases improves PFS and OS in patients who present with oligometastatic NSCLC at diagnosis and in those who respond to the initial systemic therapy.

**Table 3 Clinical trials in patients with oligometastatic non-small cell lung cancer**

| Clinical trial identifier | Title | Objective |
|---|---|---|
| NCT01185639 | Stereotactic Body Radiation Therapy (SBRT) in Metastatic Non-Small Cell Lung Cancer | To evaluate the efficacy of SBRT in oligometastatic NSCLC patients who achieve partial response or stable disease after 4 cycles of ChT. The hypothesis is that SBRT after 4 cycles of ChT is feasible, safe, with good local control, and improves time to progression |
| NCT 02314364 | A Trial of Integrating SBRT With Targeted Therapy in Stage IV Oncogene-driven NSCLC | To evaluate SBRT in patients with stage 4 NSCLC and EGFR, ALK, or ROS1 mutations who have been treated with erlotinib, gefitinib, or other targeted drugs |
| NCT03275597 | Phase Ib Study of Stereotactic Body Radiotherapy (SBRT) in Oligometastatic Non-small Lung Cancer (NSCLC) With Dual Immune Checkpoint Inhibition | To evaluate the safety and tolerability of SBRT combined with durvalumab and tremelimumab for oligometastatic NSCLC |
| NCT02975609 | Phase II Trial of SBRT Compared With Conventional Radiotherapy for Oligometastatic Non-Small Cell Lung Cancer | To compare the efficacy and safety of SBRT *vs* conventional radiotherapy after response to 4-6 cycles of chemotherapy. Outcome measures for both groups include PFS, OS, and adverse effects |
| NCT03808337 | Investigating the Effectiveness of Stereotactic Body Radiotherapy (SBRT) in Addition to Standard of Care Treatment for Cancer That Has Spread Beyond the Original Site of Disease | To determine if SBRT to all oligometastatic lesions can extend time to progression |
| NCT02417662 | Stereotactic Ablative Radiotherapy for Oligometastatic Non-small Cell Lung Cancer (SARON) | Phase III study of efficacy and safety in oligometastatic NSCLC patients comparing conventional ChT alone to ChT plus conventional radiotherapy to the primary tumor and SBRT to the metastases |

SBRT: Stereotactic body radiation therapy; NSCLC: Non-small cell lung cancer; ChT: Chemotherapy; PFS: Progression-free survival; OS: Overall survival.

As we await the results of ongoing randomized phase III trials, the main international clinical guidelines recommend a multimodal strategy to manage this subgroup of oligometastatic patients. Current guidelines recommend systemic therapy combined with local treatment of the metastases and, if applicable, the primary tumor. However, the optimal therapeutic approach for the specific type of oligometastatic disease (intracranial *vs* extracranial, synchronous *vs* metachronous) remains to be defined. Given that no studies have been performed to compare radiotherapy to surgery in this setting, treatment selection (surgery *vs* radiotherapy, with or without systemic treatment) must be based on individualized prognostic factors, which allow us to classify patients in order to select the most appropriate therapeutic strategy for that particular patient. In the future, the availability of molecular or microRNA profiles is expected to improve patient selection.

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ORIGINAL ARTICLE

Retrospective Cohort Study

# Endometrial cancer among a cohort of urban Haitian immigrants

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## Abstract

***BACKGROUND***

Black women are known to have a higher risk of aggressive endometrial cancers. Little data exist about the role of nativity as a determinant of survival outcomes in women with this disease.

***AIM***

Our objective was to evaluate a population of Haitian immigrants with endometrial cancer in an urban setting using the Florida Cancer Data System (FCDS).

***METHODS***

A search of FCDS identified 107 women born in Haiti and who received treatment for invasive endometrial cancer in Miami-Dade County between 1989 and 2013. Clinicopathologic data were extracted to describe the cohort and assess associations with overall survival. Statistical analyses were performed using Cox proportional hazards models, the log-rank test, and the Kaplan-Meier method, with significance set at $P \leq 0.05$.

***RESULTS***

Median age at diagnosis was 65 years. 63.9% of the patients had a type II, high-grade, histology, and 52.6% presented with extrauterine metastatic disease. Nearly three quarters had health insurance. Within the entire cohort, only presence of extrauterine disease was associated with worse overall survival [Hazard ratio (HR) = 2.70, 95% confidence interval (CI): 1.31-5.57, $P = 0.007$].

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However, after stratification by histologic grade, both age (HR = 0.88, 95%CI: 0.81-0.96, $P$ = 0.002) and extrauterine disease (HR = 2.49, 95%CI: 1.01-6.21, $P$ = 0.049) were independently associated with worse survival, but only in women with type II malignancies.

*CONCLUSION*
Urban Haitian women with endometrial cancer have a high burden of aggressive histologies. Additional investigation to explain the etiology of these findings is needed.

**Key words:** Endometrial cancer; Nativity; Haitian; Black; Survival



**Core tip:** Black women of Haitian nativity have a higher prevalence of type II endometrial cancers than previously reported in other large, population-based studies performed in the United States. Further investigation into the genetic, epigenetic, and behavioral determinations of this observed health outcome is necessary.

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## INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy in the United States, with nearly 62000 cases diagnosed annually[1]. Cancers of the endometrium are categorized as either low-grade or high-grade depending on specific pathologic features[2]. Low-grade, or type I tumors, have glandular endometrioid histologies, and usually arise in the setting of hyperestrogenism. In contrast, high-grade, or type II tumors, develop in the setting of aggressive driver mutations, metastasize early, and are relatively refractory to treatment. It has been well described that minority women, especially black women, have a higher risk for these aggressive tumors, with worse outcomes, as compared to white women[3,4]. In fact, the proportion of type II histologies among black women is nearly twice that of white women, with significant disparities in subsequent cancer deaths[5,6]. The full etiology of these findings has yet to be elucidated. Recent data have suggested, however, that among black women with type II endometrial cancer, nativity plays a role in determining endometrial cancer outcomes, and that women born in the Caribbean, despite limitations in access to care, have favorable survival in comparison to United States-born black women[7].

The black population in the United States is quite diverse. One in ten is foreign born, and of the non-Hispanic blacks in the United States, over 50% are Caribbean nationals[8,9]. The largest contributor to Caribbean black immigrations is Haiti. Between 1980 and 2015, the population of Haitian immigrants in the United States increased more than 7-fold to 676000, with the largest communities settling in Miami-Dade and Broward counties in South Florida and Kings county in New York[10,11]. While Haitian immigrants account for < 2% of the entire United States foreign-born population[11], they represent a large group with unique health habits and approaches to medical care[12,13]. As we continue to develop robust personalized cancer programs, understanding disease processes within unique subpopulations of patients is crucial. Our objective was to evaluate patterns of endometrial cancer among Haitian immigrants in Miami-Dade County, and determine factors that affect survival outcomes in these women.

