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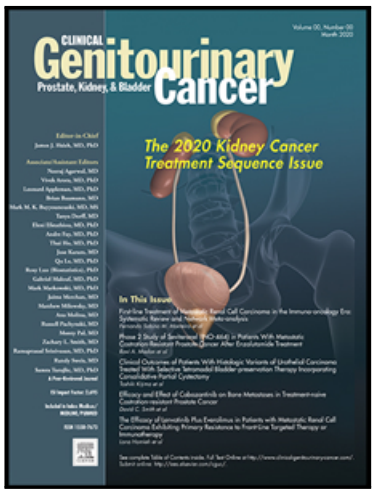

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Life-threatening hemoptysis in patients with kidney cancer chest metastases

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Clinical Practice Points:

- Kidney cancer intrathoracic metastases in proximity to large airways pose a treatment challenge.

- In this series, all patients with non-procedural life-threatening hemoptysis (LTH) had previously received stereotactic ablative radiotherapy (SAbR) to an ultra-central metastasis.
- SAbR to ultra-central RCC metastasis may be associated with a significant risk of LTH.

Background: Hemoptysis is a complication of intrathoracic tumors, both primary and metastatic, and the risk may be increased by procedural interventions as well as Stereotactic Ablative Radiation (SAbR). The risk of hemoptysis with SAbR for lung cancer is well characterized, but there is a paucity of data about intrathoracic metastases. Here, we sought to evaluate the incidence of life-threatening hemoptysis (LTH) in patients with renal cell carcinoma (RCC) chest metastases with a focus on SAbR.

Methods: We systematically evaluated patients with RCC at UT Southwestern Medical Center (UTSW) Kidney Cancer Program (KCP) from July 2005 to March 2020. We queried Kidney Cancer Explorer (KCE), a data portal and database with clinical, pathological and experimental genomic data. Patients were included in the study based on mention of "hemoptysis" in clinical documentation, if they had a previous bronchoscopy, or had undergone SAbR to any site within the chest. Records were reviewed for the development of LTH defined as life-threatening or proximal cause of death.

Results: We identified 295 patients with metastatic RCC (mRCC) that met the query criteria and manually reviewed their records. We identified 10 patients who developed LTH. Of these, 4 had LTH as an immediate procedural complication whilst the remaining 6 had prior SAbR to ultra-central (UC; abutting the central bronchial tree) metastases. These 6 patients with LTH had a total of 10 lung lesions irradiated (UC, 8; central 1, peripheral 1), with a median total cumulative SAbR dose within the lungs of 38 Gray (Gy) (range: 25-50 Gy). Other risk factors included intrathoracic disease progression (n = 4, 67%), concurrent anticoagulant therapy (n = 1, 17%) and concurrent systemic therapy (n = 4, 67%). Median time to LTH from first SAbR was 26 months (range: 8-61 months). Considering that 130 patients received SAbR to a chest lesion during the study period, the overall incidence of LTH following SAbR was 4.6% (6/130). The patient population which received SAbR (n = 130) was at particularly high risk for complications, with 67 (52%) having two or more chest metastasis treated, and 29 (22%) receiving SAbR to 3 or more lesions. However, the risk of LTH following SAbR to an central or UC lesion was 10.5% (6/57).

Conclusion: SAbR for UC RCC metastases may increase the risk of LTH.

Keywords: airway obstruction, aneurysm, bronchoscopy, hemorraghic shock, IMRT, SRS, stereotactic body radiotherapy, stereotactic radiation, SBRT

Background

With an estimated 79,000 new cases and 13,920 deaths in 2022, kidney cancer is among the top 10 diagnosed cancers in the United States.[1] National five-year survival rates for metastatic renal cell carcinoma (mRCC) are ~16%,[2] though newer treatments, including immune-oncology (IO) doublets and IO/tyrosine kinase inhibitor (TKI) combinations are significantly improving the odds.[3-7] Despite these advances, most patients ultimately develop disease progression and succumb to it.

Stereotactic radiation is increasingly deployed for mRCC. It is conventionally used for both brain and bone metastases and has an expanded role for the control of oligometastases in treatment naïve patients and oligoprogressive disease in patients on systemic therapy.[8-13] Registry studies of extracranial mRCC show local control rates following stereotactic ablative radiation (SAbR) from 71-98%.[12] In a retrospective study, we found that SAbR in patients with treatment-naïve oligometastatic RCC could delay the onset of systemic therapy by 15 months.[14] Accordingly, in a prospective study of SAbR in lieu of systemic therapy in 23 patients with oligometastatic RCC, we found that 91% of patients avoided the need for systemic therapy for one year.[15] These findings were consistent with a second prospective trial of SAbR in oligometastatic RCC, in which SAbR alone resulted in a median progression free survival of 22.7 months.[16] Two prospective studies have evaluated the use of SAbR to treat oligoprogressive mRCC, and in both studies SAbR delayed a switch in systemic therapy by over 6 months, and in many cases over a year.[17,18]

