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Management of Non-Small Cell Lung Cancer with Oligometastasis

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Abstract

Patients with oligometastatic Non-Small Cell Lung Cancer (NSCLC) present a potential opportunity for curative therapy; however, the challenge remains the definitive treatment of their localized disease and ablation of their limited overt metastatic sites of disease. In selecting patients with oligometastatic NSCLC for definitive therapy, proper staging through radiographic studies, including PET and brain MRI, and the pathologic staging of the mediastinal lymph nodes and potential sites of metastatic disease, are critical. With that in mind, the available literature suggests that in highly selected patients with solitary metastases to the brain, adrenals and other organs, long term survival may be achieved with combined definitive therapy of both the primary lung tumor and the solitary metastatic site.

Keywords

Non-Small Cell Lung Cancer; Oligometastasis; Management

Introduction

Lung cancer is the leading cause of cancer related mortality in the United States [1]. Non-small cell lung cancer (NSCLC) accounts for 85 % of all lung cancers, while small cell lung cancer accounts for about 15 % [2]. Historically, metastatic NSCLC was treated as a single disease entity, and palliative chemotherapy resulted in modest survival prolongation and preservation of quality of life [3–7]. A series of large randomized controlled phase III clinical trials established platinum-based doublets as the standard of care in metastatic NSCLC, with response rates of 20–30 % and a median survival of 8–11 months [8–12].

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Despite advances in the understanding of the molecular aberrations in lung cancer and the development of targeted therapies against the vascular epithelial growth factor (VEGF), the epidermal growth factor receptor (EGFR), and the echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) [13–22], most patients with metastatic NSCLC eventually succumb to their disease.

A small subset of patients with metastatic NSCLC will present with a solitary site of metastatic disease (about 7 % of patients) [23]. Patients with oligometastatic NSCLC present a potential opportunity for curative therapy; however, the challenge remains the definitive treatment of their localized disease and ablation of their limited overt metastatic sites of disease. This review will highlight the available literature with regard to the diagnostic and therapeutic considerations in managing the subset of patients with meta-static NSCLC with a limited number of metastatic sites.

The Oligometastatic State

The paradigm of cancer pathogenesis has been heavily influenced by the Halstead theory, which was first described by Halstead in 1894 in elucidating the mechanism of breast cancer spread [24, 25]. He proposed that cancer spread is orderly, extending in a contiguous fashion from the primary tumor through the lymphatics to the lymph nodes and then to distant sites. The more recently proposed systemic hypothesis postulates that cancer is inherently a systemic disease [26–28]. In this theory, small tumors are just an early manifestation of systemic disease, and lymph node involvement is not an orderly contiguous extension of the cancer, but rather a marker of distant metastasis or micro-metastatic disease. A more unifying hypothesis presented by Hellman synthesizes the contiguous-systemic dialect and argues that cancer comprises a biologic spectrum extending from a disease that is truly localized to one that is systemic at the time of diagnosis, but with many intermediate states [29].

Building on this theory, Hellman and Weichselbaum first proposed the concept of oligometastases in 1995 [30••]. This concept is that the anatomy and physiology of certain tumors may limit metastases to a single or a limited number of organs, and that the likelihood of an oligometastatic state correlates with the biology of tumor progression, the rough clinical correlates of which are the primary tumor size and the tumor grade. Moreover, metastasizing cells seed specific organs as a function of the seeding tumor cell number as well as the receptivity of the host organ. In this theory, the number of metastases should reflect the biologic behavior of the tumor and determines the opportunity and nature of potentially curative therapeutic interventions. Hellman and Weichselbaum propose that there is not only a spectrum of malignancy, but an accompanying spectrum of potentially curative treatments. Tumors early in their progression should be amenable to localized therapy, while patients with oligometastatic disease may be cured with ablative therapy of their metastatic lesions, and patients with more advanced disease should be treated with systemic palliative therapy alone. Though not precisely defined in terms of the exact number of metastatic foci, most clinicians use 5 lesions as the cut-off for oligometastatic disease.

