Hypofractionated radiotherapy combined with targeted therapy or immunotherapy: Dutch survey on current practice, knowledge and challenges

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Original Research Article

Hypofractionated radiotherapy combined with targeted therapy or immunotherapy: Dutch survey on current practice, knowledge and challenges

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ABSTRACT

Introduction: With the introduction of tyrosine kinase inhibitors and systemic antibodies, including immune checkpoint inhibitors, the survival of advanced-stage cancer patients has improved for many tumor types. These patients are increasingly referred for radiotherapy, but it is unclear whether radiotherapy combined with these drugs is safe. No international guidelines exist on whether or how to combine these drugs with radiotherapy. Therefore, we investigated the current clinical practice in the Netherlands regarding hypofractionated radiotherapy in patients using targeted drugs and immunotherapy.

Materials and methods: We sent a survey to all 21 Dutch radiotherapy institutes. Dedicated radiation oncologists, medical oncologists and pulmonologists were asked to fill out the survey. The questions explored their familiarity with the combination of targeted drugs and immunotherapy with radiotherapy, the encountered clinical difficulties and factors influencing treatment decisions.

Results: The survey was filled out by 54 respondents from 19 different institutes. The median annual number of patients per radiation oncologist referred for radiotherapy when using targeted drugs or immunotherapy was 10 and 15, respectively. Despite this high number, only 11% of the radiation oncologists stated that they had sufficient information (resources) for adequate treatment decision making. Among all physicians, 44% stated that there was insufficient knowledge within their institute regarding this topic. Only 17% stated that there was a multidisciplinary protocol available. The application of radiotherapy treatment adaptations (technique, dose, fractionation, field size) varied widely. Generally, there seemed to be no consensus regarding the expected toxicity of combined drug-radiotherapy treatments and the expected risk of tumor flare upon temporary drug discontinuation.

Conclusion: There is no consensus amongst involved medical specialties on expected toxicity. Consequently, it is necessary to perform clinical studies examining the safety of combined drug-radiotherapy treatments, to add radiotherapy to phase I-III clinical trials for new drugs and to incorporate outcomes into multidisciplinary, evidence-based guidelines.

Introduction

Systemic treatment options for cancer patients have changed considerably over the last few decades. With the introduction of tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (mAbs), including immune checkpoint inhibitors (ICIs), the overall survival of advanced-stage cancer patients has improved for many tumor types [1,2]. In these patients, hypofractionated radiotherapy is frequently used as a

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convenient and effective treatment option, in order to treat local symptoms or oligoprogression [3–5]. However, the use of a higher dose per fraction is less favorable for normal tissues, potentially leading to increased (particularly late-responding) normal tissue toxicity [4,6]. This risk may be further augmented by concomitant use of systemic therapy [7–9].

TKIs and mAbs are pharmacodynamically and pharmacokinetically heterogeneous drug types [10]. First, a wide variety of cellular pathways and receptors is targeted. The diverse mechanisms of action and possible off-target effects lead to different toxicity profiles and degrees of radiosensitization [10–12]. Second, the plasma half-lives vary largely [13]. Targeted drugs with long plasma half-lives (particularly mAbs) can require a discontinuation period up to several months to reach low plasma levels [13]. This is often not desirable and may lead to tumor flare [14–16]. Therefore, combining systemic drugs with concurrent radiotherapy is sometimes inevitable. Additionally, differences in distribution throughout the body may influence radiotherapy toxicity. For example, limited blood–brain barrier permeability may reduce the contribution of a drug to normal tissue radiotherapy toxicity in the brain, whereas radiotherapy may at the same time increase blood–brain barrier permeability, leading to increased drug concentrations in the brain [17,18].

For the combination of radiotherapy with targeted drugs and immunotherapy, toxicity data are often scarce and primarily based on retrospective studies and case reports [19–21]. Still, increased and even severe radiotherapy toxicity has been reported in patients treated with targeted drugs or immunotherapy [22–25]. Apart from the hazards that may arise from combining radiotherapy with targeted drugs and immunotherapy, there is also evidence for potential benefit [26–29]. Several treatment options can be considered for these patients, including concomitant therapy, temporary drug discontinuation, radiotherapy plan adaptations or radiotherapy dose reduction. However, there is no international guideline or consensus regarding the most appropriate clinical approach, which creates a challenge for radiation oncologists, medical oncologists, pulmonologists and for these patients.