SAbR for mRCC has been found to be generally safe. In pooled analyses of SAbR, grade III or higher adverse events (AE) were reported in up to 5% of patients, though the risk may vary by site and dose and is influenced by the duration of followup.[12] SAbR treatment of intrathoracic targets, particularly central lesions surrounding large airways, may be associated with higher toxicity. The airways serve as gas conduits and remove dust, bacteria and other debris. SAbR impairs pulmonary toilet predisposing patients to acute and subacute infections. In addition, it induces fibrosis resulting in strictures and possibly obstruction. Accordingly, the frequency of grade II or higher adverse events is particularly high for central (within 2 cm of the central bronchial tree) and ultra-central (UC; abutting the central bronchial tree) lesions (7-27% for central and up to 57% for UC lesions).[19-21] SAbR may also be associated with hemoptysis, including life-threatening hemoptysis (LTH). LTH from SAbR for non-small cell lung cancer (NSCLC) ranges from 0 to ~10%, with the highest rates seen following SAbR to UC lesions.[19-32]

While rates of toxicity from SAbR for primary lung cancer are available, the risk of LTH for metastatic disease is less characterized. RCC has a propensity to metastasize to the chest and the lungs are the most common destination. In addition, the most common subtype of RCC, clear cell RCC, is particularly vascular.[33] Increased vascularity may increase the risk of both spontaneous as well as treatment-related hemoptysis.

Here, we set out to investigate the risk of hemoptysis, in particular LTH, in patients with mRCC, with a focus on those receiving SAbR. We leverage our institutional experience, one of the largest SAbR experiences for mRCC worldwide[14,15,17,34-36], and present 6 extensively documented cases evaluated by a multidisciplinary team.

Patients and Methods

We identified patients with mRCC treated at the University of Texas Southwestern Medical Center (UTSW) Kidney Cancer Program (KCP) from July 2005 to March 2020. We queried Kidney Cancer Explorer (KCE), a data portal serving as a centralized resource for clinical, pathological and experimental genomic data, for mRCC patients with any of the following criteria: (i) the word "hemoptysis" occurring in any single clinical document beyond its standard inclusion in the review of systems template, so more than once; (ii) previous bronchoscopy, identified using CPT codes 31622-31661; or (iii) SAbR treatment to any site within the chest, identified from a second electronic medical record, MOSAIQ. Medical records of all patients identified in this query (n=295) were manually reviewed by at least two independent investigators (V.P., R.E., A.A., A.S.). Dosimetry data was manually reviewed by a board-certified radiation oncologist (R.T.). LTH was defined as life threatening or deadly hemoptysis. Attribution of LTH was based on a multidisciplinary approach amongst medical oncologists (J.B.), radiation oncologists (R.H., R.T.), an interventional pulmonologist (H.C.), and trainees within the particular discipline (V.P., R.E., A.S.).

Results

During the study interval, 818 patients with mRCC were identified. Of these, 295 unique patients had at least one of the following: (i) the word "hemoptysis" occurring in the medical record (see methods; n=14); (ii) previous bronchoscopy (n=131); or (iii) SAbR to any site within the chest (n=130). Manual review of these cases identified 10 patients with LTH (Figure 1). In four cases, LTH was attributable to an immediately preceding procedure (CT-guided biopsy [n=2] and bronchoscopy [n=2, one of which was for biopsy]). The remaining 6 patients all had SAbR to at least one chest metastasis prior to the development of LTH. All 6 cases had clear cell RCC and received SAbR to UC lesions with a median cumulative total dose of 38 Gy / lesion (Range: 25 – 50 Gy) (Table 1). The median time from first SAbR to LTH was 26 months (Range: 8 – 61 months). LTH incidence among patients who received SAbR to the chest was 4.6% (6/130). Among patients with LTH, multiple potentially confounding variables were identified including the concurrent use of anticoagulants (n = 1, 17%), intrapulmonary disease progression (n = 4, 67%) and concurrent treatment with tyrosine kinase inhibitor (TKI) therapy (n = 4, 67%) (Table 1 and Table 2). Of note, the patients who received SAbR to chest lesions (n=130) were at particularly high risk; 67 (52%) had two or more chest metastases, and 29 (22%) received SAbR to 3 or more pulmonary metastases. The incidence of treated central metastases was also high, with 57 (44%) receiving SAbR to at least one central lesion, and 10 (8%) receiving SAbR to 2 or more central lesions (Table 3). Importantly, among 818 patients with mRCC during the study period, there were no cases of spontaneous LTH identified, that is, in the absence of preceding SAbR or procedures.