Clinical implementation of the theory of neoplastic pathogenesis put forth by Hellman and the concept of oligometastases proposed by Hellman and Weichselbaum requires the use of the most sophisticated diagnostic techniques. In considering the case series of surgically resected solitary brain lesions from NSCLC, the 5-year survival rates for patients diagnosed in the pre-PET-era prior to 2000 are in general lower (around 13 %) than those of patients diagnosed after 2000 in the so-called PET-era (around 19 %) [31–33, 34•, 35–39]. The trend toward improved survival in the case series published in the PET-era is likely a reflection of improved staging due to the higher sensitivity of PET for sites of metastatic disease, that is, patients in the PET-era are more appropriately selected for definitive oligometastatic therapy. In evaluating patients with oligometastatic NSCLC, it is also important to consider the use of brain MRI as a more sensitive way of evaluating solitary intracranial lesions. CT alone is insensitive to potentially smaller intercurrent intracranial lesions and may lead to an underestimation of a patient's true metastatic disease burden.

When considering the treatment of the oligometastatic state in the modern molecular era, it is also crucial to keep in mind that NSCLC is no longer thought of as a single disease entity, but rather a compilation of molecularly distinct subtypes with differing biologies, natural histories and responses to therapy. Though little is known of the precise natural history of an oligometastatic wild-type NSCLC versus an oligometastatic NSCLC with an underlying EGFR or KRAS mutation or an EML4-ALK rearrangement, it is very likely that the difference in the underlying biology necessitates a difference in approach to treatment. It is reasonable to reserve aggressive treatment of both local and oligometastatic site(s) after a period of observation of 6–12 months, as this allows the natural history of the oligometastatic disease to declare itself. Identifying the patients who remain in the oligometastatic state after a period of observation and do not blossom with multiple sides of metastatic disease allows for the better selection of patients with a more favorable underlying biology who will likely gain the most benefit from aggressive surgical resection.

Oligometastatic NSCLC to the Brain

About 25–30 % of patients with newly diagnosed NSCLC will present with metastatic disease to the brain [40, 41]. Metastatic NSCLC to the brain is often incurable and is associated with an overall survival (OS) of approximately 2 months when treated with steroids alone and 6 months when treated with whole brain radiotherapy (WBRT) [42–44]. However, in retrospective case series of patients with a solitary synchronous brain metastasis who underwent aggressive treatment of both the brain metastasis and the loco-regional disease of the lung, the median OS ranges from 7 to 24 months and the 5-year survival rate ranges from 7–24 %(Table 1) [31–39].

The nodal stage of the patients had a statistically significant association with survival in several of the studies, such as in Billing et al., in which patients with N0 disease (node negative) had a superior 5-year survival compared to patients with N1/N2 disease (ipsilateral hilar/mediastinal nodal involvement) (P=0.001) [33]. In the study by Rossi et al., all of the patients surviving more than 2 years had an N0 pathologic stage and a Karnofsky performance status (KPS) of more than 50 [38]. All of the 5-year survivors in this study had node-negative NSCLC. This suggests that the benefit of a combined surgical approach to

loco-regional lung cancer and a solitary brain metastasis is most significant in highly selected patients with node-negative disease and a good performance status; this underscores the importance of adequate staging by means of diagnostic imaging, including the use of PET-CT, and the surgical staging of the hilar and mediastinal lymph nodes with cervical mediastinoscopy or endobronchial ultrasound-guided fine-needle aspiration (FNA) and biopsy.

In the series by Furak et al., an additional 46 patients were included with a metachronous solitary brain metastasis, which is brain metastasis diagnosed greater than or equal to 2 months after the original diagnosis of NSCLC [31]. This represented about two–thirds of the overall patient population treated with lung resection and brain metastatectomy between 1992–2001 in this series. The median OS for these patients was 12 months with a 5-year survival rate of 16 %, neither of which differed statistically from that of the patients who presented with a synchronous brain metastasis. Patients with a metachronous brain metastasis were also included in the series by Getman et al. (16 patients), Mussi et al. (33 patients) and Burt et al. (120 patients), and in all three series, metachronous presentation of a brain metastasis represented about 60 % of the overall patient population [32,36–37]. There was no statistical difference in the survival outcomes between patients with synchronous versus metachronous brain metastasis. This suggests that there is a similar benefit of aggressive combined surgical therapy of loco-regional NSCLC and solitary brain metastasis in both the synchronous and metachronous metastatic settings.

