Received:
16 March 2016

Revised:
1 August 2016

Accepted:
23 August 2016

<http://dx.doi.org/10.1259/bjr.20160251>

Cite this article as:

Cheung P. Stereotactic body radiotherapy for oligoprogressive cancer. *Br J Radiol* 2016; **89**: 20160251.

REVIEW ARTICLE

Stereotactic body radiotherapy for oligoprogressive cancer

PATRICK CHEUNG, MD, FRCPC

Department of Radiation Oncology, Sunnybrook Odette Cancer Centre, University of Toronto, Toronto, ON, Canada

Address correspondence to: Dr Patrick Cheung

E-mail: patrick.cheung@sunnybrook.ca

ABSTRACT

Stereotactic body radiotherapy (SBRT) is a focused tumour treatment that produces high local control rates with low toxicity. Its use in metastatic cancer is evolving rapidly, with purported benefits in the oligometastatic setting and for better palliation of symptomatic disease. Another potential indication for SBRT is in the setting of oligoprogression, where there is progression of a solitary or a few tumours while all other tumours are responding or stable on a systemic therapy strategy. SBRT to the progressing “rogue” tumours may delay the need to start or change systemic therapy. This may have clinical benefits including improved progression-free/overall survival and quality of life for patients. This review will summarize the limited published data. More prospective clinical trials are urgently needed to better identify and quantify the potential clinical benefits.

INTRODUCTION TO STEREOTACTIC BODY RADIOTHERAPY

The role of radiotherapy (RT) in the management of metastatic cancer has historically been limited to a palliative measure to improve or prevent patient symptoms. Conventional low-dose RT has been shown to be effective in palliating symptomatic metastases from various body sites.^{1–3} Typical palliative RT doses include 8 Gy in 1 fraction, 20 Gy in 5 fractions or 30 Gy in 10 fractions, depending on the clinical scenario. Such doses are not meant to be ablative, and tumours often regrow with time. However, such a paradigm is being challenged, especially in the brain, where focused stereotactic radiosurgery (SRS) is increasingly being considered instead of palliative whole-brain RT (WBRT) due to decreased neurocognitive side effects and survival advantage for some patients.^{4,5}

Stereotactic body RT (SBRT), also known as stereotactic ablative RT, is defined as: the precise delivery of highly conformal and image-guided hypofractionated external-beam RT to extracranial tumours, delivered in a single or a few fraction(s), with doses at least biologically equivalent to a conventional radical course of treatment.⁶ Usually, such treatment is delivered in 1–5 fractions. The goal of such treatment is to eradicate the treated tumour or to provide longer term local control compared with palliative RT. With SBRT, the dose per fraction is 6–20 Gy, which is much higher than the typical 1.8–2.5 Gy per fraction used in conventional high-dose RT that is delivered over several weeks. Despite the very radiobiological intense doses of

radiation delivered to the tumour by SBRT, there is significant sparing of adjacent normal tissues, making the treatment very well tolerated. Toxicities of SBRT are highly dependent on the tumour site being treated and what organs at risk are close to or adjacent to the target. Although very uncommon, severe subacute and/or late toxicities can occur, such as fatal radiation pneumonitis if treating a very large volume of lung, or radiation myelitis if overdosing the spinal cord. However, adherence to SBRT dose constraints should minimize such risks.⁷

In patients with medically inoperable Stage I lung cancer, SBRT is the standard of care in many institutions as an alternative to surgical resection^{8,9} and has become an option even for operable patients,¹⁰ given how favourable the results are. Given the convenience and high therapeutic ratio of SBRT in treating tumours in almost every body site, there has been increasing interest in using SBRT to treat metastatic tumours in certain clinical scenarios.^{11,12} Figure 1 illustrates a SBRT dose distribution used to treat a pulmonary metastasis.

Use of stereotactic body radiotherapy in metastatic cancer

Systemic therapy is the main treatment for the majority of patients with metastatic cancer. With the exception of testicular/germ cell cancers, the majority of patients with metastatic solid cancers are not cured with drugs and most succumb to their disease. Historically, the use of surgery or high-dose RT to eradicate gross visible tumours was not

Figure 1. Stereotactic body radiotherapy dose distribution for a pulmonary metastasis as seen on select axial, sagittal and coronal planes.

routinely considered because it is likely most patients with metastatic cancer have micrometastases that would become apparent with time. However, this paradigm is also being challenged, especially in patients with oligometastatic disease (usually defined as patients with <3–5 gross visible metastases).¹³ There is now tremendous interest in exploring the use of SBRT in patients with oligometastatic cancer to improve outcomes with many publications documenting the potential benefits,^{14,15} although high-level randomized data is still lacking. It is hypothesized that progression-free survival (PFS) and possibly overall survival (OS) may improve in patients with oligometastatic cancer when all visible tumours are treated with SBRT. In this situation, SBRT to all tumours can be delivered alone^{16,17} or in conjunction with systemic therapy.^{18,19} Hopefully, randomized trials will complete accrual to better quantify the potential benefits of such an approach for oligometastatic cancer.