Case I

The patient is a 63-year-old man who initially underwent a right radical nephrectomy for pT1b clear cell RCC. Six years later he developed metastatic disease to the chest (biopsy-proven) and a right upper extremity lesion which was resected. The patient was enrolled in a phase II trial evaluating concurrent SAbR and high dose IL-2 (HD-IL2) (iSAbR, NCT01463423). He underwent SAbR to a 1.7cm right lung mass (11 Gy x 3 fractions) and a 2.7cm mediastinal lesion (9 Gy x 3) (Figure 2a) followed by two cycles of HD-IL2. Nine months later the patient developed a choroid plexus metastasis, which was treated with radiosurgery, and he was started on pazopanib. Thirty-one months later a 2cm

right hilar mass was irradiated with SAbR (7 Gy x 5) (Figure 2b), and the patient started nivolumab. Imaging 7 months later revealed shrinkage of an endobronchial lesion, luminal narrowing of the distal bronchus intermedius with right middle lobe collapse as well as radiation-induced perihilar scarring (Figure 2c). Progressive disease in the pancreas prompted a therapy change to axitinib. Unfortunately, shortly thereafter (and 9 months after hilar SAbR) the patient developed fatal hemoptysis.

Case II

The patient is a 72-year-old man who was initially diagnosed with mRCC presenting with a synchronous metastasis to the left frontal lobe and a 14cm left renal mass. Following resection of both lesions, the patient remained disease free for 11 years, at which point he developed a femoral lesion (biopsy-proven metastasis) and a 4.8cm right infrahilar lesion abutting the right bronchus. The femoral lesion was resected, and the infrahilar lesion, which might otherwise have required a complex surgical resection (right lower or middle lobectomy vs bilobectomy), was treated with SAbR with curative intent (8 Gy x 5) (Figure 2d). Subsequent imaging showed shrinkage of the lesion to 3.6cm, and the patient remained off systemic therapy. Nearly 1 year later, the patient was found to have right middle lobe (RML) airway obstruction. Endobronchial biopsy and aspirate were negative for malignancy and infectious etiologies. Six months later, and 18 months after SAbR, the patient presented to the emergency department with massive hemoptysis that was accompanied by a 2 g/dL hemoglobin drop and was admitted to the intensive care unit (ICU). Emergent bronchoscopy demonstrated stricture of the right mid-bronchus intermedius, which was also evident on imaging (Figure 2e). Bleeding was localized to an aneurysmal vessel protruding into the bronchus and was controlled via catheter-directed embolization. Repeat bronchoscopy 4 days later confirmed resolution of bleeding (Figure 3a), though the aneurysm could still be seen. Follow-up bronchoscopy 3 months later revealed macerated post-radiation changes and aneurysmal vessel formation (Figure 3b,c). At this time, the patient was diagnosed with a gastric, biopsy-proven, metastasis and started nivolumab/ipilimumab. Unfortunately, the patient's course was complicated by grade III colitis, and an infection of the left femoral prosthesis. Due to recurrent hospitalizations and declining functional status he elected to pursue hospice care.

Case III

The patient is a 61-year-old man with a history of multiple pulmonary emboli (on rivaroxaban) who was diagnosed with a T1b clear cell RCC. Two years after a left radical nephrectomy, he developed a 3.1cm left hilar lymph node metastasis which was biopsied and shown to be a clear cell RCC. This was the only site of metastatic disease. Surgical resection to achieve negative margins would have required an extensive and high-risk lung dissection due to its abutting the pulmonary artery and left upper and lower lobe bronchi. Hence, he underwent SAbR with curative intent (8 Gy x 5) (Figure 2f). Four months later, he developed new soft tissue and bone lesions prompting initiation of pazopanib, which the patient remained on for 6 months. At progression, he was treated with nivolumab/ipilimumab, on which he remained for 8 months. Subsequently, he underwent resection of a brain metastasis and was transitioned to axitinib. One month after craniotomy, he underwent neuroembolization to a thoracic eighth vertebra (T8) metastasis causing symptomatic cord compression and subsequent T8 corpectomy with cage reconstruction and posterior fixation and fusion of thoracic sixth to tenth vertebrae. He also received radiation to cervical fifth to sixth

vertebrae (7 Gy x 5) and thoracic first to third vertebrae (5 Gy x 5) approximately ten months later. Thirty-one months after left hilar SAbR, the patient was admitted to the hospital with post-obstructive pneumonia thought to be secondary to chronic bronchial scarring and stricture in the region of previous radiation. Imaging at this time also revealed ectatic vessel formation in the same previously irradiated region (Figure 2g). Following resolution of pneumonia, progressive disease at skeletal sites as well as in a left hilar mass prompted transition to cabozantinib. Shortly thereafter (34 months after hilar SAbR) the patient developed fatal hemoptysis.