A number of randomized clinical trials have evaluated neurosurgical resection plus WBRT versus WBRT alone for brain metastases, and these trials suggest that the addition of neurosurgical resection to WBRT is the optimum treatment strategy for brain metastases. It should be noted that although NSCLC was a common histology in all of these studies, they were not limited to NSCLC and did include other tumor types. In a study conducted at the University of Kentucky, 48 patients with a good performance status (KPS more than 70) and solitary brain metastasis from an extra cranial cancer were randomized to complete surgical resection of the brain metastasis with WBRT versus WBRT alone [45]. Surgery with WBRT was associated with a significant increase in OS compared to WBRT alone (40 weeks versus 15 weeks, $P<0.01$) and the preservation of functional independence (38 weeks versus 8 weeks to functional deterioration, respectively, $P<0.005$). A similar study conducted in the Netherlands of 63 patients with a solitary brain metastasis demonstrated that surgery with WBRT was associated with a statistically significant OS prolongation compared to WBRT alone ($P=0.04$) and was associated with a trend toward improved preservation of functional independence [46].

Conversely, a third clinical trial conducted in Canada randomized 84 patients to neurosurgical resection with WBRT versus WBRT alone and failed to demonstrate a survival prolongation with surgery plus WBRT (5.6 months with surgery plus WBRT versus 6.3 months with WBRT alone, $P=0.24$) [47]. This study had a higher proportion of patients with an extra cranial metastatic disease burden (about 20 % of the total study population), and this higher systemic disease burden may have accounted for the lack of survival prolongation with surgery plus WBRT. In addition, MRI of the brain was not mandatory in this clinical

trial, and patients with additional lesions not detected by CT may have been included in the study.

Stereotactic radiosurgery (SRS) is a method for delivering a single, high dose fraction of ionizing radiation to a small, precisely defined target volume and has been evaluated in the treatment of patients with metastatic brain tumors. In the RTOG 9508 clinical trial, 333 patients with 1–3 newly diagnosed brain metastases were randomized to either WBRT versus WBRT with an SRS boost and were stratified based on the number of metastases and the status of the extra cranial disease [48]. The diameter of the largest lesion could not exceed 4 cm with additional lesions not exceeding 3 cm and were deemed unresectable if they were located in the deep grey matter or in the eloquent cortex. In this clinical trial, the addition of SRS to WBRT improved median OS relative to WBRT alone only for the patients with solitary brain metastasis (6.5 months for WBRT plus SBRT versus 4.9 months for WBRT alone, P=0.0393). Though in all patients (1–3 brain metastases), WBRT plus SRS was associated with a preservation in the performance status of patients at 6 months compared to WBRT alone (43 % versus 27 %, P=0.03).

In a study conducted at the University of Pittsburgh, 27 patients with 2–4 brain metastases less than 2.5 cm in diameter were randomized to WBRT alone versus WBRT plus SRS [49]. This study was stopped at 60 % of its target accrual due to the significant positive tumor control differences at the interim analysis. In this clinical trial, WBRT plus SRS was associated with a significant reduction in time to local failure compared to WBRT alone (36 months versus 6 months, respectively, P=0.0005). Though there was a trend toward improvement, survival was not significantly impacted with WBRT plus SRS versus WBRT alone (11 months versus 7.5 months, P=0.22). Taken together, these studies suggest that WBRT with SRS is a reasonable alternative to surgical resection for patients with unresectable metastatic brain disease. In addition, SRS with WBRT can be considered in patients with more than one brain metastasis (and likely not more than four), though survival is only significantly impacted in patients with solitary lesions.

A consideration in the treatment of oligometastatic brain disease is the avoidance of the neurocognitive morbidity associated with WBRT. A randomized clinical trial of 132 patients with no more than 4 brain metastases, all less than 3 cm in diameter, assigned patients to SRS alone versus SRS with WBRT [50]. This trial demonstrated similar survival between the SRS alone treated patients and the patients treated with SRS plus WBRT (8.0 months versus 7.5 months, P=0.42), though salvage brain treatment was needed more frequently in the patients treated with SRS alone (P<0.001). This implies that patients with oligometastatic brain metastases can be treated without the upfront morbidity of WBRT, and that WBRT can likely be reserved for the salvage setting.

There are no prospective clinical trials comparing neuro-surgical resection with WBRT versus SRS with WBRT, though a randomized phase III clinical trial was conducted comparing neurosurgery plus WBRT versus SRS alone in the treatment of a solitary brain metastasis no greater than 3 cm in diameter, in patients with a preserved performance status [51]. This study was terminated early due to poor accrual making the results difficult to

interpret. However, of the 64 patients enrolled, there was no significant difference in survival (P=0.8) in patients treated with SRS alone versus surgery plus WBRT.