However, there may also be a role for SBRT even when patients have more diffuse metastatic disease. Given the higher radiobiological doses delivered, SBRT results in fairly high local control rates and therefore may provide more effective and durable

palliation of symptomatic metastases. For example, spine SBRT has been associated with significant and prolonged pain relief for patients with spine metastases in a prospective trial.²⁰ Randomized trials are ongoing to see if spine SBRT provides better and more durable symptomatic relief than conventional palliative RT.

Another situation where SBRT may have role is in the setting of oligoprogression. Interestingly, this indication has very little published literature associated with it. Nonetheless, it is increasingly being considered in clinical practice and is the subject of this review.

What is oligoprogression?

Oligoprogression refers to the clinical scenario where a “few” metastases progress, whereas all other metastases are stable or responding to a systemic therapy strategy. Unlike the oligometastatic state, there can be diffuse metastatic disease, therefore there is no upper limit about how many metastases a patient has. The key point is that with the exception of a few growing tumours, the majority of other tumours are not progressing. The systemic therapy strategy being used can be anything but usually is something that is administered with the goal of longer term

control of disease. Examples include oral targeted agents, maintenance chemotherapy or even observation in patients with slowly growing indolent cancers.

Treatment options for oligoprogression include: (1) changing systemic therapy, which is the historical, conventional approach; (2) continuing the same systemic therapy strategy if the progression is minimal; or (3) use local therapy, such as SBRT, to eradicate the “rogue” growing metastases and remain on the same systemic therapy strategy as before. Ultimately, the goal of using SBRT in this situation is to delay the need to change systemic therapy, which may result in more prolonged PFS and OS if subsequent lines of systemic therapy can be delayed. Sometimes, the next line of systemic therapy may be much more toxic, therefore any delay in the need to do that may have quality of life benefits for the patient.

Publications about oligoprogression

Although oligoprogression can potentially occur with any cancer histology and systemic therapy strategy, almost all the published literature to date are retrospective and relate to non-small-cell lung cancer (NSCLC) oligoprogression while on oral targeted agents. Table 1 summarizes these NSCLC studies.

Shukuya et al²¹ reported on 17 patients with metastatic epidermal growth factor receptor (EGFR)-positive NSCLC who developed isolated intracranial oligoprogression while on a tyrosine kinase inhibitor (TKI). 14 (82%) patients had evidence of brain metastases prior to starting TKI. After irradiation of the progressing brain disease (WBRT or SRS), the TKI was

continued. The median PFS after RT was only 2.7 months for all 17 patients. Those without leptomeningeal disease had a median PFS of 4.8 months. Median extracranial PFS was 5.7 months after brain RT and staying on the same drug.

Weickhardt et al²² reported on 25 patients with metastatic EGFR or anaplastic lymphoma kinase (ALK)-positive NSCLC who developed intracranial or extracranial oligoprogression (≤ 4 progressing tumours with no evidence of leptomeningeal disease suitable for surgery or RT) while on erlotinib or crizotinib. Of the 25 patients, only 1 patient had surgery for a progressing adrenal metastasis, whereas all others received SRS, WBRT or SBRT. After surgery or RT to the progressing lesions and continuing with the same drug, the median PFS was 6.2 months. Those who had intracranial oligoprogression did better with a median PFS of 7.1 months, whereas those with extracranial oligoprogression had a median PFS of 4.0 months.

Yu et al²³ reported on 18 patients with metastatic EGFR-positive NSCLC who developed extracranial oligoprogression while on TKI therapy which was treated with surgery, radiofrequency ablation, SBRT or conventional RT. The majority of patients continued with TKI therapy. Median time to progression after local therapy was 10 months. Median time to change systemic therapy was 22 months, whereas median OS was 41 months.