Case IV

The patient is a 53-year-old man who underwent a right nephrectomy for a pT2 clear cell RCC and developed biopsy-proven pulmonary metastases 6 years later. He was initially treated with pazopanib for 6 months, at which point he developed progressive disease. He enrolled in a SAbR plus HD-IL2 clinical trial (iSAbR, NCT01463423). SAbR was delivered to a 1.5cm right upper lobe nodule (RUL) (25 Gy x 1) (Figure 2h) and an 11th rib lesion (12 Gy x 3), followed by two courses of HD-IL2. Imaging 4 months later revealed a mixed response with shrinkage of all lesions except for a 3.6cm subcarinal biopsy-proven lymph node metastasis. The patient underwent SAbR (12 Gy x 3) to the subcarinal lesion (Figure 2i) and received an additional cycle of HD-IL2. Imaging for shortness of breath one month later revealed an obstructing right lung lesion causing collapse of the RML and post-obstructive pneumonia, as well as post-radiation bronchial stenosis. In addition, the patient had a subsegmental pulmonary artery embolism. Bronchoscopy showed an erosive tumor and bronchial constriction, prompting endobronchial ablation and bronchial stent placement one month following SAbR to subcarinal lesion (Figure 3d,e). The subsegmental embolism was treated with enoxaparin followed by edoxaban for 3 months. Follow-up bronchoscopy 2 months after stent placement revealed bronchial stenosis above and below the bronchial stent secondary to a combination of tumor progression and granulation tissue, prompting a repeat ablation and balloon dilatation with good results (Figure 3f). At this time the patient started nivolumab/ipilimumab. Imaging 3 months later revealed significant progression of pulmonary metastases as well as new iliacus and gluteal muscle lesions. The patient was switched to cabozantinib, but unfortunately developed hemoptysis 6 weeks later (8 months after SAbR to the subcarinal lymph node). CT angiography upon admission revealed a 7mm pseudoaneurysm originating from the right intralobar pulmonary artery which was a possible source of bleeding, as well as redemonstration of the infiltrative hilar mass (Figure 2j). Unfortunately, the patient developed fatal hemoptysis before a procedural intervention could be performed.

Case V

The patient is a 72-year-old man initially diagnosed with localized clear cell RCC who underwent a right radical nephrectomy. The patient developed a biopsy-proven lung metastasis 1.5 years later which was resected. Nearly 7 years after nephrectomy, the patient was diagnosed with additional metastases, including a 2.4cm R hilar mass and 1cm LUL nodule, which were treated with SAbR (10 Gy x 5, 8 Gy x 5, respectively). He was also started on sunitinib at an outside institution. Imaging 6 months later showed a new pathologically-enlarged subcarinal lymph node (as well as post-radiation fibrosis in the right hilum). The patient was transitioned to nivolumab, and ipilimumab was added at progression nearly a year later. Thirty months later, there was progression at multiple sites, including an endobronchial mass causing complete RML collapse. This was treated with endobronchial balloon dilatation and systemic therapy was changed to axitinib. The patient remained on axitinib for about one year until disease progression prompted a change to cabozantinib. Five months after starting cabozantinib, and approximately 51 months after SAbR, the patient began experiencing episodic hemoptysis prompting a repeat bronchoscopy which re-demonstrated RML airway constriction and showed a LLL endobronchial tumor, which was excised

and ablated (Figure 3g). The patient did not have additional hemoptysis, but underwent a repeat bronchoscopy for worsening right bronchial obstruction seen on CT imaging (Figure 2k). This revealed resolution of the previously ablated left endobronchial tumor, but recurrence of a right endobronchial lesion which was ablated (Figure 3h). Several months later (5 years after hilar SAbR), and following a report of a recurring sensation of airway obstruction, an additional bronchoscopy was performed. This revealed an erythematous bulging lesion in the right bronchus where there was none previously (near a site of previous radiation) (Figure 3i). Attempted ablation resulted in fatal hemoptysis thought to be secondary to a pulmonary artery aneurysm.

Case VI

The patient is a 48-year-old man initially diagnosed with a pT3a clear cell RCC with rhabdoid features who underwent a radical nephrectomy. Nine months later, the patient developed a left adrenal metastasis, subcentimeter lung nodules, and a 3.3cm right hilar lymph node metastasis (biopsy-proven). The patient was enrolled in the RADVAX trial (NCT03065179), which includes nivolumab/ipilimumab and SAbR, and underwent SAbR (10 Gy x 5) to the right hilar lesion (Figure 2l). Unfortunately, two months later, he developed progressive disease in both adrenal and pulmonary sites, prompting transition to axitinib. A chest CT 6 months after hilar SAbR revealed band-like consolidation and traction bronchiectasis in the region of previous radiation. Three months later (9 months after SAbR) the patient presented to the emergency room with massive hemoptysis that was ultimately fatal. CT scans on arrival showed a right hilar mass, which appeared infiltrative, with significant narrowing of right-sided bronchi and compression of pulmonary arteries and veins (Figure 2m).