Oligometastatic NSCLC to the Adrenal

In patients with NSCLC, adrenal metastases are common and occur in 10–59 % patients in autopsy series [52]. In a series of 202 patients who underwent curative resection for lung cancer who came to autopsy within 1 month of their pulmonary resection, about 9 % patients harbored clinically unsuspected metastases to the adrenal gland [53]. Though adrenal metastases are often a harbinger of disseminated disease, a small fraction of patients will present with an isolated adrenal metastasis. In a series of 246 patients with otherwise operable NSCLC, 10 (4.1 %) patients were found to have unilateral adrenal masses [54]. Subsequent pathologic evaluation, either through FNA or adrenalectomy, demonstrated that 4 (1.6 %) patients had a unilateral adrenal metastasis from an otherwise operable NSCLC. While widely metastatic NSCLC is incurable and treated with palliative intent, patients with an isolated adrenal metastasis represent a population in whom long term survival is potentially achievable. In several retrospective case series of NSCLC patients with an isolated adrenal metastasis who underwent surgical resection of their primary tumor in addition to an adrenalectomy, the median OS ranges from 11 to 31 months and the 5-year survival rate ranges from 7–60 % (Table 2) [55–62].

As with oligometastatic NSCLC to the brain, diligent staging is integral to identifying patients that are appropriate for surgical resection of an isolated adrenal metastasis. In a retrospective series by Kim et al., 1738 patients with operable NSCLC were identified between 1997 and 2005 and were staged with PET-CT and MRI of the brain [63]. Forty patients were subsequently identified as having an adrenal mass by PET-CT. Twenty-five patients were deemed to have a radiographically benign adrenal tumor (size less than 1 cm, homogeneous low attenuation on CT, or FDG-avidity less than that of the liver) and were referred for surgical resection of their intrathoracic tumor (group 1). Fifteen patients did not fit the criteria for having benign tumors and were subsequently referred for MRI of the abdomen for further evaluation. Of these patients, 8 were thought to have benign adrenal tumors by MRI signal intensity and were referred for surgical resection of their lung tumor (group2) and 7 were deemed to have indeterminate adrenal tumors and were referred for adrenalectomy for pathologic diagnosis (group 3). One patient in group 1 (4 %) was subsequently found to have an adrenal metastasis 2 months after their lung surgery. In group 2, three patients (38 %) were found to have an adrenal metastasis as demonstrated by a radiographically enlarging adrenal mass at the time of their lung surgery, and in group 3, one patient (14 %) had a pathologically confirmed adrenal metastasis, while 6 had benign lesions. These findings highlight the limitations of MRI in delineating the nature of indeterminate adrenal masses and emphasize the necessity of pathologic staging of an adrenal mass prior to consideration of surgical resection of the primary lung tumor.

Synchronous adrenal metastases, usually defined as having presented with a disease free interval (DFI) of less than 6 months from the primary diagnosis of lung cancer, are thought to be associated with a poor prognosis compared to metachronous adrenal metastases (occurring more than 6 months from the primary diagnosis of lung cancer.) In a review

conducted by Tanvetyanon et al., data from 114 patients from 10 publications of NSCLC patients with an adrenal metastasis who underwent adrenalectomy were pooled to determine if prognosis was affected by a synchronous versus a metachronous presentation (Table 2) [57]. In this pooled analysis, 48 patients (42 %) had a synchronous metastasis and 66 patients (58 %) had a metachronous metastasis. The median OS for patients with a synchronous metastasis was significantly shorter compared to patients with a metachronous metastasis (12 months versus 31 months, respectively, generalized Wilcoxon P=0.02). However, the 5-year survival did not differ between the two groups (26 % for synchronous presentation versus 25 % for metachronous presentation.) The influence of a synchronous versus a metachronous presentation on survival outcome has not been seen in smaller retrospective case series (Table 2).