Gan et al²⁴ reported on 14 patients with metastatic ALK-positive NSCLC who developed extracranial oligoprogression (≤ 4 progressing tumours suitable for SBRT) while on crizotinib. Median PFS after SRT/SBRT was 5.5 months. For those who only had

Table 1. Published studies about treatment of oligoprogressive NSCLC

Author	Year	Cancer type	Systemic therapy strategy	Number of oligoprogressive patients treated with local therapy	Local therapy to oligoprogressive tumours	Median PFS after local therapy (months)	Median OS after local therapy (months)
Shukuya et al ²⁰	2011	NSCLC, EGFR+ve	Gefitinib or erlotinib	17: all isolated intracranial oligoprogression	SRS, WBRT	2.7; 4.8 for those without leptomeningeal disease	13.4
Weickhardt et al ²¹	2012	NSCLC, EGFR+ve and ALK+ve	Erlotinib or crizotinib	25: intracranial or extracranial oligoprogression	SRS, WBRT, SBRT, conventional RT, surgery	6.2	N/A
Yu et al ²²	2013	NSCLC, EGFR+ve	TKI	18: extracranial oligoprogression (did not include 42 patients developing intracranial progression in analysis)	radiofrequency ablation, SBRT, surgery, conventional RT	10	41
Gan et al ²³	2014	NSCLC, ALK+ve	Crizotinib	14: extracranial oligoprogression	hypofractionated RT, SBRT, surgery	5.5	N/A

+ve, positive; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; N/A, not available; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; SBRT, stereotactic body RT; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitor; WBRT, whole-brain RT.

1–2 oligoprogressive metastases, median PFS was higher at 7 months. Patients stayed on crizotinib after SBRT, and SBRT was used multiple times in some patients if further oligoprogression developed. Patients who continued to take crizotinib for more than 12 months had higher OS than those who took it for less than or equal to 12 months (2-year OS = 72% vs 12%, $p < 0.0001$).

There is also a case report about the use of SBRT in the setting of oligoprogression in metastatic renal cell carcinoma (RCC). Straka et al²⁵ reported on a patient with metastatic RCC who developed oligoprogression in an adrenal metastasis while all other tumours were stable after being on sunitinib for 14 months. SBRT was delivered to the adrenal tumour, and sunitinib was continued for another 8 months before more widespread progression occurred.

How often does oligoprogression occur?

It is unknown how common oligoprogression that is amenable to local therapy occurs. Its frequency likely depends on many factors, including the histology of the cancer, the type and effectiveness of the systemic therapy being used, whether the cancer biology is indolent or not, and the definition of what is amenable to local therapy. A clue can be gleaned from the above studies which have examined the treatment of oligoprogression with local therapy in patients with NSCLC on oral targeted agents.

In the study by Shukuya et al,²¹ 35 out of 204 (17%) patients with progressing EGFR-positive metastatic NSCLC developed brain-only oligoprogression while on TKI therapy. In the study by Weickhardt et al,²² 25 patients out of 51 (49%) patients with progressing ALK or EGFR-positive metastatic NSCLC developed intracranial or extracranial oligoprogression amenable to local therapy while on oral targeted therapy. The Yu et al²³ study had 184 patients with EGFR positive disease who progressed while on TKI therapy. 42 (23%) patients developed intracranial oligoprogression treated with local therapy and 18 (10%) developed extracranial oligoprogression amenable to local therapy. Finally, the study by Gan et al²⁴ had 33 patients with ALK-positive patients who progressed while on crizotinib. 13 patients (39%) developed intracranial only oligoprogression and 14 (42%) developed extracranial oligoprogression amenable to local therapy.

Is there a biological rationale behind oligoprogression?

Recent publications have provided a sound biological basis for the mixed response/oligoprogression state that is sometimes seen with systemic therapy. Gerlinger et al²⁶ performed an elegant study where multiple spatially separated tissue samples were obtained from the primary tumour and metastatic sites in patients with RCC. They discovered significant genetic heterogeneity within the primary tumour and between different metastatic tumours in the same patient. This suggests that systemic therapies targeting a single mutation or pathway may not be as effective for all the tumours in an individual and that systemic therapy based on a single biopsy specimen may underestimate the tumour genomics and is a challenge to successful implementation of personalized medicine. Tumour

genetic heterogeneity has also been documented in patients with EGFR mutant-positive NSCLC which can give rise to divergent resistance mechanisms in response to targeted systemic therapy and may in part explain the oligoprogression state.²⁷