In the present study, we investigated the current clinical practice in the Netherlands regarding hypofractionated radiotherapy in cancer patients using targeted drugs and immunotherapy. A survey was developed for radiation oncologists, medical oncologists and pulmonologists. Our goal was to explore their knowledge, the main clinical difficulties they encounter, the treatment decisions and the decision-making processes.

Materials and methods

We developed an online survey (Appendix A), consisting of 26 clinical questions and statements for radiation oncologists and 8 for medical oncologists and pulmonologists, since primarily these two specialties prescribe targeted therapy and immunotherapy for cancer patients in the Netherlands. As these patients are referred for primarily hypofractionated radiotherapy, of which the radiobiological effects may be different and in order to reduce heterogeneity, this survey only comprised the use of hypofractionated radiotherapy (fractions $\geq$3 Gy, including palliative and stereotactic radiotherapy). All questions and statements concerned the current patterns of care regarding the combination of hypofractionated radiotherapy with targeted drugs and with immunotherapy. Attention was paid to information resources and knowledge, multidisciplinary decision making and radiotherapy treatment adaptations. Additionally, the expected risk of toxicity or tumor flare was analyzed for different targeted therapies. For statements, a 5-point Likert scale was used to express the level of (dis)agreement.

After an internal pilot survey, the survey was distributed via the Dutch Platform for Palliative Radiotherapy (LPPR), which is part of the Dutch Society of Radiotherapy and Oncology (NVRO) and focuses on palliative and stereotactic radiotherapy. We asked members to let the survey be filled out by at least one radiation oncologist and by one or two medical oncologists and pulmonologists. This method was used in order to select radiation oncologists, medical oncologists and pulmonologists who are more actively engaged in this topic. All participating physicians gave permission for anonymized publication of the results. We analyzed data from respondents who fully completed the survey. The survey was developed using Exploratio (Newcom Research & Consultancy B.V., Enschede, The Netherlands). Data analyses were performed using SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA). Visualizations were created with Microsoft Excel 2016 (Microsoft Corp., Redmond, WA, USA).

Results

The survey was filled out by 65 respondents and fully completed by 54 respondents, which resulted in a completion rate of 83%. The responding population consisted of 27 radiation oncologists from 13 different centers, 10 medical oncologists from 7 different centers and 17 pulmonologists from 12 different centers. All tumor subspecialties were represented (Table 1). The median annual number of patients per radiation oncologist referred for hypofractionated radiotherapy when using targeted therapy or immunotherapy, was 10 and 15, respectively. However, just 11% (3/27) of the radiation oncologists stated that they had sufficient information (resources) and only 7% (2/27) considered themselves to have sufficient ready knowledge for adequate treatment decision making in these patients (Fig. 1).

Among all physicians, 44% (24/54) stated that there was insufficient knowledge within their institute regarding the possible interaction between hypofractionated radiotherapy and targeted therapy or immunotherapy. According to only 17% (9/54) there was a multidisciplinarily accepted protocol available in their institute, but in none of these institutes, all respondents agreed with that statement, which makes the

Table 1
Respondent characteristics.