The laterality (ipsilateral versus contralateral to the primary lung tumor) of an adrenal metastasis has been considered a prognostic factor in the evaluation of oligometastatic NSCLC. It is thought that retroperitoneal lymphatic passages allow for direct spread of tumor cells between the lung and the ipsilateral adrenal gland, and that an ipsilateral adrenal metastasis may be associated with better prognosis relative to a contralateral adrenal metastasis that is hematogenous in origin [64]. In the retrospective case series by Raz et al., 20 patients underwent lung resection and complete adrenalectomy for oligometastatic NSCLC (Table 2) [55]. Of these patients, 7 patients (35 %) had an adrenal metastasis ipsilateral to the primary tumor and 13 patients (65 %) had a contralateral adrenal metastasis. Patients with an ipsilateral adrenal metastasis had a 5-year survival rate of 83 % compared to 0 % for patients with a contralateral metastasis (P=0.003).

There have been no prospective trials evaluating the use of open adrenalectomy (OA) versus laparoscopic adrenalectomy (LA) for the treatment of oligometastatic cancer to the adrenal glands. In a retrospective case series of patients with adrenal metastases reported by Strong et al., patients who underwent an OA (n=63), of whom 18 had NSCLC, were compared to patients who underwent a LA (N=31), of whom 21 had NSCLC [65]. Of these patients, there was no significant difference in OS between the OA and LA groups either for the overall patient population (P=0.43) or for the patients with NSCLC (OA 1- and 3-year survival rates of 69 % and 41 % versus LA 1- and 3-year survival rates of 58 % and 49 %, P=0.96). Patients with adrenal metastases greater than 4.5 cm had inferior survival (P= 0.008) and an increased local recurrence rate with an LA compared to an OA (P=0.01). LA was associated with a shorter operative time, a lower estimated blood loss during surgery and a shorter length of hospital stay. Though a minimally invasive adrenalectomy may improve operative morbidity and may be associated with similar survival compared to an OA, the use of LA for the treatment of an adrenal metastasis remains controversial.

Similar to SRS, stereotactic body radiotherapy (SBRT) uses high doses of very conformal radiation to areas outside the CNS. There have been no prospective trials evaluating SBRT for the treatment of an isolated adrenal metastasis from NSCLC. However, a retrospective case series published by Holy et al. reported a median OS of 23 months from 13 patients treated with SBRT for an isolated adrenal metastasis from NSCLC (Table 2) [56]. SBRT was reasonably tolerated with the exception of 2 patients who developed upper gastrointestinal tract ulcers. SBRT in the treatment of oligometastatic NSCLC to the adrenal is an intriguing

approach, though it is considered investigational, and adrenalectomy remains the standard of care.

Oligometastatic NSCLC to Other Sites

There is limited literature with regard to the role of metastatectomy for the treatment of an extracranial extra-adrenal NSCLC solitary metastasis. However, a recent pooled analysis of cases from the published literature by Salah, et al. described 62 patients from 51 publications who underwent metastatectomy for solitary sites of metastasis from NSCLC, exclusive of metastasis to the brain and the adrenal [66•]. Of the 62 patients reviewed, 33 (53 %) had a non-visceral solitary metastasis and 29 (47 %) had a visceral metastasis. The most common sites were bone (n=13), liver (n=9), kidney (n=7) and spleen (n=6). Data were available with regard to the temporal presentation of the metastasis in 58 patients, and of these, 20 (34 %) were synchronous (DFI less than 6 months) and 38 (66 %) were metachronous (DFI greater than 6 months) in nature. Nodal staging was known in 37 patients: 25 patients (68 %) had N0 disease, 5 patients (14 %) had N1 disease, 6 patients (16 %) had N2 disease and 1 patient (2 %) had N3 disease. Fifty-eight patients underwent curative resection of the primary lung tumor and 4 patients were treated with definitive chemoradiotherapy. The combination of definitive therapy of the lung tumor and metastatectomy of the solitary extra cranial extra-adrenal metastasis resulted in a 5-year survival rate of 50 %.

Patients with a non-visceral metastasis had similar OS compared to patients with a visceral metastasis (5-year survival of 63 % versus 39 %, respectively, P= 0.3). There was no statistical significance based on a synchronous versus a metachronous presentation (5-year survival 57 % versus 46 %, respectively, P=0.79). Conversely, patients with mediastinal lymph node involvement (N2/N3) had inferior survival compared to patients with no mediastinal lymph node involvement (N0/N1) (5-year survival 64 % versus 0 %, respectively, p< 0.001). In multivariate analysis using a Cox Proportional hazards regression model, mediastinal lymph node involvement remained the sole independent predictor of poor prognosis. Patient with N2/N3 disease had a substantially higher risk of death compared to patients with N0/N1 disease with a hazards ratio of 8.2 (P=0.003).