CONCLUSION AND FUTURE DIRECTIONS

Despite the very limited published data regarding the role of local therapy in the setting of oligoprogression, use of SBRT for oligoprogression has already crept into clinical practice. Such an approach may delay the need to change systemic therapy strategy, improve PFS/OS and may have quality of life benefits if the next line of systemic therapy is more toxic. In fact, use of local therapy such as SBRT is already listed as a recognized treatment option for oligoprogression of patients with metastatic NSCLC in various review articles from across the world.^{28–32} It is even accepted now as a treatment strategy in national consensus guidelines.^{33,34}

However, there remain many unknowns that only prospective randomized clinical trials can address, especially with regard to quantifying the clinical benefit of using SBRT for oligoprogression compared with simply changing or continuing with the same systemic therapy. There is a proposed randomized trial from The Institute of Cancer Research (UK) and European Organisation For Research And Treatment For Cancer named HALT, where patients with oligoprogressive (up to three growing tumours) EGFR or ALK-positive metastatic NSCLC while on TKI are randomized to either SBRT to progressive tumours and continuation of TKI or to continuation of TKI alone. Primary end point will be the duration of TKI therapy measured from time of SBRT. There is also a Canadian initiative to conduct a similar study, named STOP-NSCLC, which is a randomized Phase 2 study where patients with oligoprogressive (up to five growing tumours) metastatic NSCLC while on TKI or maintenance chemotherapy are randomized to either SBRT to progressing tumours and continuing with their original drug or to whatever systemic therapy strategy is deemed appropriate by the physician (switching drug, continuing current drug or observation). Primary end point will be PFS.

To date, almost all of the published data about the use of SBRT for oligoprogression have been in the setting of NSCLC while on oral targeted agents. It is likely that SBRT for oligoprogressive disease from other cancer histologies on various systemic therapy agents may result in the same potential benefits, and this needs to be explored. In Canada, there is an ongoing single-arm multicentre Phase 2 study evaluating the use of SBRT to treat oligoprogressive tumours in patients with metastatic RCC while on sunitinib, with the primary end point being local control and secondary end point being the extra PFS after SBRT while staying on sunitinib.

In addition to potential clinical benefits for patients, such a treatment strategy may (or may not) be a cost-effective one, depending on the cost of SBRT vs changing systemic therapy strategy. This certainly is another topic of investigation for future study and will likely be very dependent on the relative costs of the continuing current systemic strategy or changing to a new one.

Treating oligoprogression in patients with SBRT is another emerging indication for RT in the metastatic cancer setting, although prospective trials are urgently needed to really quantify what those benefits potentially are. Increasingly, the use of SBRT is being considered not just in localized disease with curative intent.

Rather, high-dose RT such as SBRT can potentially be thought of as another “line” of therapy in the fight against oligometastatic and oligoprogressive cancer, with the goal not necessarily being to “cure”. Instead, incremental improvements in PFS and maybe OS may be good enough goals to justify its use.