## MATERIALS AND METHODS

Data on endometrial cancer were obtained from Florida Cancer Data System (FCDS), the state cancer registry. All reportable malignant cancer cases in the state of Florida must be reported to FCDS by legislative mandate. FCDS is nationally certified by the

North American Association of Cancer Registries, has been collecting data since 1981, and includes reporting from 230 hospitals within the state.

This study was completed under a larger, state-approved institutional review board protocol for abstraction of FCDS data. The FCDS database was searched for a cohort of women diagnosed with endometrial cancer (ICD-0 C54.1), with data further restricted by county (Miami-Dade = 86) and country of birth (Haiti = 242). Data were extracted from 1989-2013 and represented the most up-to-date entries from FCDS. Of the more than 26000 women with endometrial cancer in the FCDS, data on the women who met the specific inclusion criteria were provided to the investigators. All women were ≥ 18 years of age. Extracted variables included age at diagnosis, tumor histology, date of diagnosis, date of death or last follow-up, vital status, tobacco use, receipt of chemotherapy, radiation, or surgery, positivity of lymph nodes and number of positive lymph nodes, presence of extrauterine metastasis, and type of insurance. Presence of extrauterine metastasis acted as a surrogate for low-stage *vs* high-stage disease, as tumor outside of the uterus is what characterized stage III and IV disease by the International Federation of Obstetrics and Gynecology systems. Histologic codes were used to classify patients into low-grade (low + moderate differentiation) and high-grade (poorly differentiated + anaplastic). Histologic subtypes were cross-referenced with the grading codes to ensure appropriate designation as high-grade/low-grade subtypes. Age and number of positive lymph nodes were evaluated as continuous variables, while all others were coded as binary (yes/no) for analyses. Overall survival was defined as time from date of diagnosis to death (all-cause).

Statistical analyses were performed using STATA IC 14.2 (StataCorp, College Station, TX, United States). To avoid bias, all patients were included in the analyses, even when missing specific data points, and all available data were included. Summary statistics were used to describe the patient cohort. Univariable and multivariable Cox proportional hazards regression, the log-rank test, and the Kaplan-Meier method were utilized to assess survival outcomes, with 95% confidence interval (CI) generated. To avoid inadvertently eliminating potential confounding factors affecting survival, stepwise backwards multivariable regression analyses included covariates with $P$ values ≤ 0.10 from the univariable models. All tests were two-sided, with significance set at $P < 0.05$.

## RESULTS

### Patient characteristics

Over the study interval, 107 patients were identified who met inclusion criteria. Patient demographics are shown in Table 1. The median age was 65 years, and more than half of the patients had private insurance coverage. The majority of women were never smokers. Nearly two-thirds (63.9%) of the patients had high-grade disease, and 21.1% had positive lymph nodes at diagnosis. The number of positive lymph nodes ranged from 1-15 in these women, with a median of four. Surgery was included as a component of the treatment plan in 81.3% of patients, with similar proportions receiving chemotherapy (30.8%) and radiation (30.8%). More than half of the patients had extrauterine disease at the time of diagnosis. At the end of the study period, 41 patients had active disease, and 41 patients had died.

### Overall survival

Table 2 shows the proportional hazards models for overall survival in the cohort. In the univariable model, both chemotherapy [Hazard ratio (HR) = 1.98, 95%CI: 1.00-3.92, $P$ = 0.05] and extrauterine disease (HR = 2.81, 95%CI: 1.38-5.74, $P$ = 0.005) were negatively associated with overall survival, while histologic grade (HR = 1.89, 95%CI: 0.93-3.83, $P$ = 0.08) trended towards a negative effect. In the multivariate model, only extrauterine disease (HR = 2.70, 95%CI: 1.31-5.57, $P$ = 0.007) remained independently predictive of worse survival. Age, surgery, radiation, tobacco use, and type of health insurance had no associations with overall survival.

Because of the previously well-described negative associations between grade and survival outcomes in endometrial cancer, additional survival analyses were performed with stratification by grade (Table 3). Among type I histologies, there were no individual variables which were predictive of outcome, though extrauterine disease trended towards a negative association (HR = 2.96, 95%CI: 0.86-10.19, $P$ = 0.08). Among women with type II histologies, older age (HR = 0.89, 95%CI: 0.83-0.95, $P$ = 0.001) and extrauterine disease (HR = 2.75, 95%CI: 1.12-6.78, $P$ = 0.03) were predictive of overall survival in the univariable analyses. These relationships were maintained in the multivariable model, with both age (HR = 0.88, 95%CI: 0.81-0.96, $P$ = 0.002) and extrauterine disease (HR = 2.49, 95%CI: 1.01-6.21, $P$ = 0.049) remaining

**Table 1 Cohort demographics**

| Variable | *n* = 107 (%) |
|---|---|
| Age at diagnosis | |
| Median (range) | 65 (39-90) |
| Insurance | |
| None | 24 (26.1) |
| Government | 17 (18.5) |
| Private | 51 (55.4) |
| Tobacco use | |
| Current/Former | 15 (14) |
| Never | 92 (86) |
| Histologic grade | |
| Low-grade | 35 (36.1) |
| High-grade | 62 (63.9) |
| Surgery performed | |
| Yes | 87 (81.3) |
| No | 20 (18.7) |
| Chemotherapy | |
| Yes | 33 (30.8) |
| No/Unknown | 74 (69.2) |
| Radiation | |
| Yes | 33 (30.8) |
| No/Unknown | 74 (69.2) |
| Positive lymph nodes | |
| Yes | 12 (21.1) |
| No/Unknown | 45 (78.9) |
| Number of positive lymph nodes | |
| Median (range) | 4 (1-15) |
| Extrauterine disease | |
| Yes | 50 (52.6) |
| No | 45 (47.4) |

Totals by variable may differ due to data availability.

predictive of changes in survival outcomes. The median overall survival for patients with type I histologies was 110 mo *vs* 23 mo with type II histology (log-rank $P = 0.07$).

Graphic depiction of survival in the cohort is shown in Figure 1. The median overall survival for the cohort was 38.8 mo (range 0-176 mo), with a 5-year overall survival of 41.2%. When further evaluated by presence of risk factors associated with disease progression and dissemination, significant differences in overall survival were seen. Among women with positive pathologic lymph nodes, median survival was 16 mo *vs* 67 mo in those with negative lymph nodes (log-rank $P = 0.022$) (Figure 2). Even more profound differences were seen in overall survival when patients were classified by the presence of any extrauterine disease. Women with disease confined to the uterus had a median survival of 88 mo. In contrast, among those with tumor which had spread outside of the uterus, median survival was only 19 mo (log-rank $P = 0.003$) (Figure 3).

