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Case Report

Local management of unresectable lung atypical carcinoid tumor: a case report and review of literature

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ABSTRACT

Neuroendocrine tumors comprise a rare but increasing heterogeneous group of malignancies arising from neuroendocrine cells, most commonly from the lung and gastrointestinal tract. Due to the vast histopathological differentiation of each subtype and the scarce clinical data published, choosing the most effective therapy can be challenging. Radiotherapy can play a significant role in the treatment of locally advanced metastatic tumors, however there is a lack of randomized clinical trials in this setting. This article reviews the current knowledge on the classification and treatment of unresectable lung atypical carcinoids. We present a clinical case of a ULAC treated with systemic therapy and RT in different settings of the disease. The subject is a 48 years old male, diagnosed with a well differentiated pulmonary NET, classified as cT4N3M1b (supraclavicular and mediastinal adenopathies and an adrenal metastatic lesion) with disease progression after systemic treatment, and with superior vena cava compression. The primary tumor and involved nodal areas were treated to 54Gy/30 fractions using VMAT. SBRT was given to the metastatic left adrenal gland. Five months after RT, CT showed a volumetric reduction of <25% of the thoracic disease and adrenal gland's lesion stability. The disease remained stable for the next year and a half, when local and distant progression occurred, starting systemic treatment. A year and a half later, the patient presented with brain metastasis and underwent radiosurgery. At last follow-up, 5 years after diagnosis, the patient maintains treatment with capecitabine and temozolomide and is clinically stable. Definitive RT should be considered in the management of ULAC to improve local control.

Keywords: Neuroendocrine tumors, Radiotherapy, Local control, Unresectable

INTRODUCTION

Neuroendocrine tumors (NET) form a rare diverse group of malignancies originating from neuroendocrine cells, most commonly arising from the lung and gastrointestinal tract. Within lung NET, they can be categorized into well-differentiated types: low-grade typical carcinoids (TC) and intermediate-grade atypical carcinoids (AC); and poorly differentiated (high-grade large cell or small cell neuroendocrine carcinomas). Despite shared morphologic, ultrastructural, immunohistochemical and molecular characteristics, evidence shows that TC and AC are morphologically distinct from large-cell and small-cell carcinomas. From 5% to 20% of TC and 30% to 40% of AC metastasize, with many patients presenting with recurrent disease or metastases.[1] As a result, delays in diagnosis increase the probability of metastatic disease, which impacts prognosis. In the following, we report a clinical case of a patient diagnosed with an unresectable lung atypical carcinoid (ULAC).

CASE REPORT

The subject is a 48 years old male, with the initial diagnosis of a pulmonary oligometastatic well-differentiated NET, classified as cT4N3M1b (supraclavicular and mediastinal adenopathies and an adrenal metastatic lesion). A PET-TC (August/2018) revealed a large thoracic lesion, in the upper mediastinum/apical segment of the right upper pulmonary lobe, partially necrotic, compatible with malignancy; bilateral supraclavicular, mediastinal and right pulmonary hilar adenopathies, as well as two nodules in the left adrenal gland, with a SUVmax of 5.6. An Octreoscan (November 2018) revealed extensive right anterior superior mediastinal adenopathies, extending from the retrosternal region to the precarinal region, but also involving the left mediastinum; probable activity focus on right perihilar adenopathy; cervical adenopathy with somatostatin receptors.

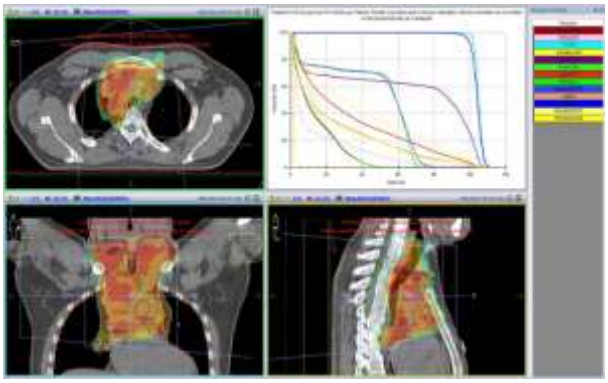

Figure 1: Thoracic VMAT-IGRT planning with corresponding isodoses. A total dose of 54 Gy/30 fractions was given to the tumor and involved lymph node areas (maximum dose possible considering high disease volume, in order to respect organs at risk constraints).