Respondent characteristics	Radiation oncologists		Medical oncologists		Pulmonologists		**Total**	
	n	%	n	%	n	%	n	%
Hospital type								
Academic hospital	16	59%	5	50%	7	41%	28	52%
General hospital	11	41%	5	50%	10	59%	26	48%
Experience								
Resident	1	4%	0	0%	0	0%	1	2%
Staff (since 0–10 years)	12	44%	5	50%	10	59%	27	50%
Staff (since 11–20 years)	9	33%	5	50%	4	24%	18	33%
Staff (since 21–30 years)	4	15%	0	0%	3	18%	7	13%
Staff (since >30 years)	1	4%	0	0%	0	0%	1	2%
Subspecialty								
Neurological tumors	8	30%	0	0%	0	0%	8	15%
Head and neck tumors	5	19%	2	20%	0	0%	7	13%
Lung tumors	9	33%	0	0%	17	100%	26	48%
Breast tumors	13	48%	4	40%	0	0%	17	31%
Gastro-intestinal tumors	10	37%	5	50%	0	0%	15	28%
Urological tumors	2	7%	5	50%	0	0%	7	13%
Gynaecological tumors	2	7%	3	30%	0	0%	5	9%
Melanoma/renal cell carcinoma	3	11%	4	40%	0	0%	7	13%
Soft tissue tumors	5	19%	1	10%	0	0%	6	11%
Hematological tumors	4	15%	0	0%	0	0%	4	7%
Palliation	20	74%	5	50%	1	6%	26	48%
Other	2	7%	1	10%	0	0%	3	6%

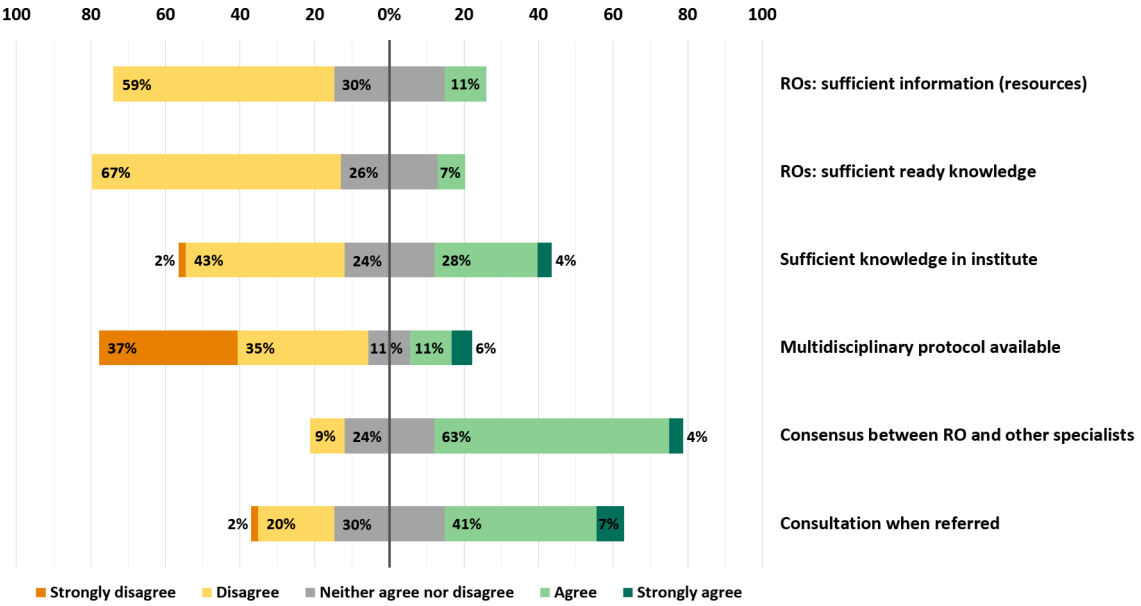

Fig. 1. Knowledge, information resources and multidisciplinary decision making. Answers on statements regarding the combination of radiotherapy with targeted therapy or immunotherapy. First two statements only answered by radiation oncologists. The proportion answering 'Neither agree nor disagree' was centered. *Abbreviation:* RO = radiation oncologist.

existence of a widely accepted protocol unlikely in these institutes. Before patients were referred for radiotherapy, interdisciplinary consultation with a radiation oncologist did not always take place. Nonetheless, 67% (36/54) stated that there was consensus between radiation oncologists and other treating physicians regarding the combination of hypofractionated radiotherapy with targeted therapy or immunotherapy (Fig. 1).