Discussion

Among 818 mRCC patients in the study period we identified 10 cases of LTH. LTH was the immediate result of procedural complication in 4 patients and occurred in 6 patients with prior SAbR to UC lesions.

SAbR is increasingly utilized for the management of mRCC, and has been shown to be effective and generally well tolerated.[8-14,16,18] This has been corroborated in our own institutional experience including retrospective analyses of SAbR for oligometastatic[14] and oligoprogressive[13] disease as well as prospective clinical trials.[15,17] However, when delivered to the chest, SAbR can be associated with particular AEs including radiation pneumonitis, bronchial obstruction, post-obstructive pneumonia, lung collapse, pleural effusions, and hemoptysis.[22,31] In a meta-analysis of ~8000 patients with various tumor types who received SAbR to the chest, the overall AE rate was 9.1% with 1.8% experiencing grade III or higher AEs. Unsurprisingly, the risk of treatment-related AEs correlated with the location of the irradiated lesion, and increased with proximity to the central airways[19,20].

In our study, 4.6% (6/130) of patients who received intrathoracic SAbR developed LTH. This relatively high incidence is likely reflective of the high-risk nature of the cohort which received intrathoracic SAbR. Over 50% of patients (n = 67, 52%) had more than one lesion treated, putting them at higher risk of dose overlap, and nearly half (n = 57, 44%) had at least one central tumor treated (Table 3). Of the index cases reported in this study, all received treatment to at least one UC lesion, thus the risk of LTH following treatment of an UC lesion was 10.5% (6/57). This finding is similar to the results of the Nordic HILUS-trial, which evaluated the safety of SAbR (7 Gy x 8 fractions) to UC lesions of various tumor types. In this study, which only included patients with treated lesions <1cm from the main bronchi, the rate of life-threatening bronchopulmonary hemorrhage was 12% (8/65)[32].

In this report, all patients that developed LTH following SAbR had at least one treated UC tumor ≥2.4cm. Bulky central tumors are at an inherent high risk for complications, where treatment options are associated with significant morbidity and limited likelihood of tumor control. Infection, uncontrolled tumor progression, invasive interventional procedures such as biopsy and dilatation, and re-irradiation all increase the risk of complications.

The contribution of SAbR to LTH is difficult to pinpoint due to confounding factors, including ongoing anticoagulant use (n=1, 17%), concurrent TKI therapy (n=4, 67%), and disease progression (n = 4, 67%). While it is likely that the ultimate cause of hemoptysis was multifactorial, it is worth noting that among the 818 patients with mRCC during the study period, we did not identify any cases of spontaneous LTH. Rather, all episodes occurred following preceding SAbR or a procedure. This suggests that intervention (SAbR or procedure) contributes more to the risk of LTH than inherent biology. While RCC can metastasize to the bronchial tree and induce arteriovenous malformations, these may predispose to lower grade (not immediately life threatening) hemoptysis.[37,38] In contrast, SAbR may lead to central airway necrosis, aneurysm formation, and vascular-bronchial fistulas, which can result in brisk bleeding and ultimately LTH.[25,39-41] In our series, aneurysm formation or ectatic vessel growth was seen in 4 (67%) cases. Nevertheless, we cannot exclude a reverse bias (i.e., tumors at highest risk of bleeding are most likely to be treated). In addition, tumor recurrence was confirmed in 4 (67%) of cases and could have contributed to LTH. Compared to other treatment modalities, SAbR has some definite advantages including its non-invasive nature, preservation of lung parenchyma, and limited disruption of systemic therapy schedules. However, for UC and central lesions, the risk of life threating hemoptysis must be considered.

This study has several limitations. First, it is limited by its retrospective nature. We cannot exclude that some cases were missed and the lack of structured prospective information collection may have introduced biases. Second, it represents a single institution experience. Third, there are limitations to our query strategy. We searched for the repetitive term “hemoptysis,” and while this may prioritize LTH, it may not be optimal. In addition, we specifically queried all mRCC patients receiving radiation to the chest and undergoing bronchoscopies, thereby giving particular weight to these interventions, which while fitting, also introduces a bias. The study is also limited by duration of follow-up and a substantial number of patients that received SAbR are still being followed up. Finally, despite engaging providers involved with the interventions (SAbR, bronchoscopic procedures and surgery) as well as an extensive multidisciplinary review of radiology and bronchoscopy images, assessing the specific contribution of the different factors to LTH is challenging. Nevertheless, to our knowledge, this is the first study to systematically evaluate LTH in patients with mRCC with specific attention to a possible role of SAbR. Our study suggests that SAbR could be a potential contributor to LTH in mRCC, particularly when administered to UC metastases, raising awareness about this possible complication.

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Consent to Participate

Retrospective clinical data was collected in compliance with institutional guidelines after approval of the UTSW Institutional Review Board (IRB).

