Stereotactic radiotherapy for adrenal oligometastases

Simona Borghesi¹, Franco Casamassima², Cynthia Aristei¹, Antonella Grandinetti¹, Rossella Di Franco⁵

¹Radiation Oncology Unit of Arezzo-Valdarno, Azienda USL Toscana Sud Est, Italy
²Ecomedica Radiotherapy, Empoli, Italy
³Radiation Oncology Section, University of Perugia and Perugia General Hospital, Perugia, Italy
⁴Radiotherapy Unit, Apuane Hospital, Azienda USL Toscana Nord Ovest, Italy
⁵Radiation Oncology Unit, Istituto Nazionale Tumori — IRCCS — Fondazione G. Pascale, Naples, Italy

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 (¹⁸FDG-PET-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 ¹⁸FDG 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 BED₁₀Gy 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

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-

Address for correspondence: Simona Borghesi, MD, Radiation Oncology Unit of Arezzo-Valdarno, Azienda USL Toscana Sud Est, Via Curtatone 54, 52100 Arezzo, Italy, tel: +39 340 9125890, fax: +39 0575 254086; e-mail: s.borghesi@gmail.com

This article is available in open access under Creative Common Attribution-Non-Commercial-No Derivatives 4.0 International (CC BY-NC-ND 4.0) license, allowing to download articles and share them with others as long as they credit the authors and the publisher, but without permission to change them in any way or use them commercially

https://journals.viamedica.pl/rpor
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)$_{10}$Gy = 41.6–75.9 Gy] is rarely used [16, 24, 26]. More common are doses of 25–48 Gy in 3–10 sessions (BED$_{10}$Gy = 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$_{10}$Gy 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
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.

Funding
This publication was prepared without any external source of funding.

Ethical permission
Ethical approval was not necessary for the preparation of this article.

References

1. Lam KY, Lo CY. Metastatic tumours of the adrenal glands: a 30-year experience in a teaching hospital. Clin Endocrinol (Oxf). 2002; 56(1): 95–101, doi: 10.1046/j.0300-0664.2001.01435.x, indexed in Pubmed: 11849252.
2. Adrenal metastases Emedicine. http://www.emedicine.com/radio/topic17.htm (2 Jan 2021).
3. Cingam SR, Makkamalla SKR, Karanchi H. Adrenal Metastasis. In: Cingam SR, ed. StatPearls. StatPearls Publishing, Treasure Island 2020: Jan.
4. Carvalho F, Louro F, Zakout R. Adrenal insufficiency in Metastatic Lung Cancer. World J Oncol. 2015; 6(3): 375–377, doi: 10.14740/wjono890w, indexed in Pubmed: 28983332.
5. Redman BG, Pazdur R, Zingas AP, et al. Prospective evaluation of adrenal insufficiency in patients with adrenal metastasis. Cancer. 1987; 60(1): 103–107, doi: 10.1002/1097-0142(19870701)60:1<103::aid-cncr2820600119>3.0.co;2-y, indexed in Pubmed: 3581024.
6. Sabet FA, Majdzadeh R, Mostafazadeh Davani B, et al. Likelihood ratio of computed tomography characteristics for diagnosis of malignancy in adrenal incidentaloma: systematic review and meta-analysis. J Diabetes Metab Disord. 2015; 15: 12, doi: 10.1186/s40200-016-0224-z, indexed in Pubmed: 27104171.
7. Kumar R, Shamim SA, Shandal V, et al. FDG PET/CT in detection of adrenal metastasis in patients with renal cell carcinoma. Clin Nucl Med. 2011; 36(7): 513–517, doi: 10.1097/RLU.0b013e3182175435, indexed in Pubmed: 21637050.
8. Low G, Dhihiwayo H, Lomas DJ. Adrenal neoplasms. Clin Radiol. 2012; 67(10): 988–1000, doi: 10.1016/j.crad.2012.02.005, indexed in Pubmed: 22486993.
9. Katz RL, Patel S, Mackay B, et al. Fine needle aspiration cytology of the adrenal gland. Acta Cytol. 1984; 28(3): 269–282, indexed in Pubmed: 6587703.
10. Berkman WA, Bernardino ME, Sewell CW, et al. The computed tomography-guided adrenal biopsy. An alternative to surgery in adrenal mass diagnosis. Cancer. 1984; 53(10): 2098–2103, doi: 10.1002/1097-0142(19840515)53:10<2098::aid-cncr2820531018>3.0.co;2-0, indexed in Pubmed: 6704899.
11. Wadih GE, Nance KV, Silverman JF. Fine-needle aspiration cytology of the adrenal gland. Fifty biopsies in 48 patients. Arch Pathol Lab Med. 1992; 116(8): 841–846, indexed in Pubmed: 1497466.
12. Tanvetyanon T, Robinson LA, Schell MJ, et al. Outcomes of adrenalectomy for isolated synchronous versus metachronous adrenal metastases in non-small-cell lung cancer: a systematic review and pooled analysis. J Clin Oncol. 2008; 26(7): 1142–1147, doi: 10.1200/JCO.2007.14.2091, indexed in Pubmed: 18309950.
13. Katayama A, Mafune K, Makuuchi M. Adrenalectomy for solitary adrenal metastasis from colorectal carcinoma.