When patients continued to use targeted therapy or immunotherapy during radiotherapy, various treatment adaptations were applied (Fig. 2). On average, radiation oncologists were more likely to adapt treatment when radiotherapy was combined with targeted therapy than with immunotherapy (32% vs. 21%). The fractionation scheme was adapted most often (44%, 12/27 and 37%, 10/27 respectively). For targeted therapy, the next most common adaptations were field size (37%, 10/27) and treatment technique (33%, 9/27). For immunotherapy, these were treatment technique (22%, 6/27) and radiation dose (15%, 4/27). However, 22% (6/27) of the radiation oncologists did not regularly adapt their treatment at all. Complete omission of radiotherapy was not often considered for these patients (Fig. 2). All radiation oncologists took the irradiated tissue type into account and 89% (24/27) took the plasma half-life of a drug into account when deciding whether or not to combine hypofractionated radiotherapy with targeted therapy or immunotherapy.

We asked all respondents which drug types would ring alarm bells when patients are referred for radiotherapy (Fig. 3). The majority of the radiation oncologists regarded VEGF(R) inhibitors (78%, 21/27) and multi-target TKIs (52%, 14/27) as potentially hazardous in combination with radiotherapy. BRAF, EGFR and CDK4/6 inhibitors followed with

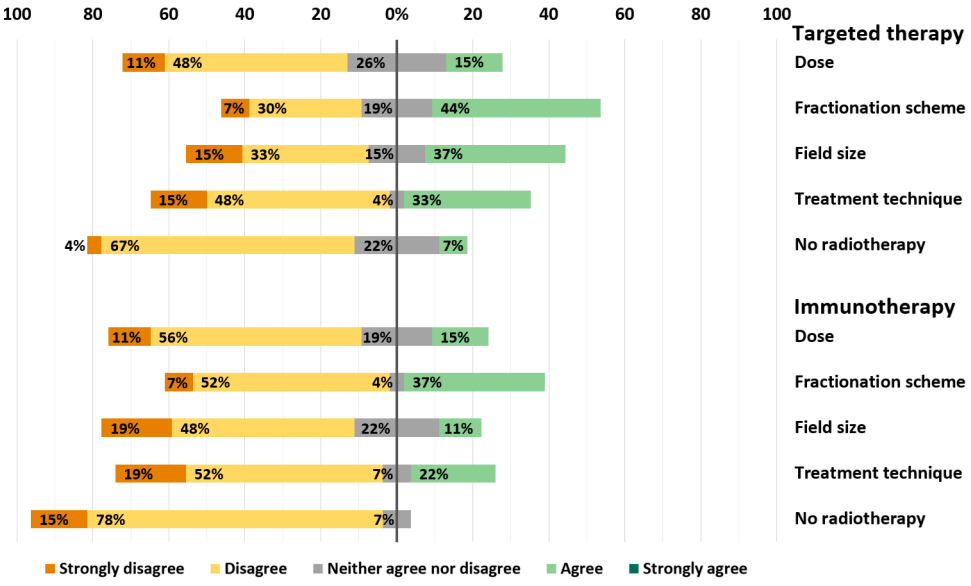

Fig. 2. Regularly applied treatment adaptations by radiation oncologists, when targeted therapy or immunotherapy is continued. The proportion answering 'Neither agree nor disagree' was centered.