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Author Contributions

Conception and design: VP, RE, JB

Development of methodology: AS, RE, AC, JB

Acquisition of data: VP, RE, AA, AS, AC, RH, HC

Analysis and interpretation of data: VP, RE, AA, AS, AC, IP, HC, RT, SR, RH, JB

Writing, review, and/or revision of manuscript: VP, RE, AA, AS, AC, IP, HC, RT, SR, RH, JB

Conflicts of Interest

R. Timmerman is a principal investigator to the institution from Varian Medical Systems, Elekta Oncology, and Accuray, Inc. not related to this work. S. Reznik is an investor in Onconano. J. Brugarolas is an advisory board member for Eisai, Johnson & Johnson, Exelixis, Arrowhead, Calithera, and reports patent applications, all outside the submitted work. The remaining authors have no relevant competing interests.

Figure Legends

Figure 1

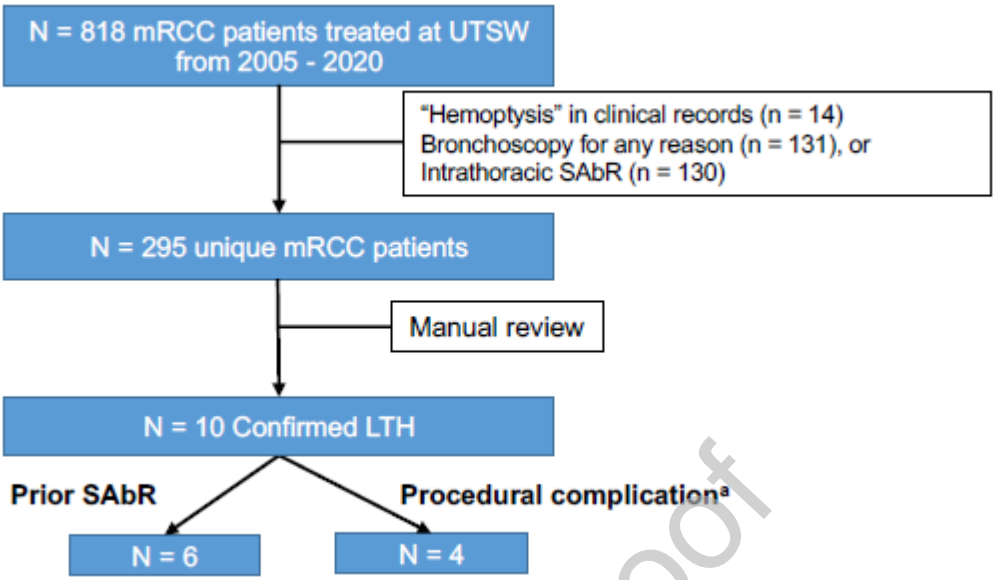

Figure 1. Study overview. We identified 818 mRCC patients at the University of Texas Southwestern Kidney Cancer Program (UTSW KCP) between July 2005 and March 2020. Of these, 295 met an inclusion criteria (see methods). These records were manually reviewed and 10 patients were confirmed to have LTH. [a]LTH Immediate procedural complication (CT guided biopsy [n =2] or bronchoscopy [n = 2]).

