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Stereotactic Radiotherapy for Metastatic Anaplastic Thyroid Cancer: A Single-center Experience and Systematic Review

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Abstract

Background/Aim: Anaplastic thyroid cancer (ATC) is a highly aggressive malignancy associated with a limited prognosis. Recent advances in targeted therapies and improved systemic therapy options have led to an increasing number of patients experiencing isolated or limited metastatic progression. Stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) have emerged as potential treatment options for metastatic ATC. This prospective observational study aimed to evaluate the role of SBRT and SRS in treating ATC metastases.

Patients and Methods: Patients with histologically confirmed ATC and an indication for radiotherapy were enrolled at a tertiary care hospital in Munich, Germany from 12/2020 to 01/2025. Treatment-related toxicity was assessed using CTCAE v3, and follow-ups occurred every three months post-radiotherapy. A systematic literature review was conducted using PubMed/Medline, Scopus and Cochrane databases, analyzing studies on SRS and SBRT for ATC metastases.

Results: Our prospective patient cohort enrolled 31 patients, with four (12.9%) receiving SBRT/SRS for metastatic disease. The systematic review identified 11 studies that met the inclusion criteria, of which two were selected for further analysis. Reported overall survival ranged between 2.1 and 3.6 months. Our prospective study demonstrated efficacy of SBRT/SRS in providing symptom relief, accompanied by manageable adverse effects.

Conclusion: SBRT and SRS are viable treatment options for metastatic ATC, providing local tumor control and symptom relief with low toxicity, particularly for bone and brain metastases. However, given the poor prognosis associated with ATC, further research is required to refine patient selection criteria and optimize treatment regimens, particularly in combination with systemic therapy.

Keywords: ATC, SRS, SBRT, local control, palliation.

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Introduction

Anaplastic thyroid cancer (ATC) is an orphan disease associated with a poor prognosis (1). Median survival ranges between 3-5 months after diagnosis in non-druggable ATC (2, 3). Radiotherapy (RT) to the primary tumor in metastatic ATC offers durable local control and effective palliation, thereby supporting prolonged symptom relief (4). The clinical implementation of next-generation sequencing (NGS) has facilitated the development of targeted therapies for ATC, which are associated with significantly improved prognoses and quality of life (5). As a result of improved outcome an increasing number of patients now experience either isolated or limited progression of metastases. Consequently, local therapies such as stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT), in combination with targeted therapy or other systemic treatment, have gained major interest in both research and clinical treatment. The aim of this prospective study is to investigate the role of local ablative radiotherapy (SRS, SBRT) in metastatic ATC.

Patients and Methods

Study design and setting. This prospective observational study was conducted at an academic tertiary care hospital in Munich, Germany from 12/2020 to 01/2025. The study was conducted in accordance with the Declaration of Helsinki and approved by the local Ethics Committee (study approval number 19-885). Written informed consent was obtained from all patients involved in the study. Inclusion criteria were as follows: patients with histological confirmed ATC and indication for radiotherapy/chemoradiotherapy.

Treatment-related toxicity were assessed using the Common Toxicity Criteria for adverse events (CTCAE) v3. Follow-up was performed every 3 months after the end of RT for the first two years. The systematic review was pre-registered with INPLASY under the registration number INPLASY2024120110 (6).

Literature research strategy: A systematic review of the literature was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The literature search was conducted in Nov 2024 using PubMed/Medline, Scopus and Cochrane databases. The Medical Subject Headings (MeSH) searched included "anaplastic thyroid cancer", "ATC", "stereotactic body radiotherapy", "SBRT", "stereotactic radiosurgery" and "SRS" and was limited to original research articles in English language. A PRISMA flow diagram is displayed in Figure 1.

Two reviewers (RR and LK) assessed all eligible articles based on the inclusion and exclusion criteria given below, with final determination by a third reviewer (JR) in cases of discrepancies.

Selection criteria. Inclusion criteria were as follows: i) histologically confirmed anaplastic thyroid cancer; ii) treatment with SBRT/SRS; iii) study on humans; iv) with sufficient data on treatment-related toxicity and outcome. Exclusion criteria were as follows: i) Case reports; ii) letters; iii) reviews; iv) guideline/ editorials; v) duplicate studies; vi) reports with histology other than ATC.

Results

We found 11 potential studies searching PubMed, MEDLINE, Scopus, and Cochrane databases. After excluding duplicates, 7 studies remained. As part of our screening, we had to exclude another 5 studies due to histology's other than ATC (n=3), one study reporting no original data (n=1), and one study was only available as a conference abstract (n=1). In the remaining studies, a total of eight patients were treated for SBRT for ATC metastases whereas 56 patients were treated with SRS for ATC brain metastases (Table I).