## DISCUSSION

The rate of endometrial cancer is increasing globally. While much of this is related to the growing epidemic of obesity, it is important to recognize the diversity of this disease and other factors that may be influencing disease propagation and development. The incidence rate of endometrial cancer is growing faster among non-Hispanic black women than other racial groups[6]. Understanding the role of nativity and shared experience beyond just race is understudied, but likely relevant. Here we present the first data on endometrial cancer in women of Haitian descent.

**Table 2 Cox proportional hazards model for overall survival in entire cohort**

| Variable | Univariable | Multivariable |
|---|---|---|
| | HR (95%CI), *P* value | HR (95%CI), *P* value |
| Age at diagnosis (continuous) | 0.97 (0.92-1.01), 0.16 | |
| Histologic grade | | |
| Low | -- | -- |
| High | 1.89 (0.93-3.83), 0.08 | 1.41 (0.68-2.96), 0.36 |
| Surgery | | |
| No | -- | |
| Yes | 0.56 (0.23-1.34), 0.20 | |
| Chemotherapy | | |
| No | -- | -- |
| Yes | 1.98 (1.00-3.92), 0.05 | 1.50 (0.72-3.12), 0.28 |
| Radiation | | |
| No | -- | |
| Yes | 0.63 (0.32-1.23), 0.18 | |
| Tobacco use | | |
| Never | -- | |
| Ever | 1.10 (0.46-2.63), 0.84 | |
| Site of disease | | |
| Uterine confined | -- | -- |
| Extrauterine | 2.81 (1.38-5.74), 0.005 | 2.70 (1.31-5.57), 0.007 |
| Insurance status | | |
| Uninsured | -- | |
| Government insurance | 0.88 (0.58-1.33), 0.55 | |
| Private insurance | 1.14 (0.43-3.02), 0.80 | |

HR: Hazard ratio; CI: Confidence interval.

Several important points are appreciated from our data, the most important of which is the large proportion of women with type II endometrial cancers. In other population-based studies completed within the United States, the proportion of black women with type II histologies is reported to be between 29% and 43%, a stark contrast to the 63.9% of Haitian women in our cohort with high-grade histologies[5,6,14]. While there are limitations in cross-study comparisons, it should be noted that these data were evaluated using the Surveillance, Epidemiology, and End Results Program, which does not include states with significant Afro-Caribbean representations[5,6], or from Health Care Financing Administration data files with representation from the western United States[14]. Other studies which have evaluated populations inclusive of more women with either African or Afro-Caribbean roots have demonstrated similar findings to ours. For example, Creque *et al*[15] evaluated a cohort of women in Brooklyn, nearly two-thirds of which had Afro-Caribbean ancestry, and found that 59.3% of women had high-grade cancers. In a single-institution study completed in Miami, the proportion of women with endometrial cancer of Afro-Caribbean nativity with a type II endometrial histology was 72.2%[7]. It is clear that women from the Caribbean, including the population of Haitian immigrants in our current study, demonstrate a higher proportion of type II endometrial cancer than black women elsewhere in the United States. Additional study into the etiology of disease in these women and mediators of disease development is required.

More than 52% of the women presented with extrauterine disease in this cohort. This proportion is greater than the 42.9% reported among non-Hispanic black women in other large series[6]. Stage at presentation is a complex issue, but should be evaluated through a number of lenses, one of which is genetic determinants of aggressive disease. Based on data from The Cancer Genome Atlas, the most frequently mutated gene among black women is *TP53*. *TP53* is a tumor suppressor gene present in the majority of type II endometrial cancer histologies. In the tumors of black women with a *TP53* mutation, it has been reported that there are more than double the number of somatic copy number variations associated with tumor aggressiveness as compared with white women[16,17]. Additionally, tumors from black

**Table 3 Cox proportional hazards models for overall survival among Haitian immigrants**

| Variable | Type I | | Type II | |
|---|---|---|---|---|
| | Univariable | Multivariable | Univariable | Multivariable |
| Age at diagnosis (continuous) | 1.04 (0.94-1.14), *P* = 0.47 | -- | 0.89 (0.83-0.95), *P* = 0.001 | 0.88 (0.81-0.96), *P* = 0.002 |
| Surgery | | | | |
| No | -- | -- | -- | -- |
| Yes | Not calculated | | 0.70 (0.26-1.86), *P* = 0.47 | |
| Chemotherapy | | | | |
| No | -- | -- | -- | -- |
| Yes | 1.26 (0.27-5.98), *P* = 0.77 | | 1.99 (0.84-4.71), *P* = 0.12 | |
| Radiation | | | | |
| No | -- | -- | -- | -- |
| Yes | 0.33 (0.07-1.56), *P* = 0.17 | | 0.52 (0.23-1.17), *P* = 0.12 | |
| Tobacco use | | | | |
| Never | -- | -- | -- | -- |
| Ever | 1.97 (0.24-16.03), *P* = 0.52 | | 0.69 (0.26-1.84), *P* = 0.46 | |
| Site of disease | | | | |
| Uterine confined | -- | -- | -- | -- |
| Extrauterine | 2.96 (0.86-10.19), *P* = 0.08 | | 2.75 (1.12-6.78), *P* = 0.03 | 2.49 (1.01-6.21), *P* = 0.049 |
| Insurance status | | | | |
| Uninsured | -- | -- | -- | -- |
| Government insurance | 1.22 (0.41-3.69), *P* = 0.72 | | 0.86 (0.54-1.37), *P* = 0.53 | |
| Private insurance | 3.69 (0.41-33.34), *P* = 0.25 | | 0.74 (0.21-2.61), *P* = 0.64 | |

women more frequently demonstrate amplifications of chr1q, a region that codes for a family of S100A proteins[16]. These proteins are associated with higher recurrence rates in breast cancer, as well as activation of the epithelial-to-mesenchymal transition, a driver of metastasis, in endometrial malignancies[16,18]. At present, there have been no studies to evaluate tumor-level genomics in Haitian women, so the roles of these genes are unknown. Whole exome sequencing may be of use to identify molecular drivers of disease and metastasis, and potentially assist in optimization of oncologic treatment planning.

When examining disparities in care between immigrants and United States-nationals, a number of sociodemographic factors are typically evaluated as mediators of outcome. Access to care, and specifically insurance acquisition, is a frequent limitation in immigrant populations, and may explain delays in disease diagnosis and stage shifts for foreign-nationals. Inability to find enrollment offices, language barriers confounding communication with enrollers, and perceived discrimination against immigrants have all been identified as barriers to insurance enrollment[19-21]. These obstacles prevent access to primary care and cancer screenings, with subsequent negative downstream effects[22,23]. Interestingly, in our population of women, nearly 74% of women had coverage either through private insurance (55.4%) or federal/state programs (18.5%). These findings reflect Miami-Dade County census bureau data, which reported that among the Haitian immigrant population, approximately 79% have insurance coverage[11]. While Haitian immigrants are three times more likely to be uninsured than persons born in the United States, they have higher rates of public/government insurance coverage than other immigrants in the county[11]. In evaluating this population to understand why women present at late stages, it is thus insufficient to attribute stage shifts to socioeconomic factors alone, and that tumor biology and genetics warrant equal attention.