REFERENCES

- Lutz S, Berk L, Chang E, Chow E, Hahn C, Hoskin P, et al. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. *Int J Radiat Oncol Biol Phys* 2011; **79**: 965–76. doi: <http://dx.doi.org/10.1016/j.ijrobp.2010.11.026>
- Rodrigues G, Videtic GM, Sur R, Bezjak A, Bradley J, Hahn CA, et al. Palliative thoracic radiotherapy in lung cancer: an American Society for Radiation Oncology evidence-based clinical practice guideline. *Pract Radiat Oncol* 2011; **1**: 60–71. doi: <http://dx.doi.org/10.1016/j.prro.2011.01.005>
- Tsao MN, Rades D, Wirth A, Lo SS, Danielson BL, Gaspar LE, et al. Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): an American Society for Radiation Oncology evidence-based guideline. *Pract Radiat Oncol* 2012; **2**: 210–25. doi: <http://dx.doi.org/10.1016/j.prro.2011.12.004>
- Sahgal A, Aoyama H, Kocher M, Neupane B, Collette S, Tago M, et al. Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: individual patient data meta-analysis. *Int J Radiat Oncol Biol Phys* 2015; **91**: 710–7. doi: <http://dx.doi.org/10.1016/j.ijrobp.2014.10.024>
- Soliman H, Das S, Larson DA, Sahgal A. Stereotactic radiosurgery (SRS) in the modern management of patients with brain metastases. *Oncotarget* 2016; **7**: 12318–30. doi: <http://dx.doi.org/10.18632/oncotarget.7131>
- Sahgal A, Roberge D, Schellenberg D, Purdie TG, Swaminath A, Pantarotto J, et al. The Canadian Association of Radiation Oncology scope of practice guidelines for lung, liver and spine stereotactic body radiotherapy. *Clin Oncol (R Coll Radiol)* 2012; **24**: 629–39. doi: <http://dx.doi.org/10.1016/j.clon.2012.04.006>
- Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. *Med Phys* 2010; **37**: 4078–101. doi: <http://dx.doi.org/10.1118/1.3438081>
- Senthi S, Lagerwaard FJ, Haasbeek CJ, Slotman BJ, Senan S. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. *Lancet Oncol* 2012; **13**: 802–9. doi: [http://dx.doi.org/10.1016/S1470-2045\(12\)70242-5](http://dx.doi.org/10.1016/S1470-2045(12)70242-5)
- Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010; **303**: 1070–6. doi: <http://dx.doi.org/10.1001/jama.2010.261>
- Chang JY, Senan S, Paul MA, Mehran RJ, Louie AV, Balter P, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol* 2015; **16**: 630–7. doi: [http://dx.doi.org/10.1016/S1470-2045\(15\)70168-3](http://dx.doi.org/10.1016/S1470-2045(15)70168-3)
- Kirkpatrick JP, Kelsey CR, Palta M, Cabrera AR, Salama JK, Patel P, et al. Stereotactic body radiotherapy: a critical review for nonradiation oncologists. *Cancer* 2014; **120**: 942–54. doi: <http://dx.doi.org/10.1002/cncr.28515>
- Timmerman RD, Herman J, Cho LC. Emergence of stereotactic body radiation therapy and its impact on current and future clinical practice. *J Clin Oncol* 2014; **32**: 2847–54. doi: <http://dx.doi.org/10.1200/JCO.2014.55.4675>
- Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol*. 1995; **13**: 8–10.
- Salama JK, Milano MT. Radical irradiation of extracranial oligometastases. *J Clin Oncol* 2014; **32**: 2902–12. doi: <http://dx.doi.org/10.1200/JCO.2014.55.9567>
- Tree AC, Khoo VS, Eeles RA, Ahmed M, Dearnaley DP, Hawkins MA, et al. Stereotactic body radiotherapy for oligometastases. *Lancet Oncol* 2013; **14**: e28–37. doi: [http://dx.doi.org/10.1016/S1470-2045\(12\)70510-7](http://dx.doi.org/10.1016/S1470-2045(12)70510-7)
- Milano MT, Katz AW, Zhang H, Okunieff P. Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of prospective study. *Int J Radiat Oncol Biol Phys* 2012; **83**: 878–86. doi: <http://dx.doi.org/10.1016/j.ijrobp.2011.08.036>
- Salama JK, Hasselle MD, Chmura SJ, Malik R, Mehta N, Yenice KM, et al. Stereotactic body radiotherapy for multisite extracranial oligometastases: final report of a dose escalation trial in patients with 1 to 5 sites of metastatic disease. *Cancer* 2012; **118**: 2962–70. doi: <http://dx.doi.org/10.1002/cncr.26611>
- De Ruyscher D, Wanders R, van Baardwijk A, Dingemans AM, Reymen B, Houben R, et al. Radical treatment of non-small-cell lung cancer patients with synchronous oligometastases: long-term results of a prospective phase II trial (Nct01282450). *J Thorac Oncol* 2012; **7**: 1547–55. doi: <http://dx.doi.org/10.1097/JTO.0b013e318262caf6>
- Iyengar P, Kavanagh BD, Wardak Z, Smith I, Ahn C, Gerber DE, et al. Phase II trial of stereotactic body radiation therapy combined with erlotinib for patients with limited but progressive metastatic non-small-cell lung cancer. *J Clin Oncol* 2014; **32**: 3824–30. doi: <http://dx.doi.org/10.1200/JCO.2014.56.7412>
- Wang XS, Rhines LD, Shiu AS, Yang JN, Seleku U, Gning I, et al. Stereotactic body radiation therapy for management of spinal metastases in patients without spinal cord compression: a phase 1–2 trial. *Lancet Oncol* 2012; **13**: 395–402. doi: [http://dx.doi.org/10.1016/S1470-2045\(11\)70384-9](http://dx.doi.org/10.1016/S1470-2045(11)70384-9)
- Shukuya T, Takahashi T, Naito T, Kaira R, Ono A, Nakamura Y, et al. Continuous EGFR-TKI administration following radiotherapy for non-small cell lung cancer patients with isolated CNS failure. *Lung Cancer* 2011; **74**: 457–61. doi: <http://dx.doi.org/10.1016/j.lungcan.2011.04.007>
- Weickhardt AJ, Scheier B, Burke JM, Gan G, Lu X, Bunn PA Jr, et al. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. *J Thorac Oncol* 2012; **7**: 1807–14. doi: <http://dx.doi.org/10.1097/JTO.0b013e3182745948>
- Yu HA, Sima CS, Huang J, Solomon SB, Rimmer A, Paik P, et al. Local therapy with continued EGFR tyrosine kinase inhibitor therapy as a treatment strategy in EGFR-mutant advanced lung cancers that have developed acquired resistance to EGFR tyrosine kinase inhibitors. *J Thorac Oncol* 2013; **8**: 346–51. doi: <http://dx.doi.org/10.1097/JTO.0b013e31827e1f83>
- Gan GN, Weickhardt AJ, Scheier B, Doebele RC, Gaspar LE, Kavanagh BD, et al. Stereotactic radiation therapy can safely and