In this prospective study, all ATC patients were enrolled consecutively resulting in 31 patients in the period from 12/2020 to 01/2025. Four (12.9%) patients were treated with SBRT/SRS for their metastases. All patients had histologically confirmed ATC and next-

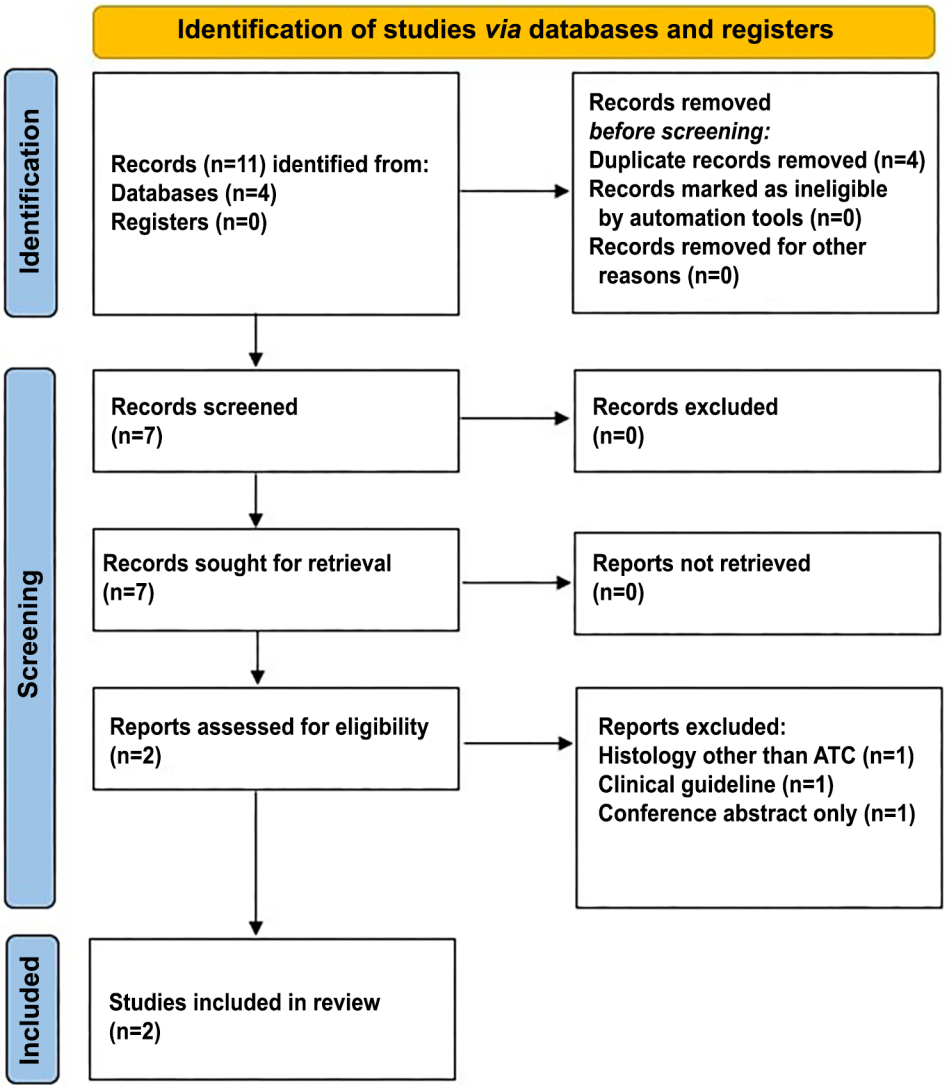

Figure 1. *PRISMA 2020 flow diagram for the systematic review regarding ATC patients undergoing SRS/SBRT. ATC: Anaplastic thyroid cancer; SBRT: stereotactic body radiotherapy; SRS: stereotactic radiosurgery.*

generation sequencing (NGS) was accordingly performed. Treatment-related side effects were assessed using CTCAE v3 before and after treatment.