Conclusion

There are a number of important considerations in selecting patients with oligometastatic NSCLC for definitive therapy. The most important is the assurance of proper staging through radiographic studies including PET and brain MRI, and the pathologic staging of the mediastinal lymph nodes and potential sites of metastatic disease. Patients with oligometastatic NSCLC with mediastinal lymph node involvement will remain at a high risk of recurrence and death, despite definitive therapy for their oligometastatic NSCLC, and therefore should not be considered for a combined surgical approach for their disease. It is also necessary for patients to have an adequate performance status prior to consideration for definitive therapy for oligometastatic NSCLC, as this is an important predictor of patient outcome.

In considering the treatment of oligometastatic NSCLC, it is important to keep in mind that the bulk of the data are retrospective in nature and are also subject to publication bias, that is, case series with negative outcomes are unlikely to be reported. In the age of molecular profiling of NSCLC tumors, it is also important to consider that molecular subtypes have a distinct biology that likely necessitates distinct oligometastatic therapy. With that in mind, the available literature suggests that in highly selected patients with solitary metastases to the brain, adrenals and other organs, long term survival may be achieved with combined definitive therapy of both the primary lung tumor and the solitary metastatic site.

Future strategies might include the ongoing development of innovative approaches to local therapy, as well as therapy directed to the oligometastatic site(s). Certainly, SBRT represents an intriguing approach of targeted oligometastatic therapy that minimizes the morbidity associated with surgery. Future research should also focus on the biologic differences that distinguish the oligometastatic disease state from widely metastatic NSCLC and the biologic differences that distinguish an indolent course of oligometastatic disease from an oligometastatic disease course that blossoms to disseminated disease with time.

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Table 1

Retrospective case series of patients with surgically resected synchronous solitary brain metastasis from NSCLC

Study	No. Patients by Nodal Stage				Survival influenced by N stage	Median Survival (months)	5-Year Survival (%)
	All	N0	N1	N2/N3			
Furak, et al. (2005) [31]	19	9	2	8	No	19	24
Getman, et al. (2004) [32]	16	8	3	5	No	9	19
Billing, et al. (2001) [33]	28*	17	5	6	Yes	24	21
Bonnette, et al. (2001) [34]	103*	40	23	36	No	12	11
Saitoh, et al. (1999) [35]	24	11	3	10	No	7	8
Mussi, et al. (1996) [36]	15	8	7*		Yes	18	7
Burt, et al. (1992) [37]	65	27		30	No	21	16
Rossi, et al. (1987) [38]	40	15	15	10	Yes	24	13
Magilligan, et al. (1986) [39]	41				No		21

N denotes nodal status.

*Two patients in the Billing et al. study and 4 patients in the Bonnette et al. study had more than 1 brain metastasis. In the study by Mussi et al., 7 patients had N1/N2 disease

Table 2

Retrospective case series of patients with oligometastatic NSCLC to the adrenal undergoing adrenalectomy

Study	No. Patients by Presentation			Survival influenced by presentation (S versus M)	Median Survival (months)	5-Year Survival (%)
	All	S	M			
Raz, et al. (2011) [55]	20	12	8	No	19	34
Holy, et al. (2011)* [56]	13				23	
Tanvetyanon, et al. (2008)* [57]	114	48	66	Yes	S: 12M: 31	S: 26M: 25
Mercier, et al. (2005) [58]	23	6	17	No	13	23
Pfannschmidt, et al. (2005) [59]	11	5	6	No	13	
Porte, et al. (2001) [60]	43	32	11	No	11	7
Ambrogi, et al. (2001) [61]	5	5	0			60
Beitler, et al. (1998)* [62]	32	19	13	No	24	33

S denotes patients with a synchronous adrenal metastasis. M denotes patients with a metachronous adrenal metastasis.

* Holy, et al. reviewed cases of adrenal metastases treated with SBRT. The studies by Tanvetyanon, et al. and Beitler, et al. were pooled analyses of published case series. The analysis from Tanvetyanon, et al. included the case series from Mercier, et al. and Pfannschmidt, et al.