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Stereotactic radiotherapy for adrenal oligometastases

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ABSTRACT

Approximately 50% of melanomas, 30–40% of lung and breast cancers and 10–20% of renal and gastrointestinal tumors metastasize to the adrenal gland.

Metastatic adrenal involvement is diagnosed by computed tomography (CT) with contrast medium, ultrasound (which does not explore the left adrenal gland well), magnetic resonance imaging (MRI) with contrast medium and 18F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}FDGPET-CT) which also evaluates lesion uptake. The simulation CT should be performed with contrast medium; an oral bolus of contrast medium is useful, given adrenal gland proximity to the duodenum. The simulation CT may be merged with PET-CT images with ^{18}FDG in order to evaluate uptaking areas. In contouring, the radiologically visible and/or uptaking lesion provides the gross tumor volume (GTV). Appropriate techniques are needed to overcome target motion. Single fraction stereotactic radiotherapy (SRT) with median doses of 16–23 Gy is rarely used. More common are doses of 25–48 Gy in 3–10 fractions although 3 or 5 fractions are preferred. Local control at 1 and 2 years ranges from 44 to 100% and from 27 to 100%, respectively. The local control rate is as high as 90%, remaining stable during follow-up when BED_{10Gy} is equal to or greater than 100 Gy. SRT-related toxicity is mild, consisting mainly of gastrointestinal disorders, local pain and fatigue. Adrenal insufficiency is rare.

Key words: stereotactic radiotherapy; radiosurgery; oligometastasis; adrenal metastases; organ motion; hypofractionation; BED; local control; toxicity

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Incidence and diagnostic work-up

Approximately 50% of melanomas, 30–40% of lung and breast cancers and 10–20% of renal and gastrointestinal tumors metastasize to the adrenal gland in the natural history of the disease [1–3].

Symptoms of adrenal metastases are mainly epigastric pain, frequently radiating posteriorly, and adrenal insufficiency, such as weakness, anorexia, nausea, skin hyperpigmentation, hypotension and electrolyte balance disorders. Acute adrenal insufficiency is rare [4, 5].

Metastatic adrenal involvement is diagnosed by detecting gland anatomical alterations [6]. Nodular abnormalities of the adrenal medullary are visualized by computed tomography (CT) with contrast medium, ultrasound (which does not explore the left adrenal gland well), magnetic resonance imaging (MRI) with contrast medium and positron emission tomography-computed tomog-

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raphy (PET-CT) with 18F-fluorodeoxyglucose (^{18}FDG) [7]. Diagnostic accuracy is good with all these techniques which also assess adrenal size and structure. PET-CT also evaluates lesion uptake [6–8].

All these imaging techniques are non-specific as they do not differentiate metastases from benign lesions, such as adenomas. Therefore, biopsy is essential, especially in cases of solitary lesions. Micro-histological sampling by eco- or CT-guided needle biopsy is more sensitive than cytology in defining the histological type [9–11].

Surgery has long been, and is, the main therapy for isolated adrenal metastases. It significantly prolongs survival [12–13], particularly of patients with metacrone metastases. Katayama et al. described 5/11 patients with isolated adrenal metastases from colon cancer who remained alive and disease-free after surgical adrenalectomy in follow-ups ranging from 8 months to 9 years [13].

Mercier et al. reported 5-year overall survival (OS) rates of 23% in patients with non small cell lung carcinoma (NSCLC) adrenal metastases which rose to 38% in patients with metastases occurring within 6 months or later of surgery for the primary tumor [3, 14–15].

Suggested doses, fractionations and constraints

The adrenal gland is located in close proximity to organs at risk (OARs), such as the stomach, duodenum, intestine, kidney, liver and spinal cord. Consequently, since the risk of toxicity is a dose-limiting factor, conventional external beam radiotherapy (EBRT), which administers low doses and is associated with transient and/or incomplete response rates, has never been considered a valid alternative to surgical resection of solitary adrenal metastases. A 6-month survival rate of 28% dropped to 12.5% when symptoms were present in 14 patients with adrenal metastases who received up to 60 Gy [3, 16]. As a result, EBRT is used only for pain palliation [17, 18].