A biopsy of the supraclavicular node was obtained, revealing a well-differentiated neuroendocrine tumor with pulmonary origin. The immunochemical study showed strong positivity for cytokeratins 7, 8/18, TTF-1, chromogranin A, synaptophysin and CD56, and negativity for cytokeratin 20 and CDX-2. From October-December 2018, the patient underwent chemotherapy with carboplatin and etoposide, however no clinical/ imagiological response was seen. Biopsy was repeated in January/2019, revealing by that time a neuroendocrine G2 AC. Both biopsies showed an absence of necrosis and a Ki67 of 10%. In contrast with the first biopsy, the latter showed 3 mitosis/mm². Positivity for cytokeratins was still present. The patient started therapy with octreotide in February 2019. No clinical response was seen and disease progression was observed five months later.

At multidisciplinary tumor-board discussion, the case has been considered as unresectable, the thoracic mass was compressing the superior vena cava with reduction of caliber and it has been proposed for radiotherapy (RT). At the time of the first appointment at the Radiation Oncology department (September/2019), given unresectable, oligometastatic, progressive disease, with no other therapeutical alternatives at that time and considering the patient's good performance status (PS), definitive RT was offered. Volumetric Modulated Arch Therapy with Image Guided Radiotherapy (VMAT-IGRT) was given to the tumor and involved lymph node areas, to a total dose of 54Gy in 30 daily fractions (maximum dose possible considering the high disease volume, in order to respect organs at risk constraints) (Figure 1).

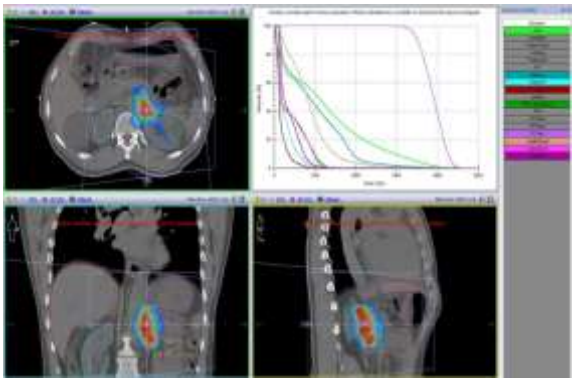

Figure 2: Left metastatic adrenal SBRT planning with corresponding isodoses. A total dose of 35 Gy/5 fractions was given to the metastatic left adrenal gland.

Stereotactic Body Radiation Therapy (SBRT) was given to the metastatic left adrenal gland, to a total dose of 35Gy in 5 fractions (Figure 2). Treatment was well tolerated; the patient only experienced grade 1-2 radiodermatitis, grade 2 dysphagia and asthenia. Four months after thoracic RT and five months after adrenal SBRT, thoracoabdominal CT showed a volumetric reduction of less than 25% of the thoracic disease and adrenal gland's lesion stability (Figure 3). By that time, the patient was asymptomatic. The disease remained stable for the next year and a half in the control CT scans. However, in June 2021, an 18-FDG-PET revealed de novo inferior paraesophageal, para-aortic and laterocervical nodal hypercaptation and an iliac lytic lesion; as well as hypercaptation persistence of some mediastinal and supraclavicular nodal areas Consequently, the patient started chemotherapy with carboplatin-etoposide, followed by everolimus due to another disease progression. In December 2022, cutaneous disease progression (presternal and scalp lesions) was observed. At the same time, cerebral TC revealed a left parietal brain lesion (Wernicke's area) and other millimetric ones in the cerebellum and brainstem without vasogenic edema or mass effect. By that time, the patient had experienced one episode of seizures. The patient started chemotherapy with capecitabine - temozolamide. The cutaneous lesions responded completely to chemotherapy. Nevertheless, the brain metastasis (BM) continued increasing, achieving 1.93 cm (AP) x 2.45 cm (T) x 1.78 cm (CC) size.

Multidisciplinary tumor board decided neurosurgery wasn't the best option for this patient.