Case 1. A 59-year-old male patient initially presented with left-sided cervical swelling, and sonography suggestive of thyroid cancer. He underwent a left hemithyroidectomy, which was histopathologically confirmed as anaplastic thyroid cancer with R1-resection and underwent right hemithyroidectomy and subsequent resection achieving R0 margins. Positron emission tomography/computed tomography (PET/CT) imaging revealed cervical, mediastinal, hilar, pulmonary, and adrenal metastases, with local tumor residue in the right thyroid bed. Additional cranial magnetic resonance imaging (cMRI) staging showed two contrast-enhancing lesions: one at the left vertex (0.6 cm × 0.6 cm) and another in the left cerebellum (0.5 cm × 0.5 cm).

Table I. *Overview included anaplastic thyroid cancer (ATC) studies investigating stereotactic radiosurgery/stereotactic body radiotherapy (SRS/SBRT).*

Author, year (Ref)	Number of patients with ATC	Treatment site	Dose concept	Outcome regarding ATC (sub)-group
Lee *et al.* 2022 (11)	12/12	lung, *n*=5; bone, *n*=4; lymph node, *n*=2; liver, *n*=1	3×9 Gy within 2 weeks of 1 cycle durvalumab and tremelimumab	-median OS was 3.3 months -all patients showed at least ≥ grade 2 toxicities. -7 patients had ≥ grade 3 toxicity -2 patients experienced grade 4 events
Blomain *et al.* 2022 (institutional) (12)	8/33	Brain, *n*=8	Treatment consisted of whole brain radiotherapy or stereotactic radiosurgery	-median OS was 3.6 months -no subgroup analysis for ATC patients regarding radiation necrosis
Blomain *et al.* 2022 (NCDB) (12)	44/289	Brain, *n*=44	Treatment consisted of whole brain radiotherapy or stereotactic radiosurgery or no brain-directed radiotherapy	-median OS 2.1 months -no difference in OS regarding radiotherapy treatment

The patient exhibited no neurological deficits, no signs of increased intracranial pressure, and maintained a performance status of KPS 100%. NGS was performed; however, no druggable mutations were found.

Palliative chemotherapy was initiated with carboplatin Area under the curve of 5 (AUC5) and paclitaxel (175 mg/m^2) every three weeks. After multidisciplinary tumor board discussion, stereotactic radiosurgery (SRS) was performed for the two brain metastases from the anaplastic thyroid cancer: 15 Gy to the left cerebellar lesion (1× 15 Gy, 80% isodose, with dose reduction due to proximity to the brainstem) and 20 Gy to the other lesion (1× 20 Gy, 80% isodose). The patient experienced no treatment-related side effects. Six weeks after SRS, the irradiated lesions were barely distinguishable, indicating a good therapeutic response.

However, multiple new lesions outside of the previously treated volumes were noted. Palliative whole-brain radiotherapy (WBRT) was initiated, delivering 3 Gy to 30 Gy, with a simultaneous integrated boost (SIB) to the metastases with 4 Gy to 40 Gy. Extracranial CT staging showed stable disease, and treatment was switched to pembrolizumab (200 mg) and lenvatinib (10 mg) according to the ATLEP trial.

Three months after WBRT, cMRI revealed significant progression in the left insular metastasis, while the other lesions remained stable. The patient developed increasing confusion, which improved temporarily with dexamethasone therapy. CT staging showed multiple progressions in the liver, lungs, and paratracheal region. The patient passed away three months later due to tumor-related complications.

Case 2. A 77-year-old female patient presented with a rapid onset swelling of the thyroid gland. Based on patient´s history of colon cancer two years earlier, we decided to perform an ^{18}F-fluorodeoxyglucose (FDG)- positron emission tomography/computed tomography PET/CT scan within three weeks after clinical presentation and a biopsy confirmed the histopathological diagnosis of ATC.

The PET/CT revealed a highly centrally necrotic, metabolically active, tumor of the thyroid gland (11×7×12 cm) with displacement of the trachea to the right and plotting of the trachea. In addition, multiple lymph node metastases were found in levels II to IV. There was no evidence of local recurrence of the colon cancer.

The patient underwent definitive chemoradiotherapy (CRT) including a total dose of 69.96 Gy administered to the PET-positive primary tumor and involved lymph nodes in 2.12 Gy fractions. Additionally, the elective lymphatic drainage areas received a total dose of 54.45 Gy delivered in 1.65 Gy fractions. Concurrent chemotherapy

was performed with carboplatin (AUC 2) and paclitaxel 50 mg/m^2, administered weekly for six cycles. An NGS analysis revealed a *BRAF* V600E mutation, thus we decided to start an adjuvant treatment with dabrafenib in combination with trametinib.