Indications for radiation therapy in the treatment of solitary adrenal metastases have changed in recent years, with advances in diagnostic imaging, treatment planning, radiation therapy techniques (intensity modulated radiotherapy — IMRT, volumetric-modulated arc therapy — VMAT, Tomotherapy®, Cyberknife®) and the introduction of image-guided radiation therapy (IGRT).

Stereotactic radiotherapy (SRT) administers highly precise, ablative doses of radiation that closely conform to the target neoplastic volume. Small margins and steep dose gradients minimize the impact on OARs [19–22].

Target and OAR identification by means of appropriate imaging are essential for successful SRT. The simulation CT, preferably with contrast medium, should be performed with 3 mm thick slices. An oral bolus of contrast medium is suggested, given adrenal gland proximity to the duodenum. The simulation CT may usefully be merged with PET-CT images with ^{18}FDG, in order to evaluate uptaking areas.

For contouring, the gross tumor volume (GTV) is the radiologically visible and/or uptaking lesion. Systems for organ movement assessment and/or control are useful [23]. When 4-dimensional computed tomography (4D-CT) images are acquired, an internal target volume (ITV) is identified and expanded by 3–5 mm to obtain the planning target volume (PTV).

ICRU 91 recommendations [24] should be followed to optimize the treatment plan and spare the OARs while respecting constraints.

Various doses and fractions were reported. Single fraction SRT with median doses of 16–23 Gy [biologically effective dose $(BED)_{10Gy}$ = 41.6–75.9 Gy] is rarely used [16, 24, 26]. More common are doses of 25–48 Gy in 3–10 sessions (BED_{10Gy} = 41.6–75.9 Gy) although 3 or 5 sessions are preferred [20, 27–30] (Tab. 1).

Results and toxicity

Outcomes of SRT on adrenal metastases varied in terms of local control (LC) and overall survival (OS). At 1 and 2 years, LC ranged from 44 to 100% and from 27 to 100%, respectively [31].

The LC rate was as high as 90%, remaining stable during follow-up when BED_{10Gy} was equal to or greater than 100 Gy [27, 32, 33]. The type of primary tumor, metachronous or synchronous onset and presence of other metastatic sites did not impact significantly on disease control.

At a median of 23 months OS was similar to surgical adrenalectomy [22, 34, 35] and was obviously better for isolated metastases. Comparing outcomes

Table 1. Examples of doses and fractions most frequently used

Author, year	Median dose/fractions (dose range)/(fraction range)
Arcidiacono et al. (2020) [28]	30 Gy/5
Scouarnec et al. (2019) [50]	45 Gy/3 (30-55)/ (3-9)
Zhao et al. (2018) [45]	44.4 Gy/5 (32–50 Gy)/ (3–8)
Buergy et al. (2018) [46]	35 Gy/7 (20-60 Gy)/ (4–25)
Palacios et al. (2018) [47]	50 Gy/5, 60 Gy/8, 24 Gy/3
Franzese et al. (2017) [48]	40 Gy /4
Haidenberger et al. (2017) [51]	40.5 Gy/3 (20–45)/(1–3)
Desai et al. (2015) [19]	54.5 Gy/3 (13–30)/ (1–5)
Li et al. (2013) [49]	30–50 Gy/ (3–5)
Casamassima et al. (2012) [33]	36 Gy/ 3 (21–54 Gy)/3
Torok et al. (2011) [26]	22 Gy/1 (10–36)/ (1–3)

after SRT and surgery is not, however, informative due to the lack of randomized studies and different selection criteria. In fact, isolated, small metastases were more frequent in patients in the surgical series [15, 21, 34, 36, 37].

Although insufficient, the RECIST criteria are commonly used to evaluate response to treatment. Many authors suggested that PET uptake data [38, 39] should be associated with contrast medium CT anatomical data.

Treatment-related toxicity was mild in all reports, consisting mainly of gastrointestinal disorders, local pain and fatigue [21, 34, 40, 41]. Adrenal insufficiency was rare [27, 42, 43]. These data encourage further clinical studies to assess the effects of SRT on LC and progression-free survival (PFS) in patients with oligometastatic adrenal [44].

Table 1 shows the SRT schemes in different series.

Conflicts of interest

The authors have no conflict of interest to declare.

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