Our study has several limitations. As the data were acquired from a large tumor registry, it is subject to the inherent biases associated with such databases. Data entry error, inconsistency in reporting, and heterogeneity in reporting sites are all potential confounders. The sample size was very low, and over the long duration inclusive of our study, it is highly likely that the numbers of Haitian women with endometrial cancer are underreported. This may be due in part to a hesitation of Haitian patients to declare their immigrant status and place of birth. It has been well-documented that legal status and preoccupations about both disclosure and deportation are of significant concern for immigrants[24]. As such, the small cohort limited statistical

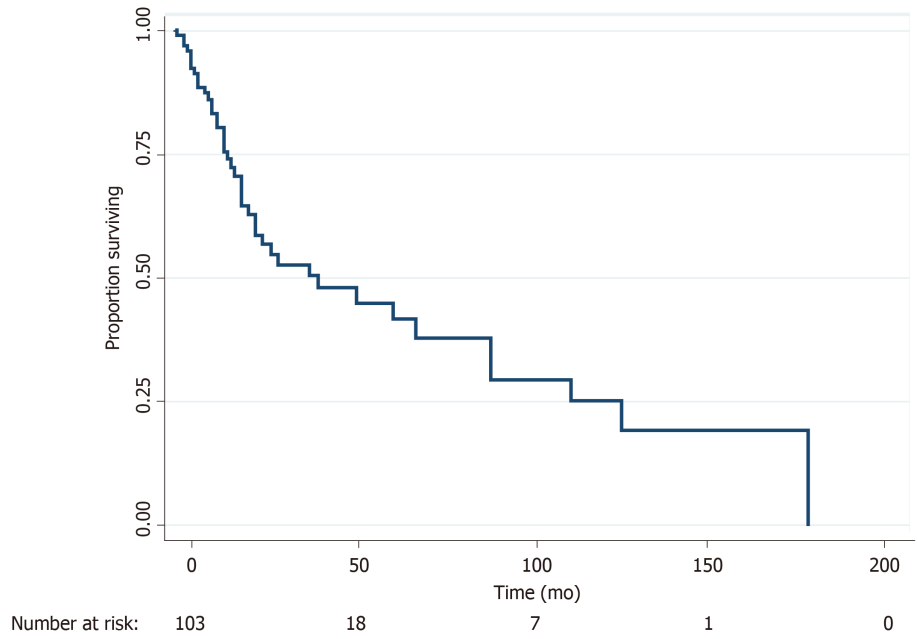


**Figure 1 Overall survival among Haitian immigrants with endometrial cancer.** Median overall survival for the cohort was 38.8 mo, with a 5-year overall survival of 41.2%.

analyses; larger populations may provide better and more accurate associations between clinicodemographic variables and outcome. Even so, this is the first report of endometrial cancer in Haitian women. It generates a number of additional questions regarding etiology of disease, cancer risk, and modifiers of outcome, which should be further explored. Additionally, since Miami-Dade County has the highest number of Haitian immigrants nationally in an urban setting, these data may be applicable to other centers where Haitian immigrant women may be residing.

## *Conclusion*

As more is learned about endometrial cancer in minority patients, it is becoming clearer that evaluation of racial subpopulations, especially among black women, will be increasingly important. Understanding variations in genetic determinants of disease, epigenetic modifications present from environmental exposure or life habits, and the social context of the disease is needed. Nativity as a mediator of both risk and outcome should also be explored. Among Haitian women with endometrial cancer, there is a clear departure from the typical patterns seen among United States-blacks in terms of histologic distribution and stage at presentation. Clinicians should be aware of this risk, particularly when the Haitian patient presents with symptoms of a gynecologic cancer, such as postmenopausal bleeding. A lower threshold to order imaging to rule out metastasis, as well as early tumor marker acquisition, should be considered. Knowledge of this disease pattern may also impact counseling, as with only few exceptions, high-grade endometrial cancer will require chemotherapy. Further work with this population in the form of community advocacy, patient education, and physician awareness should be encouraged as a way to identify improved strategies for screening, prevention, and treatment.

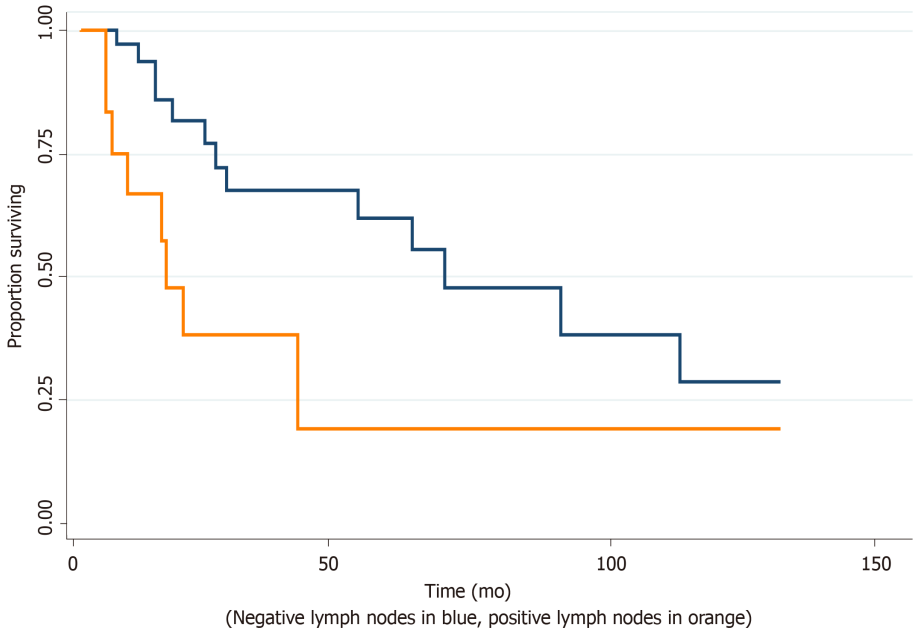


**Figure 2 Overall survival by patterns of metastatic spread.** Significant reductions in survival were seen in patients with lymph node metastasis (log-rank *P* = 0.022).