### 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) |
Jpn J Clin Oncol. 2000; 30(9): 414–416, doi: 10.1093/jjco/hyd104, indexed in Pubmed: 11095141.

14. Mercier O, Fadel E, de Perrot M, et al. Surgical treatment of solitary adrenal metastasis from non-small cell lung cancer. J Thorac Cardiovasc Surg. 2005; 130(1): 136–140, doi: 10.1016/j.jtcvs.2004.09.020, indexed in Pubmed: 15999053.

15. Sarela AI, Murphy I, Coit DG, et al. Metastasis to the adrenal gland: the emerging role of laparoscopic surgery. Ann Surg Oncol. 2003; 10(10): 1191–1196, doi: 10.1245/aso.2003.04.020, indexed in Pubmed: 14654476.

16. Chawla S, Chen Y, Katz AW, et al. Stereotactic body radiotherapy for treatment of adrenal metastases. Int J Radiat Oncol Biol Phys. 2009; 75(1): 71–75, doi: 10.1016/j.ijrobp.2008.10.079, indexed in Pubmed: 19250766.

17. Soffen EM, Solin LJ, Rubenstein JH, et al. Palliative radiotherapy for symptomatic adrenal metastases. Cancer. 1999; 65(6): 1318–1320, doi: 10.1002/1097-0142(19990315)65:6<1318::aid-cncr2820650611>3.0.co;2-4, indexed in Pubmed: 11590517.

18. Short S, Chaturvedi A, Leslie MD. Palliation of symptomatic adrenal gland metastases by radiotherapy. Clin Oncol (R Coll Radiol). 1996; 8(6): 387–389, doi: 10.1016/s0936-6555(96)80087-2, indexed in Pubmed: 8973857.

19. Desai A, Rai H, Haas J, et al. A Retrospective Review of CyberKnife Stereotactic Body Radiotherapy for Adrenal Tumors (Primary and Metastatic): Winthrop University Hospital Experience. Front Oncol. 2015; 5: 185, doi: 10.3389/fonc.2015.00185, indexed in Pubmed: 26347852.

20. Katoh N, Onimaru R, Sakuhara Y, et al. Real-time tumor-tracking radiotherapy for adrenal tumors. Radiology. 2008; 87(3): 418–424, doi: 10.1016/j.radonc.2008.03.013, indexed in Pubmed: 18439693.

21. Holy R, Piroth M, Pinkawa M, et al. Stereotactic body radiation therapy (SBRT) for treatment of adrenal gland metastases from non-small cell lung cancer. Strahlenther Onkol. 2011; 187(4): 245–251, doi: 10.1007/s00066-011-2192-2, indexed in Pubmed: 21424513.

22. Ahmed KA, Barney BM, Macdonald OK, et al. Stereotactic body radiotherapy in the treatment of adrenal metastases. Am J Clin Oncol. 2013; 36(5): 509–513, doi: 10.1097/COC.0b013e3182569189, indexed in Pubmed: 22781389.

23. Voglhuber T, Kessel KA, Oechsner M, et al. Single-institutional outcome-analysis of low-dose stereotactic body radiation therapy (SBRT) of adrenal gland metastases. BMC Cancer. 2020; 20(1): 536, doi: 10.1186/s12885-020-07030-w, indexed in Pubmed: 32513136.