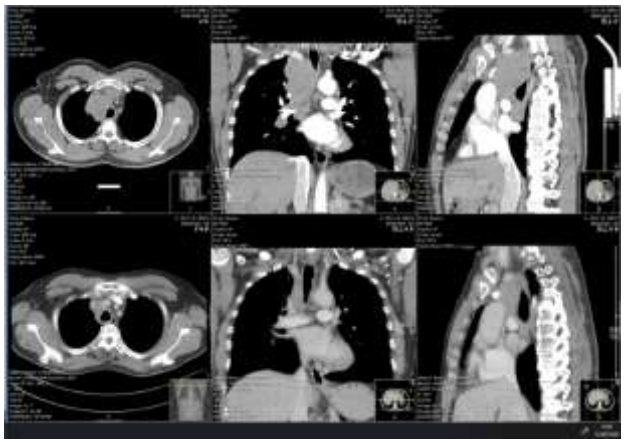

Figure 3: Imagiological response before and after thoracic RT. Above: thoracic CT June 2019 (3 months before RT); below: thoracic CT from April 2020 (6 months after RT).

Considering the optimal response to chemotherapy, the patient's good PS and the absence of any other therapy, the board decided on stereotactic radiosurgery (SRS). A single fraction of 20Gy was given to the largest metastasis (4.7cc) in march/2023 (Figure 4).

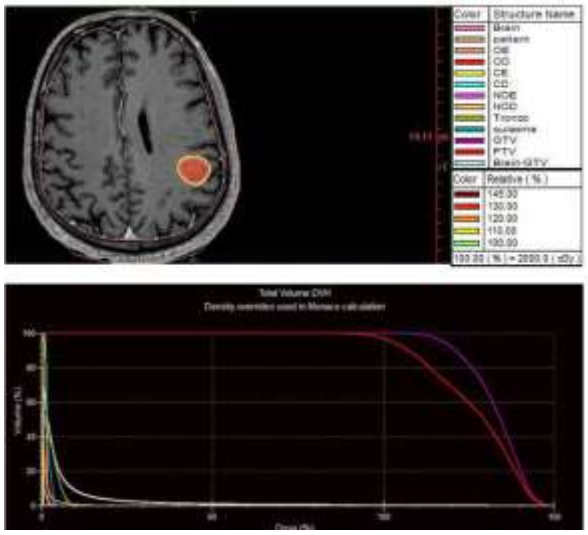

Figure 4: SRS planning and corresponding isodoses (20Gy in a single fraction to the 4.7cc brain metastasis in March 2023).

Three months later, the MRI showed reduction of the irradiated lesion and stability of the millimetric ones. However, six months after SRS, a new MRI revealed an increase of the irradiated lesion with associated vasogenic edema. The clinical board decided on surgical resection and the patient was submitted to surgery in august/2022. The postoperatory MRI documented tumor persistence and posteriorly the histopathological result reported a metastasis of a carcinoid carcinoma with pulmonary origin. The patient presented post-operative dyslexia, dysgraphia and mixed aphasia. Consequently, the multidisciplinary tumor board decided on adjuvant stereotactic fractionated radiosurgery (SFRS). Twenty-four Gray in 3 fractions was given to the tumor bed (14.3 cc), 7 weeks after surgery (Figure 5).

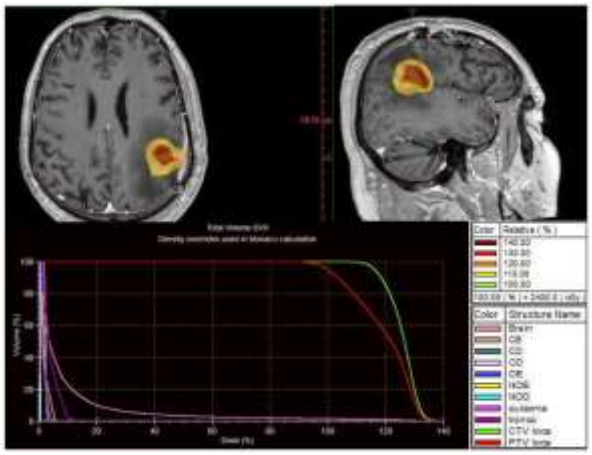

Figure 5: SFRS planning and corresponding isodoses (24Gy in 3 fractions was given to the 14.30cc tumor bed).

At the last follow-up (FU), one month after SFRS, the patient maintains treatment with capecitabine and temozolomide and is clinically stable. The speaking impairment improved with therapy. The first follow up MRI at 2 months after SFRS is due to be in two weeks.