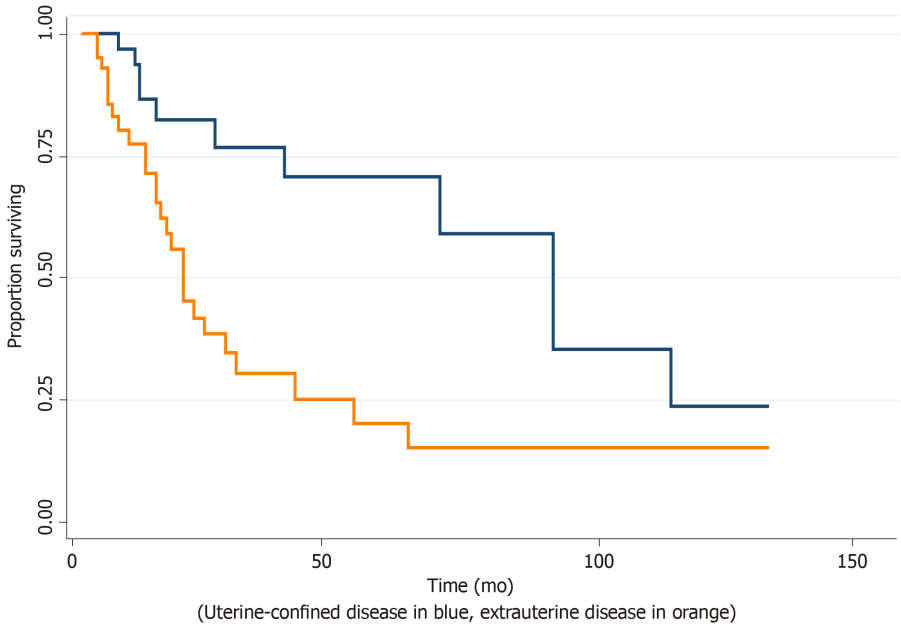


**Figure 3 Overall survival by patterns of metastatic spread.** Significant reductions in survival were seen in patients with any extrauterine disease (log-rank *P* = 0.003).

## ARTICLE HIGHLIGHTS

### *Research background*

Endometrial cancer is the most common gynecologic cancer. Aggressive, type II histologies are known to disproportionately affect black women, but further risk stratification within this group has not been performed.

### *Research motivation*

Miami-Dade County in South Florida is the home to the largest cohort of Haitian immigrants in the United States. A recent single-institution review was performed to evaluate if Caribbean-born black women had different outcomes. Haitian women were under-represented in that study, so the decision was made to utilize a larger state registry to evaluate the burden of disease

in this group.

### Research objectives
The primary objective was to describe a cohort of urban Haitian immigrant women with endometrial cancer and evaluate disease patterns as they compare to other populations of black women.

### Research methods
Utilizing the Florida Cancer Data System, a retrospective cohort study was performed following STROBE guidelines.

### Research results
Sixty-three point nine percent of the patients had a type II, high-grade, histology, and 52.6% presented with extrauterine metastatic disease. After stratification by histologic grade, both age [Hazard ratio (HR) = 0.88, 95% confidence interval (CI): 0.81-0.96, $P$ = 0.002] and extrauterine disease (HR = 2.49, 95%CI: 1.01-6.21, $P$ = 0.049) were independently associated with worse survival, but only in women with type II malignancies.

### Research conclusions
A greater proportion of Haitian women have type II endometrial cancer compared to other black populations in the United States. Prognostic variables for type II histologies were similar to previous reports.

### Research perspectives
The roles of nativity, ancestry, and acculturation in defining endometrial cancer risk are poorly understood in black women. Our results demonstrate that Haitian women have a greater burden of aggressive endometrial cancer than previously reported among black women. Additional research on the hereditary, somatic, and environmental causes of these findings is required.

## ACKNOWLEDGEMENTS

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CASE REPORT

# Vedolizumab in combined immune checkpoint therapy-induced infliximab-refractory colitis in a patient with metastatic melanoma: A case report

Manreet Randhawa, Gregory Gaughran, Christine Archer, Paul Pavli, Adrienne Morey, Sayed Ali, Desmond Yip

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**Author contributions:** Randhawa M, Gaughran G and Archer C contributed equally to this work and wrote the paper; Randhawa M, Gaughran G, Archer C, Pavli P, Morey A, Ali S and Yip D were involved in care of this patient and review and revision of this paper.

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## Abstract

### *BACKGROUND*

Dual checkpoint inhibition improves response rates in treatment naïve patients with metastatic melanoma compared to monotherapy. However, it confers a higher rate of toxicity, including immune-related colitis. Steroids may not resolve symptoms in all cases. The use of vedolizumab, a humanized monoclonal antibody against α4β7 integrin has proven effective in cases refractory to standard treatment.

### *CASE SUMMARY*

We report the case of a 27-year-old female with Stage IVd metastatic melanoma treated with ipilimumab and nivolumab. She developed severe colitis refractory to methylprednisolone, infliximab and mycophenolate mofetil but responded to vedolizumab.

### *CONCLUSION*

This case report supports vedolizumab use in severe immune related colitis refractory to standard immunosuppression.

**Key words:** Ipilimumab; Nivolumab; Metastatic melanoma; Steroid-refractory colitis;

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**Core tip:** Dual checkpoint inhibition improves response rates in treatment naïve patients with metastatic melanoma compared to monotherapy. However, it confers a higher rate of toxicity, including immune-related colitis. The use of vedolizumab, a humanized monoclonal antibody against α4β7 integrin has proven effective in cases refractory to standard treatment. This is a case report of a 27-year-old female with Stage IVd metastatic melanoma treated with ipilimumab and nivolumab. She developed severe colitis refractory to methylprednisolone, infliximab and mycophenolate mofetil but responded to vedolizumab. This supports its use in severe immune related colitis refractory to standard immunosuppression.

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## INTRODUCTION

Combined blockade of cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death protein-1 (PD-1) is the standard of care in selected patients with metastatic melanoma given the improved response rates and overall survival compared with PD-1 inhibitors alone[1]. The use of combined immune checkpoint inhibitors (ICPI's), ipilimumab and nivolumab however also confers a higher rate of toxicity including gastrointestinal immune related adverse events (irAE) which tend to occur earlier when compared to monotherapy[1,2]. Severe irAE's are more common with CTLA-4 inhibitors than with PD-1 blockade, with rates of diarrhea and colitis in melanoma patients on ipilimumab being as high as 34% and 11% respectively compared to 21% and 2% with nivolumab monotherapy[1]. IrAE affecting the gastrointestinal tract are currently managed using algorithms based on severity of symptoms. Mild, grade 1 events can generally be monitored and are managed expectantly. Grade 2-4 events require corticosteroid use, and may require withholding the immunotherapy agent in severe cases and the addition of immunomodulatory agents.

Steroid sparing agents such as mycophenolate mofetil (MMF), tacrolimus or infliximab are established treatment strategies, if no response is seen within 3-5 d[2,3]. Vedolizumab, an IgG1 monoclonal antibody directed against α4β7 integrin has an established role in treating inflammatory bowel disease. It has been shown to be effective in immune-related colitis and in 2017, it was reported as an alternative to infliximab in the European Society of Medical Oncology (ESMO) guidelines[2]. This case illustrates its use in the combined immunotherapy field, specifically after three failed attempts of immunomodulation with agents recommended in current guidelines.