24. ICRU Report 91, Prescribing, Recording, and Reporting of Stereotactic Treatments with Small Photon Beams. https://icru.org/link-index (3 Jan 2021).

25. Ippolito E, D’Angelillo RM, Fiore M, et al. SBRT: A viable option for treating adrenal gland metastases. Rep Pract Oncol Radiother. 2015; 20(6): 484–490, doi: 10.1016/j.rpor.2015.05.009, indexed in Pubmed: 26696789.

26. Torok J, Wegner RE, Burton SA, et al. Stereotactic body radiation therapy for adrenal metastases: a retrospective review of a noninvasive therapeutic strategy. Future Oncol. 2011; 7(1): 145–151, doi: 10.2217/fon.10.165, indexed in Pubmed: 21174545.

27. Gunjur A, Duong C, Ball D, et al. Surgical and ablative therapies for the management of adrenal oligometastases: A systematic review. Cancer Treat Rev. 2014; 40(7): 838–846, doi: 10.1016/j.ctrv.2014.04.001, indexed in Pubmed: 24791623.

28. Arcidiacono F, Aristei C, Marchionni A, et al. Stereotactic body radiotherapy for adrenal oligometastasis in lung cancer patients. Br J Radiol. 2020; 93(1115): 20200645, doi: 10.1259/bjr.20200645, indexed in Pubmed: 32822540.

29. Figura NB, Oliver DE, Mohammadi H, et al. Novel Dose Escalation Approaches for Stereotactic Body Radiotherapy to Adrenal Oligometastases: A Single-Institution Experience. Am J Clin Oncol. 2020; 43(2): 107–114, doi: 10.1097/COC.0000000000000634, indexed in Pubmed: 31764023.

30. Helis CA, Hughes RT, Nieto K, et al. Adrenal SBRT: a multi-institutional review of treatment outcomes and toxicity. Clin Exp Metastasis. 2020; 37(9): 585–592, doi: 10.1007/s10585-020-10052-0, indexed in Pubmed: 32700208.

31. König L, Häfner MF, Katayama S, et al. Stereotactic body radiotherapy (SBRT) for adrenal metastases of oligometastatic or oligoprogresive tumor patients. Radiat Oncol. 2020; 15(1): 30, doi: 10.1186/s13014-020-1480-0, indexed in Pubmed: 32019553.

32. Chen WC, Baal JD, Baal U, et al. Stereotactic Body Radiation Therapy of Adrenal Metastases: A Pooled Meta-Analysis and Systematic Review of 39 Studies with 1006 Patients. Int J Radiat Oncol Biol Phys. 2020; 107(1): 48–61, doi: 10.1016/j.ijrobp.2020.01.017, indexed in Pubmed: 32001383.

33. Casamassima F, Livi L, Masciullo S, et al. Stereotactic radiotherapy for adrenal gland metastases: University of Florence experience. Int J Radiat Oncol Biol Phys. 2012; 82(2): 919–923, doi: 10.1016/j.ijrobp.2011.10.060, indexed in Pubmed: 21300473.

34. Oshiro Y, Takeda Y, Hirano S, et al. Role of radiotherapy for local control of asymptomatic adrenal metastasis from lung cancer. Am J Clin Oncol. 2011; 34(3): 249–253, doi: 10.1097/COC.0b013e3181e2b727, indexed in Pubmed: 20498589.

35. Chance WW, Nguyen QN, Mehran R, et al. Stereotactic ablative radiotherapy for adrenal gland metastases: Factors influencing outcomes, patterns of failure, and dosimetric thresholds for toxicity. Pract Radiat Oncol. 2017; 7(3): e195–e203, doi: 10.1016/j.prro.2016.09.005, indexed in Pubmed: 27743801.

36. Rudra S, Malik R, Ranck MC, et al. Stereotactic body radiation therapy for curative treatment of adrenal metastases. Technol Cancer Res Treat. 2013; 12(3): 217–224, doi: 10.7785/tcrt.2012.500320, indexed in Pubmed: 23369155.

37. Filippi AR, Franco P, Ricardi U. Is stereotactic ablative radiotherapy an alternative to surgery in operable stage I non-small cell lung cancer? Rep Pract Oncol Radiother. 2014; 19(4): 275–279, doi: 10.1016/j.rpor.2013.05.005, indexed in Pubmed: 25061521.