Figure 2

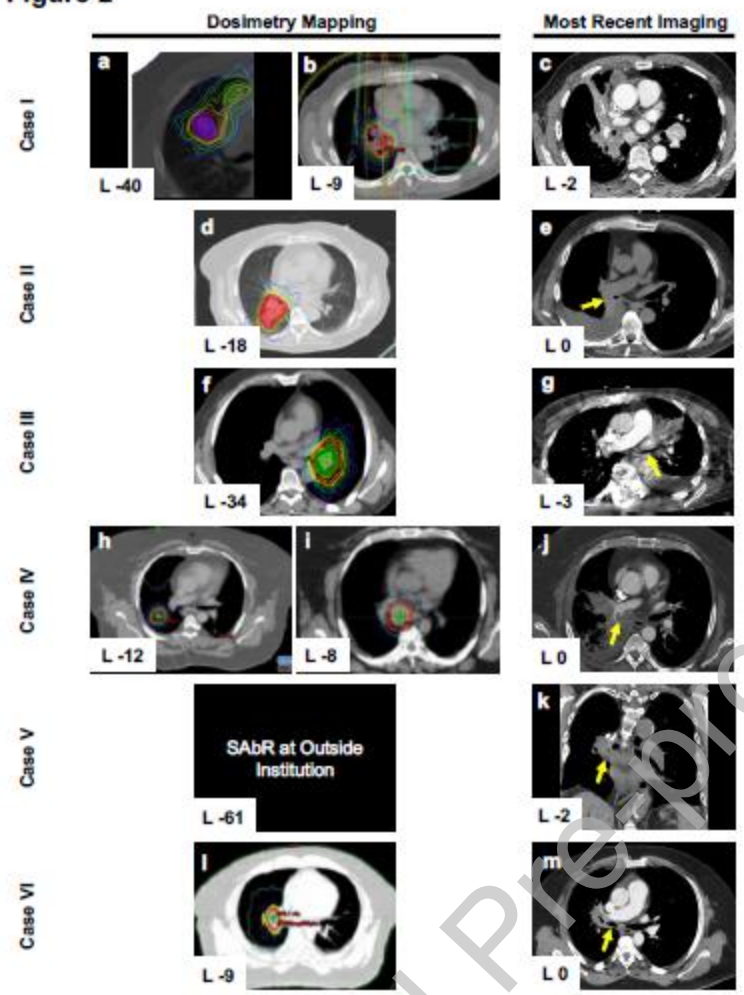

Figure 2. Integrated SAbR dosimetry mapping and chest imaging preceding massive hemoptysis. Axial and coronal images of the cases with time in months from image to development of life-threatening hemoptysis (insert [L -months]). *Case I.* (a) Dosimetry mapping of planned SAbR for 1.7cm right lung nodule and 2.7cm mediastinal lesion. (b) Dosimetry mapping for planned SAbR to 2cm right hilar mass. (c) CT chest with IV contrast 2 months prior to LTH showing right bronchial obliteration and endobronchial lesions. *Case II.* (d) Dosimetry mapping of planned SAbR for a 4.8cm right infrahilar mass. (e) CT chest on day of LTH revealing right bronchial constriction (arrow). *Case III*. (f) Dosimetry mapping of planned SAbR for 3.1cm left hilar mass. (g) CT angiogram of the chest 3 months prior to LTH showing radiation fibrosis, bronchial narrowing (arrow), and ectatic vessel formation. *Case IV.* (h) Dosimetry mapping of planned SAbR to a 1.5cm RUL mass. (i) Dosimetry mapping of planned SAbR to a 3.6cm subcarinal lymph node. (j) CT angiography on the day of hemoptysis revealing a 7mm pseudoaneurysm (arrow) originating from the right intralobar pulmonary artery. *Case V.* Dosimetry mapping unavailable. (k) CT chest 2 months prior to LTH revealing a bronchial mass (arrow) leading to obstruction of multiple right lung segments prompting bronchoscopy. *Case VI*. (l) Dosimetry mapping of planned SAbR to a 3.3 cm R hilar mass prior to SAbR. (m) CT scan with contrast on the day of LTH reveals an infiltrative-appearing mass compressing the right pulmonary artery and vein, with narrowing of multiple bronchi (arrow).

Figure 3

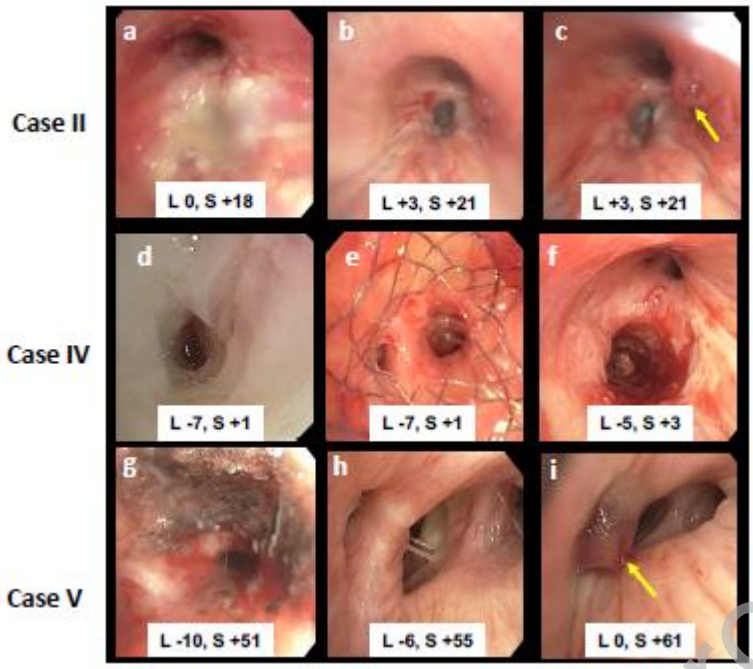

Figure 3. Bronchoscopy findings. Bronchoscopic images of cases over time with time to life threatening hemoptysis (L -months) and time from SAbR (S +months). Negative values indicate time preceding event. *Case II*. (a) Boggy appearance of bronchus intermedius near site of bleeding 18 months after SAbR to right infrahilar region and 4 days after hemoptysis onset. Macerated post-radiation changes 3 months after massive hemoptysis with ectatic vessels in bronchus intermedius (b) and aneurysmal vessel (arrow) (c). *Case IV.* (d) Bronchoscopy one month after SAbR to a subcarinal metastasis demonstrating occlusion of the bronchus intermedius. (e) Successful bronchus intermedius stent placement. (f) Bronchoscopy 2 months later showing patent, but boggy appearing bronchus after bronchial stent removal. Infiltrative tumor no longer seen. *Case V*. (g) Endobronchial tumor causing obstructive symptoms in LLL more than 4 years after SAbR to right hilum and LUL metastases and 10 months prior to massive hemoptysis. (h) Bronchus intermedius 6 months prior to hemoptysis without aneurysm. (i) Pulmonary arterial truncus aneurysm (arrow) in bronchus intermedius, minutes from rupture and massive hemoptysis.