In the first re-staging (8 weeks after CRT) a solitary posterior metastasis on the left parietal region of the brain was revealed. Based on the multidisciplinary tumor board discussion, we decided to perform SRS of the brain metastasis with 18 Gy (prescribed to the 80% isodose).

After the intervention, the patient suffered from a seizure CTCAE grade II and received anticonvulsants without interfering with activities of daily living. Three weeks after SRS, the patient was hospitalized for influenza A pneumonia. The patient died four days after admission due to respiratory insufficiency, unrelated to the tumor.

Case 3. A 62-year-old male patient in a good performance status (Karnofsky index: 80%) presented with a newly developed mass in the neck area. CT staging and MRI of the head neck region revealed a 6.5 cm mass in the left lobe of the thyroid gland and another mass in the left upper lobe of the lung. Additionally, osseous metastases were detected in the thoracic spine and the 9th rib on the left side. A cMRI excluded brain metastases.

Two days after these examinations, a biopsy of the thyroid mass was conducted. As it was initially unclear whether the lung mass represented metastasis or a secondary malignancy, a bronchoscopy, a CT-supported biopsy of the lung mass, and a PET/CT were performed. Despite the acquisition of multiple samples, no definitive histological clarification could be obtained, prompting the performance of a video-assisted thoracoscopic surgery (VATS). Histopathological analysis from the VATS suggested lung metastasis originating from thyroid carcinoma.

Four weeks after the initial clinical presentation, concurrent CRT including a total dose of 69.96 Gy was administered to the PET-positive primary tumor and involved lymph nodes in 2.12 Gy fractions. Additionally, the elective lymphatic drainage areas received a total dose of 54.45 Gy delivered in 1.65 Gy fractions. Concurrent chemotherapy consisted of carboplatin AUC2 and paclitaxel 50 mg/m^2 weekly. Additionally, SBRT was administered in 5 fractions of 6 Gy each, prescribed to the 80% isodose line, for a symptomatic metastasis in the 9th left rib. During the follow-up period, the patient completed three cycles of adjuvant chemotherapy (carboplatin/paclitaxel) with a constant KPS.

Subsequent CT neck/thorax staging revealed progression of the pulmonary metastases and the appearance of new metastatic lesions. In response to these findings, systemic therapy with pembrolizumab and lenvatinib was initiated following an interdisciplinary meeting.

A follow-up staging examination conducted six weeks after initiating systemic therapy revealed stability in the patient's condition. Four months later, worsening dysphagia required bougienage of the esophagus. Eight months after that, the procedure had to be repeated. A CT scan of the neck and chest at the time showed a stable status. One month later, the patient returned in a severely deteriorated state and presumably died from tumor related causes.

Case 4. A 56-year-old male patient with a Karnofsky Performance Status of 90% presented in December 2023 with progressive cervical swelling. MRI of the neck revealed a 4 × 4.5 cm mass in the left thyroid lobe, along with incidental cutaneous neurofibromas. In January 2024, the patient underwent total thyroidectomy with partial lymph node dissection on the left side. Histopathological analysis confirmed a poorly differentiated thyroid carcinoma with areas of anaplastic transformation, staged as pT3a pN0 (0/7 lymph nodes) L0 V1 Pn0 R0.

A staging PET/CT in February 2024 showed no evidence of residual tumor or distant metastases. From February to April 2024, the patient received adjuvant concurrent CRT to the thyroid bed, with a total dose of 66 Gy in 2 Gy fractions, combined with weekly carboplatin and paclitaxel. This was followed by six cycles of adjuvant chemotherapy (carboplatin/paclitaxel) administered from April to September 2024.

A restaging PET/CT on October 24, 2024, revealed no signs of locoregional recurrence or lymph node involvement. However, a newly developed osteolytic lesion in the left pedicle of the seventh thoracic vertebra (T7) was detected, raising suspicion for bone metastasis. This finding was discussed at the institutional tumor board in late October 2024, where local ablative radiotherapy to the metastatic site was recommended. In addition, germline testing had revealed deletions in exons 15 and 16 of the *BRCA1* gene, prompting evaluation for off-label systemic therapy with olaparib.

A follow-up MRI of the thoracic spine on November 22, 2024, confirmed the T7 lesion. The patient subsequently underwent local ablative radiotherapy using a SIB technique, delivering 5 × 5 Gy to the vertebral body and 5 × 6 Gy to the metabolically active portion of the metastasis. The treatment was well tolerated, and no acute adverse events were reported. Maintenance therapy with olaparib was initiated in December 2024.