## CASE PRESENTATION

### *Chief complaints*

A 27-year-old female with metastatic melanoma presented to the Emergency Department with diarrhea, rectal bleeding, abdominal pain and nausea 1 d after the fourth cycle of combined immunotherapy with nivolumab and ipilimumab.

### *History of present illness*

The patient presented to the Emergency Department 24 h after cycle 4 with an acute onset of grade 3 diarrhea, per rectal (PR) bleeding, abdominal cramping, nausea and vomiting. She was already receiving oral prednisolone 50 mg daily for resolving grade 2 dermatitis and grade 2 hepatitis.

### *History of past illness and treatment course*

She was diagnosed with a superficial spreading melanoma of her forehead. This was excised in August 2017 and showed a Breslow thickness of 0.5 mm, Clark level III, without ulceration or lymphovascular invasion but positive margins requiring re-excision, achieving clear resection on reattempt.

The patient presented to the emergency department the following month with right upper quadrant pain, headache and mild generalized abdominal discomfort. Computed tomography (CT) chest and abdomen showed bilateral lung nodules and cystic-like structures in the pancreas and positron emission tomography (PET) showed uptake in bone, soft tissue, lung, pancreas, peritoneum, mesentery, left gluteal region and upper abdominal lymph nodes. Fine needle aspirate of the palpable gluteal soft tissue mass was consistent with metastatic melanoma (BRAF wild type). At time of diagnosis, lactate dehydrogenase (LDH) was mildly elevated at 296 IU/L and magnetic resonance imaging (MRI) brain showed a T1 enhancing lesion measuring 13 mm × 12 mm in the left anterior temporal lobe without surrounding vasogenic oedema.

Given her age, BRAF status, high disease burden and good performance status, she was commenced on combined immunotherapy with nivolumab and ipilimumab. Post cycle 1, the patient presented with grade 2 dermatitis over the torso, face and limbs and was commenced on 50 mg prednisolone with prompt resolution. Over the following fortnight, steroids were tapered, LDH normalized and the left gluteal lesion was no longer palpable. After the second cycle, she complained of dizziness, nausea and anorexia. Liver function tests (LFTs) were deranged from a normal baseline with aspartate transaminase (AST) of 265 IU/L, alanine transaminase (ALT) of 233 IU/L, gamma glutamyl transferase of 185 IU/L and alkaline phosphatase of 203 IU/L. She was recommenced on 50mg prednisolone for grade 2 hepatitis. Cycle 3 proceeded while receiving 10 mg prednisolone given the patient was symptom free and LFTs were improving. This was however increased to 50 mg as the ALT again increased from 51 to 144. MRI brain performed at this time, showed a partial decrease in volume of the single brain metastasis. A decision was made by the neurosurgical team to continue surveillance MRI imaging given this early response. On day 65 (1 d after the 4$^{th}$ cycle), the patient presented with grade 3 colitis with diarrhea, PR bleeding, worsening abdominal cramps, nausea and vomiting.

### Personal and family history

Her co-morbidities included asthma and an inflammatory arthropathy with previous steroid use (last acute flare 7 years prior). There was no significant family history.

### Physical examination upon admission

Vital signs were within normal limits. There was generalized tenderness on abdominal palpation but no signs of peritonism. Rectal examination was normal.

### Laboratory examinations

Baseline laboratory results on the day of presentation to the Emergency Department were as follows: Fasting blood glucose 154 g/L; WCC 18.3 × $10^9$/L; Plt 287 × $10^9$/L; Neutrophils 14.84 × $10^9$/L; Bilirubin 7 μmol/L; ALT 97 U/L; LDH 215 U/L; Albumin 39 g/L; Sodium 138 mmol/L; potassium 3.9 mmol/L; Creatinine 66 μmol/L; Urea 5.7 mmol/L; eGFR > 90; TSH 1.90 mu/L; fT3 3.4 pmol/L; fT4 12.2 pmol/L.

### Imaging examinations and other diagnostic work up

CT showed features of colitis and a reduction in the intra-abdominal metastases. Intravenous methylprednisolone was administered (1 g daily for 5 d, subsequently 1 mg/kg prednisolone maintenance) and despite this, an increase in frequency and severity of symptoms to grade IV was seen. Stool culture was negative and colonoscopy showed features consistent with acute colitis with patchy inflammation and ulceration macroscopically to the splenic flexure with no evidence of cytomegalovirus inclusion bodies on histopathology. Nine days after symptom onset, the first dose of infliximab was administered followed by a second dose 3 d later. Initially a reduction in frequency to 5 motions/d was seen, however symptoms worsened 3 d later. On day 20 after symptom onset, she commenced MMF 500 mg bd. Three days later, MMF was increased to 1 g bd with no improvement. A flexible sigmoidoscopy was performed, given concerns of perforation. Macroscopically, she had a high van der Heide score, on histology, increased cellularity of the lamina propria, apoptotic debris, neutrophilic infiltration and crypt abscesses were shown, with an absence of intraepithelial lymphocytes and eosinophils (Figure 1).

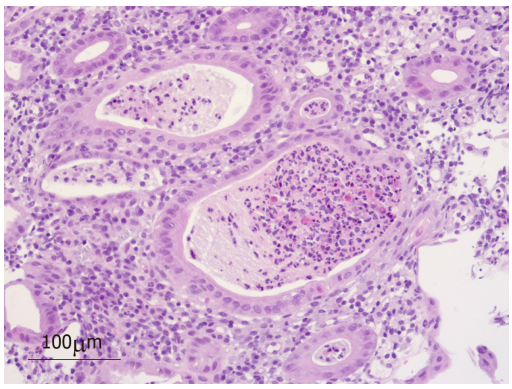


**Figure 1 High power (200 ×) haematoxylin and eosin stained section showing neutrophilic crypt abscesses, no viral inclusion bodies seen.**

## MULTIDISCIPLINARY EXPERT CONSULTATION

***Professor Paul Pavli, Department of Gastroenterology, The Canberra Hospital***

Gastroenterology team was consulted within 24 h of emergency department presentation. Investigations including stool microscopy, culture and sensitivity were performed and steroid sparing agents administered as advised.

## FINAL DIAGNOSIS

Diagnosis was confirmed by colonoscopy showing diffuse moderate inflammation in the sigmoid colon characterized by erosions, erythema, friability, granularity and a loss of vascularity (Figure 2) and histopathology of colonic biopsies showing neutrophilic crypt abscesses (Figure 1).

## TREATMENT

First dose of vedolizumab was administered 42 d from symptom onset resulting in marked attenuation of symptoms 3 d later. A second and third dose were given two weeks apart with complete resolution of diarrhea seen. No side effects were shown with this regime and complete resolution occurred before the third and final dose (Figure 3).