DISCUSSION

Histopathology

Pulmonary NET exhibit subtle histopathologic differences, particularly in small biopsy specimens or cytologic samples. This can lead to substantial interobserver variability among pathologists when distinguishing between TC and AC and, less often, over diagnosis of SCLC. This complicates the ability to accurately classify patients with pulmonary NET, compromising the selection of appropriate treatment and ultimately prognosis. NET rarely exhibit mitotic figures. These cells also express intense immunohistochemical positivity for neuroendocrine markers such as synaptophysin, chromogranin A, somatostatin receptors (SSTRs), or CD56. In contrast, NEC (neuroendocrine carcinoids) present as a solid proliferation of less monomorphic cells with either scant (small-cell types) or abundant (large-cell types) cytoplasm and high mitotic rates. NEC commonly exhibit areas of necrosis.[1]

The classification of NET according to tumor grade is of the utmost importance since it correlates with prognosis and therefore influences treatment. However, this classification causes great confusion for clinicians, as the defining criteria and terminology of each entity are not

universal for every organ and have changed throughout the years. The World Health Organization (WHO) initially introduced the terms typical carcinoid, atypical carcinoid, and NEC (either small-cell or large-cell) for pulmonary NET. In 2018, the WHO proposed a standard classification for NET, regardless of their origin site. Tumors with predominant neuroendocrine differentiation based on immunohistochemical criteria, whether well or poorly differentiated, were categorized as neuroendocrine neoplasms. Overall, NET present mostly non-neoplastic histology, while NEC have high-grade histological characteristics. Thus, "neuroendocrine tumor" should be used for well-differentiated NET and "neuroendocrine carcinoma" for poorly differentiated NET. Finally, a grading system was implemented for most NET. NET should generally be graded as G1, G2 and G3, representing low-grade, intermediate-grade and high-grade, respectively. NEC need no further grading, as they are, by definition, high-grade. To grade NET, three parameters out of 19 parameters must be reported: mitotic count, Ki67 labeling index, and the presence or absence of necrosis.[1] In 2021, the WHO Classification of Thoracic Tumors classified lung NET as TC, AC, and high-grade carcinoma with small or large cells. In 2022, the WHO published its latest Classification of Endocrine and Neuroendocrine Tumors, officially endorsing the aforementioned grading system for most NET. Lung and thymus NET are categorized as low-grade carcinoids and intermediate-grade AC corresponding to G1 and G2 grades, respectively (based on the proliferative rate). Besides the pathology examination, clinical and imaging features should also be considered to establish an accurate diagnosis. NET can be detected on functional imaging, as they can remain undetected on PET/MRI. Therefore, Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) is recommended in NEC as part of functional imaging. NET are typically positive for specific hormones and strongly express SSTRs. Conversely, NEC do not express specific hormones and are mostly negative or weakly positive for SSTRs, except for a few large-cell NEC. The cutoff value of 10 mitoses/2 mm² is the criterion that distinguishes carcinoids from carcinomas. While not mandatory, the latest WHO classification considers Ki67 a "desirable" feature to be reported, particularly on small biopsies for differentiating carcinoids from carcinomas. On biopsy samples, Ki67 seems to better predict the definitive proliferative activity of the resected tumor than the mitotic count. The cutoff value of the Ki67 index used to define each category of lung NET, and its prognostic value remain up for debate.[1]

In our case, a fine needle aspiration biopsy of a supraclavicular node initially revealed a well-differentiated neuroendocrine tumor with pulmonary origin. The immunochemical study showed strong positivity for cytokeratins 7, 8/18, TTF-1, chromogranin A, synaptophysin and CD56, and negativity for cytokeratin 20 and CDX-2. Due to the fact that Ki67 index was reported, differentiating between a carcinoma and a carcinoid was already possible. After the start of chemotherapy and no therapeutical response was seen, biopsy was repeated, revealing by that time a neuroendocrine G2 AC. Both biopsies showed an absence of necrosis and a Ki67 of 10%. In contrast with the first biopsy, which showed absence of mitosis, the latter showed 3 mitosis/mm², which ultimately made the diagnosis of an AC. The histopathology result of the BM reported a metastasis of a carcinoid carcinoma with pulmonary origin. No mention of Ki67 index or mitosis was made, thus differentiating between the two entities was not possible.