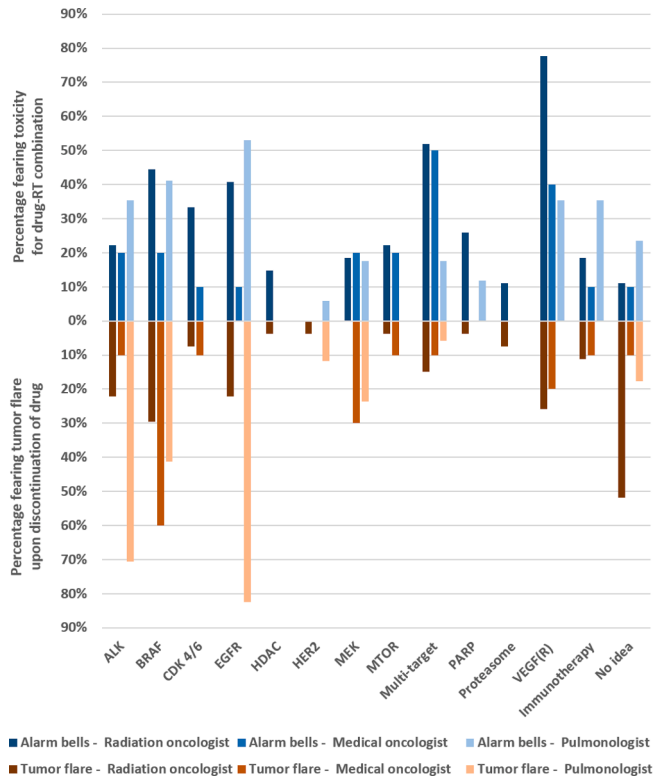

Fig. 3. Percentage of respondents that fear toxicity from a drug-radiotherapy combination (alarm bells) vs. fear of tumor flare upon discontinuation of a drug. Bars are per drug target, split by radiation oncologist vs. medical oncologist vs. pulmonologist. *Abbreviation:* RT = radiotherapy.

44% (12/27), 41% (11/27) and 33% (9/27), respectively. Other drug types, including immunotherapy, were considered less harmful. Among medical oncologists, particularly multi-target TKIs (50%, 5/10) and VEGF(R) (40%, 4/10) inhibitors were mentioned. Pulmonologists mentioned EGFR (53%, 9/17) and BRAF (41%, 7/17) inhibitors, but also ALK, VEGF(R) inhibitors and immunotherapy (all 35%, 6/17). Among radiation oncologists, 11% (3/27) stated that they had insufficient ready knowledge to answer the question. Among medical oncologists and pulmonologists, this answer was given by 10% (1/10) and 24% (4/17), respectively.

The respondents were asked whether they expected a real risk of tumor flare upon temporary drug discontinuation (Fig. 3). Particularly, many radiation oncologists (52%, 14/27) stated that they had insufficient ready knowledge to answer the question, but they also regularly mentioned BRAF (30%, 8/27), VEGF(R) (26%, 7/27), EGFR and ALK inhibitors (both 22%, 6/27). Medical oncologists expected a real risk of tumor flare upon discontinuation of BRAF (60%, 6/10) and MEK (30%, 3/10) inhibitors. Pulmonologists primarily expected tumor flare for EGFR (82%, 14/17), ALK (71%, 12/17) and BRAF (41%, 7/17) inhibitors.

Discussion

This study demonstrates a knowledge gap among physicians regarding the implications of combining radiotherapy with targeted agents or immunotherapy in cancer patients. This important issue is regularly faced in clinical practice. Despite the number of patients who are referred for radiotherapy when using targeted therapy or immunotherapy, the amount of information resources and knowledge among physicians and within institutes is often regarded insufficient. The expected toxicity of the combination of specific targeted drugs with radiotherapy varies widely. Furthermore, this study demonstrates the lack of consensus regarding radiotherapy treatment adaptations. When systemic therapy is continued, the application of adaptations to the radiotherapy dose, fractionation scheme, field size and treatment technique is highly physician-dependent. This, combined with the potential toxicity and the lack of knowledge, stresses the need for the implementation of multidisciplinary guidelines.

During guideline development, all relevant disciplines should be involved, in order to increase quality and acceptance. The different expertise per discipline with regard to radiosensitization and tumor flare is illustrated by the answers shown in Fig. 3. Additionally, the low number of physicians expecting toxicity from the combination with PARP inhibitors, which are known to increase radiosensitivity [30–33], underlines the need for the involvement of experts on the field of radiosensitization. Finally, the guidelines should encompass the radiobiological, preclinical and clinical evidence, along with hands-on recommendations for clinical practice.