Case	Age at LTH	Sex	Subtype	NG	S/R	Location of irradiated pulmonary lesions	Size of lesion (cm)	Location	Total Dose (Gy)	Fx	BED (Gy)	Time to LTH (mo)	AC	Systemic therapies prior to LTH	Systemic therapies concurrent with LTH	Bronchscopy within 1yr of LTH	Hemoptysis Grade
I	63	M	ccRCC	1	N	R lung	1.7	UC	33	3	72	40	No	HD-IL2, Pazo, Nivo, Axi	Axi	N	V
						Mediastinum	2.7	UC	27	3	51	40					
						R hilar	2	UC	35	5	60	9					
II	72	M	ccRCC	n.a.	n.a.	R infrahilar	4.8	UC	40	5	40	18	No	None	None	Y	IV
III	61	M	ccRCC	2	N	L hilar	3.1	UC	40	5	40	34	Yes	Pazo, Ipi+Nivo, Axi, Cabo	Cabo	N	V
IV	53	M	ccRCC	2	N	R upper lobe	1.5	C	25	1	1	12	No	Pazo, HD-IL2, Ipi+Nivo, Cabo	Cabo	Y	V
						subcarinal lymph node	3.6	UC	36	3	3	8					
V	72	M	ccRCC	n.a.	n.a.	R hilum	2.4	UC	50	5	5	61	No	Sun, Pazo, Nivo, Ipi+Nivo, Axi, Cabo	Cabo	Y	V
						L upper lobe	1	P	40	5	5	61	No				
VI	48	M	ccRCC	4	Y	R hilar	3.3	UC	50	5	50	9	No	Ipi+Nivo, Axi	None	N	V

Table 1. Detailed clinical characteristics of patients with life threatening hemoptysis. Abbreviations: AC, anticoagulation; Axi, axitinib; BED, biologically effective dose; Cabo, cabozantinib; ccRCC, clear cell renal cell carcinoma; Fx, Fraction; Gy, Gray; HD-IL2, high-dose interleukin-2; Ipi, ipilimumab; LTH, life threatening hemoptysis; NG, Nuclear Grade; Nivo, nivolumab; Pazo, pazopanib; SAbR, Stereotactic ablative radiotherapy; Sun, sunitinib

Characteristics	Number (%), or Median (range)
Age at LTH (years)	62 (48-72)
Histology:	
ccRCC	6 (100%)
Lines of systemic therapy prior to LTH:	
0	1 (17%)
1	0 (0%)
2	1 (17%)
3+	4 (67%)
Location of irradiated lesions*:	
Ultra-central Central Peripheral	8 (80%) 1 (10%) 1 (10%)
Irradiated lesion size (cm)*	2.6 (1-4.8)
Cumulative dose of radiation / lesion (Gy)	38 (25-50)
Time to LTH from first SAbR (months)	26 (8-61)
Number of irradiated metastases	
1	3 (50%)
2	2 (33%)
3	1 (17%)
Concurrent anticoagulation	1 (17%)

Concurrent systemic therapy at LTH	
None	2 (33%)
Axitinib	1 (17%)
Cabozantinib	3 (50%)
Hemoptysis Grade	
Life threatening	1 (17%)
Deadly	5 (83%)
Intrathoracic disease progression	4 (67%)
Prior bronchoscopy (anytime)	6 (100%)
*Of 10 total pulmonary lesions irradiated	

Table 2. Summary Characteristics of patients with life threatening hemoptysis

Table 3. Characteristics of intrathoracic SAbR cohort

Characteristics	Frequency (%), or Median (range)
Total patients	N = 130
Number of chest metastases	
>1	67 (52%)
Number of treated central / ultra-central pulmonary lesions	
≥1	57 (44%)
≥2	10 (8%)
Number of treated chest lesions	
1	63 (48%)
2	38 (29%)
≥3	29 (22%)
Site of Irradiated Lesions	N = 247
Peripheral (Boney Structure)	40 (16.2%)
Peripheral (Lung)	138 (55.8%)
Central	14 (5.7%)
Ultra-central	55 (22.3%)
Median Dose	36 (25-40)
Median Fractions	3 (3-5)
Median BED	79.2 (14.4-300)