Systemic therapy

Both TC and AC are capable of regional lymph node or distant metastases, with AC being more aggressive than TC. In a large multi-institutional study, AC exhibited higher rates of lymph node involvement at diagnosis (36%) and distant metastases (26%) compared to TC (9% and 4%, respectively). AC are associated with poorer 5- and 10-year survival rates than TC. Moreover, there is a lack of consensus regarding the management of unresectable advanced or metastatic disease due to the lack of prospective clinical trials, that include primarily patients with lung carcinoids. Studies of cytotoxic chemotherapy regimens in the advanced or metastatic lung carcinoid setting have been limited to small prospective studies or retrospective analyses, showing minimal, short-lasting activity, particularly for AC. Consequently, there is no established standard chemotherapeutic regimen. The NCCN guidelines on NET suggest considering cytotoxic chemotherapy for patients with progressive metastases only when no other treatment options are available.[2,3] In contrast, the NCCN SCLC guidelines used to recommend cisplatin-etoposide (preferred first-line in stage IV AC) or other cytotoxic regimens (e.g., temozolomide-based) for advanced TC and AC. Nevertheless, in our case, no clinical/ imagiological response was seen after first-line chemotherapy with carboplatin-etoposide.

European Neuroendrocine Tumor Society (ENETS) guidelines suggest that the clinical response of TC to Somatostatin analogues (SSAs) (octreotide and lanreotide) is expected to be similar to that of low-grade NET from other sites. They recommend using SSAs as a first-line treatment for patients with lung carcinoids exhibiting hormone-related symptoms (carcinoid syndrome or Cushing's syndrome). Furthermore, considering that most patients with TC or AC have a positive SSTR (Somatostatin Receptors) status when assessed by Octreoscan, ENETS guidelines recommend first-line antiproliferative treatment for a slowly progressive TC or AC with a low proliferative index (preferably Ki-67 <10%), provided there is a strongly positive SSTR status.[4,5] In our case, the patient's Octreoscan showed positivity for SSTR and therapy with octreotide was started. However, disease progression was observed short time after its start. Additionally, according to the ENETS guidelines, systemic chemotherapy is generally reserved for AC after the failure of other therapies and only under

certain conditions (Ki-67 >15%, rapidly progressive disease, and SSTR-negative disease), and they note that temozolomide monotherapy has shown the most clinical benefit. Capecitabine-temozolomide has shown moderate activity in a small, single-institution study of patients with advanced lung carcinoids (N=19), with 11 of 17 patients (65%) demonstrating stable disease or partial response.[1] After the diagnosis of disease progression, our patient started capecitabine-temozolomide with complete response of the cutaneous lesions, even though the BM continued increasing. The efficacy of Everolimus in patients with advanced, well-differentiated, nonfunctional NET of GI/lung origin receiving best supportive care (excluding SSAs) was demonstrated, leading to its approval by the US Food and Drug Administration in 2016. However, our patient presented disease progression with everolimus.

Radiotherapy

While surgery is the mainstay of definitive treatment for localized NET, over half of patients that have unresectable or metastatic disease at diagnosis may not qualify for surgery due to medical comorbidities. Thus, there is a need for treatment that can provide adequate local control (LC). Although carcinoid tumors have been considered as radioresistant, several reports highlight successful outcomes using RT for both AC and TC.[6] Current evidence for the use of RT in NET is limited and mostly comes from single-institution retrospective reviews with small sample sizes. While RT has long been used for palliation in the metastatic setting, the development of highly conformal RT techniques allows for the delivery of definitive dose of radiation not only to localized disease but also to limited sites of metastatic disease without major toxicity. Chen et al review endorses the use of RT for NET demonstrating excellent LC across various primary disease sites, grades, and tumor differentiation. 60% of patients had well-differentiated neuroendocrine tumors (N=27), and 40% had poorly differentiated NET (N=18). At the time of RT, 49% of patients had either localized or locally advanced disease (N=22), while 51% had metastatic disease (N=23). The median Biologically Effective Dose (BED) of the radiation courses was 72 (IQR 60-85), with prescriptions ranging from 60Gy in 3 fractions (BED 180) to 70Gy in 33 fractions (BED 85). In the majority of cases, high-dose radiation was delivered to the primary site of disease (N=23, 51%), with the remainder delivered to metastatic sites such as bone (N=9, 20%), lymph nodes (N=6, 13%), and other (N=7, 16%). Nearly half of the patients (N=22, 49%) received a treatment course of 5 fractions or less. Within this study, 68% of patients treated with high-dose radiation achieved either a partial or a complete radiographic response in the treated lesion. After a median substitute follow up for FU of 24 months, the 2-year actuarial rates of local relapse-free survival, new metastasis-free survival, progression free survival (PFS), and overall survival (OS) following RT were 98%, 45%, 41%, and 69%, respectively. The median PFS after RT was 19 months, and median OS after RT was 43 months. Among the patients, 28% (N=7) had a complete response, 40% (N=10) had a partial response, and 32% (N=8) had stable disease at the irradiated site. The best response was achieved at a median time of 4.2 months after irradiation.[6] In our case, given unresectable, oligometastatic, progressive disease, with no other therapeutic alternatives, definitive RT was offered. VMAT-IGRT was given to the primary tumor and involved nodal areas, totalizing a dose of 54Gy in 30 daily fractions (maximum dose possible considering the high disease volume, in order to respect organs at risk constraints). Five months after RT, thoracoabdominal CT showed a volumetric reduction of less than 25%. For the next year and a half, there was no evidence of disease progression.