Kroeze et al. show similar results among radiation oncologists, concerning the combination of stereotactic body radiotherapy (SBRT) and targeted therapy in German-speaking countries [34]. In their study, consensus was reached regarding the statements that SBRT should not be combined with antiangiogenic agents, BRAF inhibitors and sorafenib, which roughly corresponds to our results [34]. However, in our survey, there was less agreement regarding these drug-radiotherapy combinations. Furthermore, in their study almost no radiation dose reductions were applied, while several respondents in our survey considered radiotherapy treatment adaptations, including dose adaptations. This might be explained by their specific focus on SBRT, while our survey comprised all (heterogeneous) types of hypofractionated radiotherapy, including SBRT. In case of SBRT, there is often an indication for radical treatment, whereas other, often palliative indications for hypofractionated radiotherapy may allow more room for alternative dose-fractionation schemes [34,35]. Additionally, the steep dose gradient of SBRT may allow for better normal tissue sparing, reducing the need for dose reduction [34].

Two other surveys recently evaluated the combination of radiotherapy with immunotherapy [36,37]. As in our study, the vast majority of the radiation oncologists did not adapt the radiation dose when combined with immunotherapy [36] and immunotherapy was regularly continued during radiotherapy [37]. In the survey of Amin et al., radiation oncologists primarily based their treatment decisions on personal or colleagues' experience and on experience with concurrent chemoradiotherapy and radiotherapy [36]. In accordance with our results, this shows that there is a lack of information resources. This is further illustrated by the survey of Kraus et al., where only 29% of the radiation oncologists gave their own knowledge about ICIs a grade higher than 6 on a scale of 1 (very limited knowledge) to 10 (excellent knowledge) [37].

This study has some limitations. The limited size of the study and the varying number of respondents per center limit reliable extrapolation of the results. Also, the lack of consensus regarding the expected toxicity and risk of tumor flare is inevitably influenced by the level or absence of experience with specific drug types. Additionally, by aiming to create a compact survey with clear questions, it was not possible to pay attention to all different aspects influencing clinical decision making, including the radiotherapy target area, the treatment indication and preferences of patients. Furthermore, treatment choices also depend on the indication of radiotherapy. For example, for radical radiotherapy in case of oligometastatic disease, higher toxicity risks might be accepted than for palliative radiotherapy. Nonetheless, for both indications, there are many uncertainties regarding the safety of the combination with targeted therapy or immunotherapy, but the amount of toxicity data for particularly the combination with immunotherapy has increased [24,38].

To conclude, this study clearly illustrates the consequences of the absence of high-quality clinical data and evidence-based clinical guidelines, combined with the clinical complexity of these drug-

radiotherapy combinations. This emphasizes the urgent need to perform clinical studies examining the safety of these combined treatments and to incorporate radiotherapy into phase I-III clinical trials for new targeted drugs and immunotherapy. Furthermore, this study shows that there is a need for multidisciplinary, evidence-based clinical guidelines, encompassing the radiobiological, preclinical and clinical evidence, along with hands-on recommendations for clinical practice.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendices. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2022.01.002.