38. Zhang Xu, Liu H, Balter P, et al. Positron emission tomography for assessing local failure after stereotactic body radiotherapy for non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2012; 83(5): 1558–1565, doi: 10.1016/j.ijrobp.2011.10.035, indexed in Pubmed: 22572078.

39. Solanki AA, Weichselbaum RR, Appelbaum D, et al. The utility of FDG-PET for assessing outcomes in oligometastatic cancer patients treated with stereotactic body radiotherapy: a cohort study. Radiat Oncol. 2012;
40. Shah MM, Isrow D, Fareed MM, et al. Single institution experience treating adrenal metastases with stereotactic body radiation therapy. J Cancer Res Ther. 2019; 15(Supplement): S27–S32, doi: 10.4103/jcrt.JCRT_655_16, indexed in Pubmed: 30900616.

41. Burjakow K, Fietkau R, Putz F, et al. Fractionated stereotactic radiation therapy for adrenal metastases: contributing to local tumor control with low toxicity. Strahlenther Onkol. 2019; 195(3): 236–245, doi: 10.1007/s00066-018-1390-3, indexed in Pubmed: 30374590.

42. Onishi H, Ozaki M, Kuriyama K, et al. Serious gastric ulcer event after stereotactic body radiotherapy (SBRT) delivered with concomitant vinorelbine in a patient with left adrenal metastasis of lung cancer. Acta Oncol. 2012; 51(5): 624–628, doi: 10.3109/0284186X.2012.671957, indexed in Pubmed: 22582719.

43. Wardak Z, Meyer J, Ghayee H, et al. Adrenal insufficiency after stereotactic body radiation therapy for bilateral adrenal metastases. Pract Radiat Oncol. 2015; 5(3): e177–e181, doi: 10.1016/j.prro.2014.08.020, indexed in Pubmed: 25413390.

44. Alongi F, Arcangeli S, Filippi AR, et al. Review and uses of stereotactic body radiation therapy for oligometastases. Oncologist. 2012; 17(8): 1100–1107, doi: 10.1634/theoncologist.2012-0092, indexed in Pubmed: 22723509.

45. Zhao X, Zhu X, Fei J, et al. Short-term outcomes and clinical efficacy of stereotactic body radiation therapy (SBRT) in treatment of adrenal gland metastases from lung cancer. Radiat Oncol. 2018; 13(1): 205, doi: 10.1186/s13014-018-1152-5, indexed in Pubmed: 30348187.

46. Buergy D, Rabe L, Siebenlist K, et al. Treatment of Adrenal Metastases with Conventional or Hypofractionated Image-guided Radiation Therapy - Patterns and Outcomes. Anticancer Res. 2018; 38(8): 4789–4796, doi: 10.21873/anticancerres.12788, indexed in Pubmed: 30061250.

47. Palacios MA, Bohoudi O, Bruynzeel AME, et al. Role of Daily Plan Adaptation in MR-Guided Stereotactic Ablative Radiation Therapy for Adrenal Metastases. Int J Radiat Oncol Biol Phys. 2018; 102(2): 426–433, doi: 10.1016/j.ijrobp.2018.06.002, indexed in Pubmed: 29902559.

48. Franzese C, Franceschini D, Cozzi L, et al. Minimally Invasive Stereotactical Radio-Ablation of Adrenal Metastases as an Alternative to Surgery. Cancer Res Treat. 2017; 49(1): 20–28, doi: 10.4143/crt.2016.057, indexed in Pubmed: 27121718.

49. Li J, Shi Z, Wang Z, et al. Treating adrenal tumors in 26 patients with CyberKnife: a mono-institutional experience. PLoS One. 2013; 8(11): e80654, doi: 10.1371/journal.pone.0080654, indexed in Pubmed: 24278303.

50. Scouarnec C, Pasquier D, Luu J, et al. Usefulness of Stereotactic Body Radiation Therapy for Treatment of Adrenal Gland Metastases. Front Oncol. 2019; 9: 732, doi: 10.3389/fonc.2019.00732, indexed in Pubmed: 31448234.

51. Haidenberger A, Heidorn SC, Kremer N, et al. Robotic Radiosurgery for Adrenal Gland Metastases. Cureus. 2017; 9(3): e1120, doi: 10.7759/cureus.1120, indexed in Pubmed: 28451479.