Adrenal SBRT

The increased use of routine CT or PET-CT staging has led to a rise in the identification of patients with asymptomatic adrenal metastases. However, the current literature on adrenal SBRT is still limited. A recent meta-analysis identified over 1000 patients treated with SBRT for adrenal metastases in 39 studies published between 2009 and September 2019. SBRT demonstrated excellent one-year LC, effective pain relief and tumor reduction with a notably low clinically significant toxicity rate of only 1.8%.[7] In the analysis of Koenig et al, adrenal SBRT led to promising LC in 28 patients, accompanied by only mild toxicity. The one-year and two-year LC rates was 84.8%, which compares favorably to other studies. According to the RECIST criteria, 29% of lesions achieved a complete response, 57% a partial response and 7% remained stable. Two patients were diagnosed with local relapse at 7.0 and 8.2 months.[8] Both Scouarnec et al and Toesca et al reported LC rates of 92.4-96.5% after one year and 80.8-92.6% after two years.[9,10] Koenig's analysis also detected a non-significant trend for superior LC if a BED_{10} ≥75Gy was applied (p=0.101). Both patients diagnosed with a local recurrence were treated with a BED_{10} <67.5 Gy. However, due to the proximity of the adrenal glands to the stomach, the duodenum and the small bowel and their intrinsic radiosensitivity, a higher dose often could not be safely delivered without potentially increasing toxicity. The SARON trial, a UK-based randomized trial comparing SBRT to chemotherapy in oligometastatic NSCLC, allows for a prescription dose for adrenal metastases between 30 to 45Gy in 3 fractions with at least 95% PTV coverage.[11] This spectrum of dose corresponds to a wide range of BED_{10} (60-100Gy). Regarding our patient, SBRT was given to the metastatic left adrenal gland, to a total dose of 35Gy in 5 fractions (BED=59.50Gy), in order to respect organs at risk constraints, namely the kidney and small bowel. Five months after RT, thoracoabdominal CT showed adrenal gland's lesion stability.

Radiosurgery

Carcinoid tumors are among the most unusual sources of BM with reported incidences of 1.5-5%. Some even large

series of intracranial metastatic neoplasms do not include cases of carcinoid tumors. BM predominantly occur in more aggressive carcinoid tumors and in the late phases of the disease. The size of the primary tumor is another important prognostic factor associated with brain localizations. Indeed, according to Mauri et al., all cases with intracranial metastases had large primary tumors (more than 3-4 cm and often up to 7-8 cm). Most of the patients with BM have single intraparenchymal lesions and the median interval between diagnosis of the primary and development of a BM is 16 months. There is limited data available on the survival in patients with carcinoid metastases to the brain with OS rates around 20% at 2 years and less than 5% at 5 years.[12]