- durably control sites of extra-central nervous system oligoprogressive disease in anaplastic lymphoma kinase-positive lung cancer patients receiving crizotinib. *Int J Radiat Oncol Biol Phys* 2014; **88**: 892–8. doi: <http://dx.doi.org/10.1016/j.ijrobp.2013.11.010>
25. Straka C, Kim DW, Timmerman RD, Pedrosa I, Jacobs C, Brugarolas J. Ablation of a site of progression with stereotactic body radiation therapy extends sunitinib treatment from 14 to 22 months. *J Clin Oncol* 2013; **31**: e401–3. doi: <http://dx.doi.org/10.1200/JCO.2012.47.7455>
 26. Gerlinger M, Rowan AJ, Horswell S, Larkin J, Endesfelder D, Gronroos E, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N Engl J Med* 2012; **366**: 883–92. doi: <http://dx.doi.org/10.1056/NEJMoa1113205>
 27. Soucheray M, Capelletti M, Pulido I, Kuang Y, Paweletz CP, Becker JH, et al. Intratumoral heterogeneity in EGFR-mutant NSCLC results in divergent resistance mechanisms in response to EGFR tyrosine kinase inhibition. *Cancer Res* 2015; **75**: 4372–83. doi: <http://dx.doi.org/10.1158/0008-5472.CAN-15-0377>
 28. Ho JC, Tam TC, Lam SK. Salvage therapy beyond targeted therapy in lung adenocarcinoma. *Semin Respir Crit Care Med* 2013; **34**: 837–44. doi: <http://dx.doi.org/10.1055/s-0033-1358553>
 29. Matikas A, Mistriotis D, Georgoulas V, Kotsakis A. Current and future approaches in the management of non-small-cell lung cancer patients with resistance to EGFR TKIs. *Clin Lung Cancer* 2015; **16**: 252–61. doi: <http://dx.doi.org/10.1016/j.clcc.2014.12.013>
 30. Rusthoven CG, Yeh N, Gaspar LE. Radiation therapy for oligometastatic non-small cell lung cancer: theory and practice. *Cancer J* 2015; **21**: 404–12. doi: <http://dx.doi.org/10.1097/PPQ.0000000000000143>
 31. Shultz DB, Diehn M, Loo BW Jr. To SABR or not to SABR? Indications and contraindications for stereotactic ablative radiotherapy in the treatment of early-stage, oligometastatic, or oligoprogressive non-small cell lung cancer. *Semin Radiat Oncol* 2015; **25**: 78–86. doi: <http://dx.doi.org/10.1016/j.semradi.2014.11.005>
 32. Simone CB 2nd, Burri SH, Heinzerling JH. Novel radiotherapy approaches for lung cancer: combining radiation therapy with targeted and immunotherapies. *Transl Lung Cancer Res* 2015; **4**: 545–52. doi: <http://dx.doi.org/10.3978/j.issn.2218-6751.2015.10.05>
 33. Ettinger DS, Wood DE, Akerley W, Bazhenova LA, Borghaei H, Camidge DR, et al. Non-small cell lung cancer, version 6.2015. *J Natl Compr Canc Netw* 2015; **13**: 515–24.
 34. Gridelli C, de Marinis F, Cappuzzo F, Di Maio M, Hirsch FR, Mok T, et al. Treatment of advanced non-small-cell lung cancer with epidermal growth factor receptor (EGFR) mutation or ALK gene rearrangement: results of an international expert panel meeting of the Italian Association of Thoracic Oncology. *Clin Lung Cancer* 2014; **15**: 173–81. doi: <http://dx.doi.org/10.1016/j.clcc.2013.12.002>