A follow-up PET/CT at the end of January 2025 demonstrated no evidence of local recurrence or metabolically active lymph node metastases. However, a new lesion in segment II of the liver, suspicious for metastasis, was identified alongside persistent metabolic activity at the previously irradiated T7 metastasis. The hepatic lesion was treated with interstitial high-dose-rate brachytherapy. A total dose of 20 Gy was prescribed to cover 100% of the planning target volume (PTV; D100). The patient remains on maintenance therapy with olaparib.

Discussion

SBRT and SRS are well-established local-ablative treatment modalities for metastases of various solid tumors (7, 8). However, robust evidence supporting their specific role in patients with metastatic ATC remains limited (6). Given the inherent radioresistance and aggressive biological behavior of ATC, the application of hypofractionated radiotherapy with high doses per fraction is particularly intriguing, as this approach has demonstrated increased biological effectiveness and improved local control rates in radioresistant malignancies (9). Thus, employing SBRT or SRS with ablative radiation doses could effectively delay local progression and improve symptom control in patients with ATC.

A distinct advantage of SBRT and SRS is their short overall treatment duration, typically delivered within one to five fractions. This aspect is especially beneficial for patients with ATC, who frequently present with compromised performance status and rapidly deteriorating clinical conditions. Modern immobilization and motion management techniques further enhance treatment precision, effectively overcoming anatomical challenges such as respiratory-induced tumor movement.

International guidelines, notably from the European Society for Medical Oncology (ESMO) and the American Thyroid Association (ATA), underline the importance of incorporating local therapies into comprehensive treatment strategies, particularly for symptomatic lesions or oligometastatic presentations (10, 11). Typical metastatic sites in ATC include the lungs, bones, and lymph nodes, while clinically evident brain metastases occur in fewer than 15% of all cases (12, 13).

Blomain *et al.* analyzed radiotherapy outcomes for thyroid cancer-related brain metastases, including ATC, within both an institutional cohort and a national cohort from the National Cancer Database (NCDB) database (14). In their institutional analysis (n=33; ATC subgroup n=8), median overall survival (OS) for patients with ATC was only 3.6 months, compared to 10.7 months for those with differentiated thyroid carcinoma (p=0.06). In the NCDB national cohort (n=289; ATC subgroup 15%), median OS was significantly shorter for patients with ATC (2.1 months *vs*. 17.7 months, p<0.001). Notably, an increasing trend towards using stereotactic radiosurgery (SRS) was observed for patients with ATC (p=0.0497), achieving comparable rates of local control (6.4%) and regional intracranial failure (17.9%) as those seen in differentiated thyroid cancer. Furthermore, the incidence of radiation-induced necrosis following SRS was minimal (3.3%). WBRT, despite being used less frequently, showed

no significant survival advantage compared to SRS within the ATC subgroup. Limitations of the Blomain *et al*. study include the small sample size of patients with ATC, retrospective design, and limited details regarding specific treatment parameters and treatment-related toxicity (14).

This systematic review identified a single phase I trial examining SBRT combined with the immune checkpoint inhibitors durvalumab and tremelimumab in metastatic ATC (15). In this trial, SBRT delivered 27 Gy in three fractions across different metastatic sites in 12 patients with ATC. Unfortunately, confirmed tumor responses were lacking, with only one patient demonstrating stable disease after ≥4 cycles of immunotherapy. The median OS was 14.5 weeks, and only one patient survived beyond one year.

In our prospective cohort, we observed effective local tumor control without severe toxicity following SBRT/SRS. In our cohort, notably, one patient experienced a grade II adverse event per CTCAE criteria post-SRS, underlining the favorable risk-benefit ratio of stereotactic radiation in carefully selected patients with oligometastatic ATC. However, our study is limited by a small patient population and single-center design. Therefore, larger-scale prospective multicenter trials or registry studies are warranted to further substantiate these findings and guide clinical decision-making (16).

In conclusion, our findings suggest that SBRT and SRS represent safe and effective therapeutic options for patients with metastatic ATC, offering significant symptom relief with minimal treatment-related toxicity. However, given the poor prognosis associated with ATC and limited patient number, further research is required to refine patient selection criteria and optimize treatment regimens, particularly in combination with systemic therapy.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization: LK; Data curation: RR; Formal analysis: LK; Investigation; LK, RG, RR, JR; Methodology: LK; Project administration: LK; Resources: CB; Supervision: JR; Visualization: LK; Writing - original draft: RR,LK; Writing - review & editing: all Authors. All Authors have read and agreed to the published version of the manuscript.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation and analysis of this manuscript.

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