There are no established treatment guidelines for patients with BM from carcinoid tumors. Treatment options include surgery, RT such as whole brain radiotherapy (WBRT) or SRS, or chemotherapy, either as monotherapy or in combination. In cases of a single BM, surgery is often the method of choice, especially if causing a focal neurological deficit. The combination of WBRT and surgery has been shown to improve survival for carcinoid BM, with a median survival time of 3.2 years compared to 4.8 months for surgery alone and 6.0 months for WBRT alone. SRS has not been extensively studied in carcinoid BM due to the rarity of presentation. However, a phase III clinical trial comparing postoperative SRS versus WBRT in resected solitary BM from multiple tumor types showed no difference in OS between the two approaches. Remarkably, WBRT was associated with more frequent decline in cognitive function than SRS, suggesting that SRS may be a less toxic adjuvant for the treatment of solitary BM.[13] Our patient was not initially considered a candidate for neurosurgery, as he did not present focal deficits, nor vasogenic edema and the lesion was in the Wernicke's area, which could compromise speaking. Besides, there were also other millimetric metastatic brain foci, which is why WBRT was initially considered. However, since the cutaneous lesions responded completely to capecitabine and temozolomide and the latter has an optimal central nervous system penetration, SRS was ultimately offered, since the millimetric foci could respond to temozolomide. 20Gy in a single fraction was given to the 4.7cc BM and lesion's reduction was observed 3 months later. Nevertheless, six months after SRS, a new MRI revealed an increase of the irradiated lesion with associated vasogenic edema.

Stereotactic reirradiation

The optimal treatment for patients facing local failure in BM after prior SRS remains uncertain. Salvage options encompass chemotherapy, surgery, WBRT, supportive care or stereotactic reirradiation. However, there is no clear evidence establishing the superiority of one modality over another, and as of now, no clear consensus has emerged on this matter. Surgical resection is often considered a preferred salvage modality, as it allows for pathological assessment, addressing both radiation necrosis (RN) or tumor progression, with prompt symptoms relief and resulting in satisfactory LC rates ranging from 62% to 93% at 1 year and a median survival of 8.7 months after surgery.[14,15] However, a neurosurgical approach does not obviate for subsequent use of reirradiation to confer additional LC benefit in most cases. In the last decade, there has been an increasing use of stereotactic reirradiation for recurrent BM. However, this approach has been questioned in terms of both efficacy and tolerability. There is controversy regarding the effectiveness of a second course of RT following prior selection of radio-resistant clones.[16] Moreover, stereotactic reirradiation might be correlated to an unacceptable risk of adverse events, with a cumulative 1-year symptomatic RN incidence of 20%.[17] In the meta-analysis of Mauro et al, "eleven retrospective studies on stereotactic reirradiation for local failure of brain metastases following RS", 335 patients were included.[18] The most significant finding was a pooled 24% one-year local failure rate, indicating that LC rates following stereotactic reirradiation do not dramatically differ from those reported by prospective trials of upfront SRS.[19-21] The median survival in the pooled population was 14 months from the date of the reirradiation, comparable to median survival following a first course of SRS in selected subsets, that is approximately 11 months in patients with high score at GPA prognostic index.[22] In patients experiencing in-site recurrence of BM following upfront SRS, a second course of SRS seems to be an effective strategy. According to the meta-analysis, SRS results in median OS exceeding 12 months, with LC rates comparable to results from surgical series. However, stereotactic reirradiation was associated with the development of symptomatic RN in 13% of pooled patients. Stereotactic reirradiation was offered to the 14.2cc tumor bed (24Gy in 3 fractions). The reirradiation took place in the last month, and a new MRI is scheduled for this month. At the last substitute follow up for FU he was clinically stable. Five years after diagnosis and 4 years after the first course of RT, our patient is still alive. A definitive RT approach should be considered in the management of oligometastatic unresectable NET, if the patients are suitable. The correct diagnosis and an accurate staging of the disease are crucial, as more aggressive strategies may increase LC and PFS.

CONCLUSION

The correct histopathological diagnosis of the neuroendocrine tumor subtype is of extreme importance, as it has direct effect on treatment and prognosis. Definitive RT is an important treatment option to consider for young patients, with good PS and limited sites of unresectable disease and appears effective in LC. SBRT of adrenal metastases provides good one-year LC with an excellent safety profile. SRS may be a newer modality for the treatment of solitary carcinoid brain metastasis with similar efficacy but reduced toxicity. Prospective randomized trials are needed to validate these findings and determine whether there are subsets of

patients for whom carcinoid metastases–directed therapy may confer a survival advantage.

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