## OUTCOME AND FOLLOW-UP

The patient did not commence maintenance nivolumab due to the severe immune related colitis. A post treatment PET showed near complete metabolic response with a stable MRI Brain and the patient returned to work. Twelve months from treatment, PET has shown an ongoing complete metabolic response.

## DISCUSSION

Combined immunotherapy with ipilimumab and nivolumab is an established approach in higher risk metastatic melanoma, particularly in cases of M1d disease[4]. Other features favouring combination therapy include high LDH at time of diagnosis and high burden of particularly visceral disease[1]. Combined therapy is associated with higher rates of grade 3/4 toxicity compared to nivolumab monotherapy (59% *vs* 21%) with a discontinuation rate of 39.3% predominately due to treatment-related adverse effects[1].

Gastrointestinal toxicity is the most prevalent irAE seen in immunotherapy[1]. It is also the most common cause of grade 3/4 toxicities, occurring in 17% of patients on combined therapy and 4% of patients on nivolumab alone[1]. Colitis, defined as diarrhea, associated with either or both abdominal pain and endoscopic/radiological inflammation, is often the first event leading to discontinuation of therapy[3,5,6]. Up to half of these cases will be steroid-refractory necessitating further

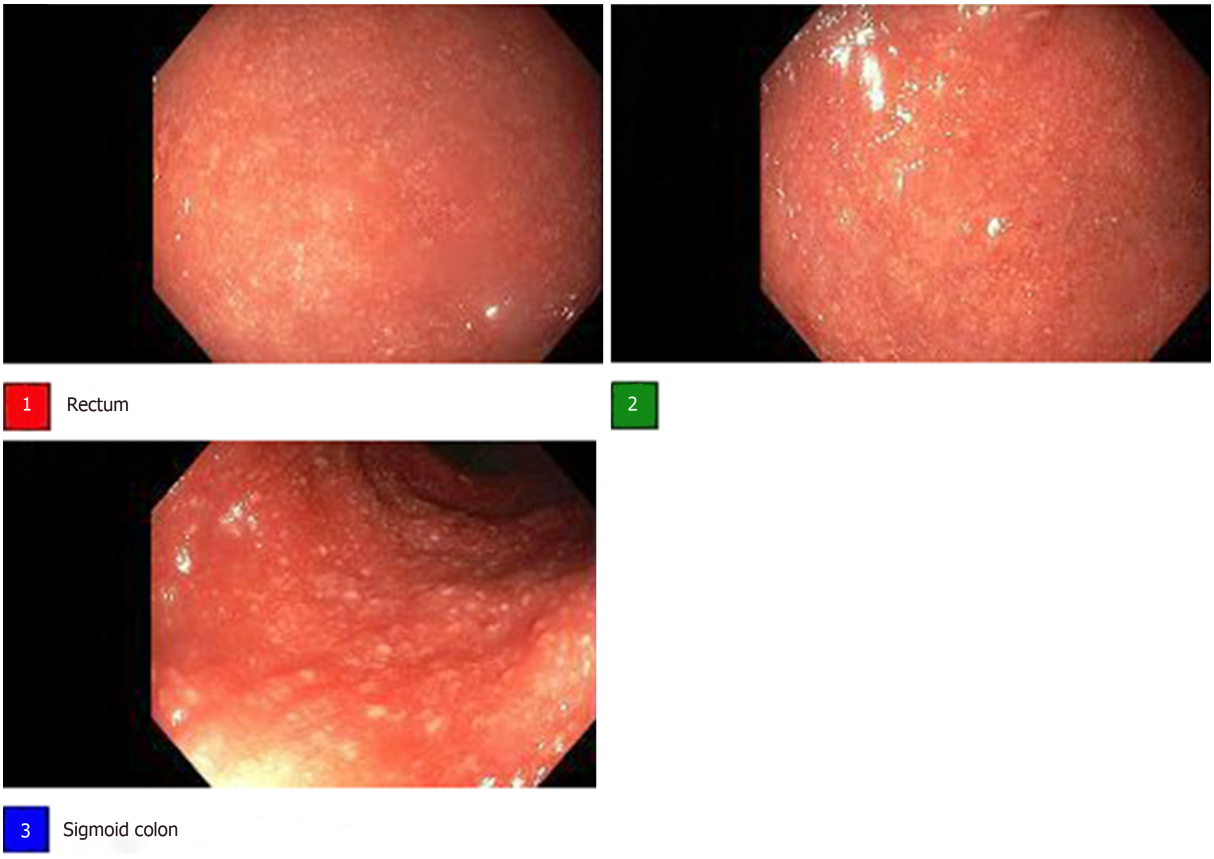


**Figure 2 Colonoscopy prior to infliximab showing diffuse moderate inflammation in the sigmoid colon characterized by erosions, erythema, friability, granularity and a loss of vascularity.**

immunomodulation[7]. It remains challenging to predict who will get colitis and no correlation has been shown with abdominal pain, grade of diarrhea or endoscopic features and the requirement for infliximab[7]. Those with a high score on inflammatory indices, *e.g.*, Van der Heide score on colonoscopy, bloody stools, presence of ulceration or pancolitis will more likely be steroid-refractory[7,8]. No biomarker has to date been consistently shown to predict risk for colitis. However, faecal calprotectin provides a non-invasive measurement of neutrophil flux to the intestine, however[5,7].

Recent literature has made efforts to describe the histology typically encountered in colitis induced by both PD-1 and CTLA-4 inhibitors. This becomes particularly relevant in cases of diagnostic dilemma or in steroid-refractory patients. Findings may include increased lamina propria cellularity, neutrophilic infiltration, crypt abscesses and intraepithelial lymphocytosis usually in the absence of chronic inflammation[5,7]. In most series, the sigmoid is involved and is therefore a reliable biopsy site obtainable with flexible sigmoidoscopy. Particularly in severe cases, Geukes Foppen *et al*[9] advise against performing a colonoscopy if ulceration is seen in the lower colon, in order to avoid perforation. In the case of those without sigmoid involvement, in their analysis, 8% had ascending-only colitis on endoscopy[9]. A large proportion of cases studied also show concomitant upper gastrointestinal involvement on endoscopy[5,7,10].

In managing colitis, along with considering concomitant medications, the clinician must exclude infection with stool culture, cytomegalovirus screening *via* biopsy to rule out inclusion bodies, as well as contemplating the potential for gastrointestinal metastases[11]. As described in current published guidelines, the approach to grade 3/4 diarrhea/colitis, includes withholding the immune checkpoint inhibitor, commencing intravenous methylprednisolone 1-2 mg/kg and obtaining a gastroenterology consult and colonoscopy[2]. If no improvement is shown within 72 h, infliximab 5 mg/kg should be considered[2]. Infliximab as the standard treatment for steroid-refractory patients has a median time to response of 2 d as shown in the case series by Gonzalez *et al*[7].

Vedolizumab is an IgG1 monoclonal antibody that inhibits α4β7 integrin, disabling its interaction with mucosal addressin cell adhesion molecule-1 on intestinal vasculature and stopping T cell migration into the gut[12,13].

Vedolizumab's landmark trial was in patients with ulcerative colitis and Crohn's

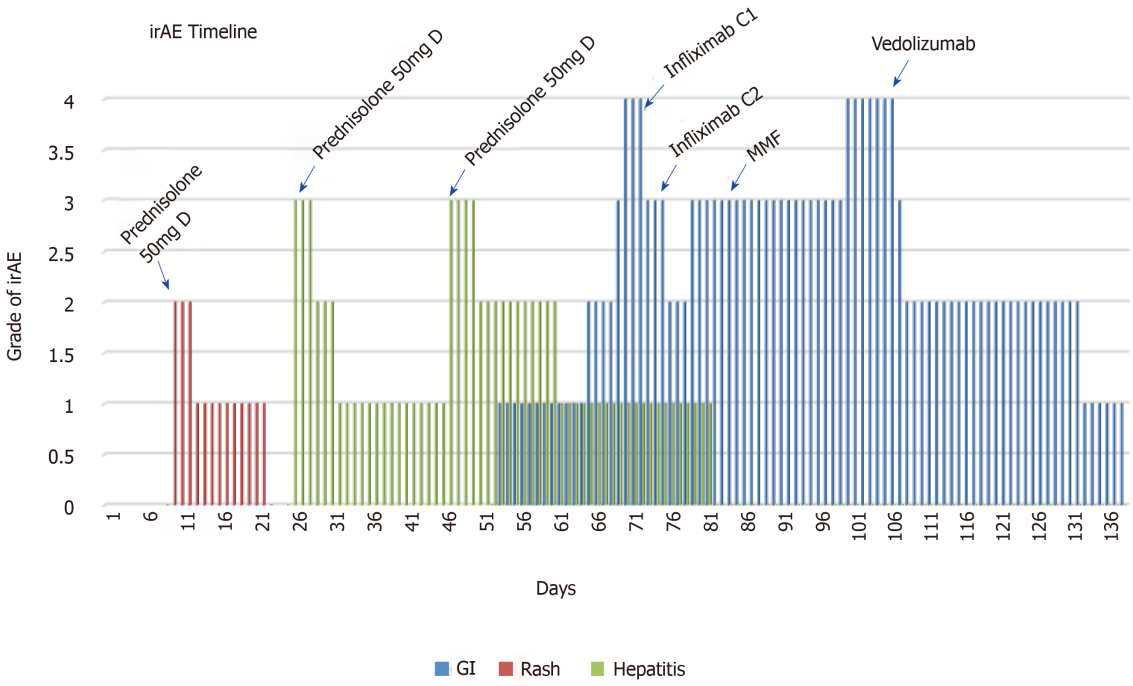


**Figure 3 Immune-related adverse event timeline, showing type and severity of toxicity and time points of treatment intervention.** irAE: Immune-related adverse event.

disease refractory to standard treatments, where it was administered intravenously at 0, 2, 6 wk then every 8 wk as maintenance[13,14]. It had a tolerable side effect profile with mild nasopharyngitis, headache, arthralgia, nausea and fatigue, but no increased rates of infection[12-14].

At the time our patient was treated, literature pertaining to the use of vedolizumab was scarce but was mentioned in several guidelines in the management of immune-related toxicities[15,16]. We have conducted a literature review by searching Pubmed upto April 2019 using the following search strategy: ((“vedolizumab”[Supplementary Concept] OR “vedolizumab” [All Fields]) AND (“cell cycle checkpoints”[MeSH Terms] OR (“cell”[All Fields] AND “cycle”[All Fields]) AND “checkpoints”[All Fields]) OR “cell cycle checkpoints”[All Fields] OR “checkpoint”[All Fields]) AND (“antagonists and inhibitors”[Subheading] OR (“antagonists”[All Fields] AND “inhibitors”[All Fields]) OR “antagonists and inhibitors”[All Fields] OR “inhibitors”[All Fields]))) AND (“colitis”[MeSH Terms] OR “colitis”[All Fields]).

In the context of immune-checkpoint therapy-induced colitis, one of the first case reports published assessing the use of vedolizumab was by Hsieh *et al*[17] in 2016. In the first case series published the year after by Bergqvist *et al*[18], 7 patients with melanoma or lung cancer were assessed. The median time from onset of enterocolitis to start of vedolizumab was 79 d and all patients had monotherapy with ipilimumab for metastatic melanoma[18]. All patients but one had a steroid-free remission with a median time of 56 d from first dose of vedolizumab[18]. The time to onset in our patient was 54 d and overlapped a resolving grade 2 hepatitis.

Abu-Sbeih *et al*[19] assessed outcomes of 28 patients receiving vedolizumab therapy and showed a longer duration of steroid use in patients receiving infliximab compared to no infliximab prior to vedolizumab (131 d compared to 85 d) and higher success rates in the latter group (67% compared to 95%). The median time from the first ICPI infusion to onset of diarrhea was 10 wk, mean duration of corticosteroid therapy was 96 d and median duration from first vedolizumab infusion to improvement of symptoms was 5 d[19].

Abu-Sbeih *et al*[20] also recently performed a retrospective review of patients at MD Anderson Cancer Centre receiving selective immunosuppressive therapy in patients with immune-mediated colitis. A total of 179 patients had colitis and 84 received selective immunosuppressive therapy[21]. Almost half of these patients had grade 3-4 colitis and 95% of patients who had faecal calprotectin tested yielded a positive result[20]. Fifty patients had infliximab and 34 patients had vedolizumab[20]. Rates of recurrence of symptoms were 15/50 in the infliximab group compared to 1/34 in the vedolizumab group[20]. However those receiving infliximab also had fewer infusions[20] which may explain this finding. The authors concluded that receiving infliximab

rather than vedolizumab was a risk factor for recurrence after steroid weaning[20]. Furthermore, early introduction of selective immunosuppressive therapy in the disease course (*i.e.*, < 10 d from onset of colitis) instead of waiting until failure of steroid therapy led to fewer hospitalizations and shorter duration of symptoms[20].

It is encouraging in this case that in spite of this severe episode of colitis, complete metabolic response has been shown on recent imaging despite treatment discontinuation. This correlation of severity of immune-related side effects and efficacy of treatment has been observed in a case series showing a higher response rate in those requiring early discontinuation of therapy due to immune-related toxicity (58.3% *vs* 50%)[21].

## CONCLUSION

This case report adds to the available evidence supporting the use of vedolizumab in the setting of infliximab-refractory immune-mediated colitis. This is the first report in the literature in the combined immunotherapy setting whereby there were three unsuccessful attempts using standard immunomodulatory agents.

Although there have been recent publications in this area, given the increasing indications for immunotherapy in multiple tumour types, further research is still needed in the prospective setting with larger patient groups.

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