References

[1] Sundquist M, Brudin L, Tejler G. Improved survival in metastatic breast cancer 1985–2016. Breast 2017;31:46–50. https://doi.org/10.1016/j.breast.2016.10.005.
[2] Luke JJ, Flaherty KT, Ribas A, Long GV. Targeted agents and immunotherapies: optimizing outcomes in melanoma. Nat Rev Clin Oncol 2017;14(8):463–82. https://doi.org/10.1038/nrclinonc.2017.43.
[3] Lievens Y, Guckenberger M, Gomez D, Hoyer M, Iyengar P, Kindts I, et al. Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document. Radiother Oncol 2020;148:157–66. https://doi.org/10.1016/j.radonc.2020.04.003.
[4] Lutz ST, Chow EL, Hartsell WF, Konski AA. A review of hypofractionated palliative radiotherapy. Cancer 2007;109(8):1462–70. https://doi.org/10.1002/cncr.22555.
[5] Cheung P. Stereotactic body radiotherapy for oligoprogressive cancer. Br J Radiol 2016;89(1066):20160251. https://doi.org/10.1259/bjr.20160251.
[6] Nahum AE. The radiobiology of hypofractionation. Clin Oncol (R Coll Radiol) 2015;27(5):260–9. https://doi.org/10.1016/j.clon.2015.02.001.
[7] Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys 2010;76(3):S10–9. https://doi.org/10.1016/j.ijrobp.2009.07.1754.
[8] Wijsman R, Dankers F, Troost EGC, Hoffmann AL, van der Heijden EHFM, de Geus-Oei L-F, et al. Multivariable normal-tissue complication modeling of acute esophageal toxicity in advanced stage non-small cell lung cancer patients treated with intensity-modulated (chemo-)radiotherapy. Radiother Oncol 2015;117(1):49–54. https://doi.org/10.1016/j.radonc.2015.08.010.
[9] Wopken K, Bijl HP, van der Schaaf A, van der Laan HP, Chouvalova O, Steenbakkers RJHM, et al. Development of a multivariable normal tissue complication probability (NTCP) model for tube feeding dependence after curative radiotherapy/chemo-radiotherapy in head and neck cancer. Radiother Oncol 2014;113(1):95–101. https://doi.org/10.1016/j.radonc.2014.09.013.
[10] Gharwan H, Groninger H. Kinase inhibitors and monoclonal antibodies in oncology: clinical implications. Nat Rev Clin Oncol 2016;13(4):209–27. https://doi.org/10.1038/nrclinonc.2015.213.
[11] Belgioia L, Desideri I, Errico A, Franzese C, Daidone A, Marino L, et al. Safety and efficacy of combined radiotherapy, immunotherapy and targeted agents in elderly patients: A literature review. Crit Rev Oncol Hematol 2019;133:163–70. https://doi.org/10.1016/j.critrevonc.2018.11.009.
[12] Tofilon PJ, Camphausen K. Molecular targets for tumor radiosensitization. Chem Rev 2009;109(7):2974–88. https://doi.org/10.1021/cr800504x.
[13] Gao Bo, Yeap S, Clements A, Balakrishnar B, Wong M, Gurney H. Evidence for therapeutic drug monitoring of targeted anticancer therapies. J Clin Oncol 2012;30(32):4017–25. https://doi.org/10.1200/JCO.2012.43.5362.
[14] Amirault M, Choo S, Waxweiler T, Weisdack SD, Breaker K, Flaig TW, et al. Tumor flare of brain metastases upon dose interruption of sunitinib in a patient with metastatic renal cell carcinoma. Cancer Treat Res Commun 2021;27:100367. https://doi.org/10.1016/j.ctarc.2021.100367.
[15] Chaft JE, Oxnard GR, Sima CS, Kris MG, Miller VA, Riely GJ. Disease flare after tyrosine kinase inhibitor discontinuation in patients with EGFR-mutant lung cancer and acquired resistance to erlotinib or gefitinib: implications for clinical trial design. Clin Cancer Res 2011;17(19):6298–303. https://doi.org/10.1158/1078-0432.CCR-11-1468.
[16] Pop O, Pirvu A, Toffart A-C, Moro-Sibilot D. Disease flare after treatment discontinuation in a patient with EML4-ALK lung cancer and acquired resistance to crizotinib. J Thorac Oncol 2012;7(8):e1–2. https://doi.org/10.1097/JTO.0b013e318257fc1d.
[17] Zhang I, Zaorsky NG, Palmer JD, Mehra R, Lu Bo. Targeting brain metastases in ALK-rearranged non-small-cell lung cancer. Lancet Oncol 2015;16(13):e510–21. https://doi.org/10.1016/s1470-2045(15)00013-3.
[18] Appelboom G, Detappe A, LoPresti M, Kunjachan S, Mitrasinovic S, Goldman S, et al. Stereotactic modulation of blood-brain barrier permeability to enhance drug delivery. Neuro Oncol 2016;18(12):1601–9. https://doi.org/10.1093/neuonc/now137.
[19] Kroeze SGC, Fritz C, Hoyer M, Lo SS, Ricardi U, Sahgal A, et al. Toxicity of concurrent stereotactic radiotherapy and targeted therapy or immunotherapy: A systematic review. Cancer Treat Rev 2017;53:25–37. https://doi.org/10.1016/j.ctrv.2016.11.013.
[20] Arcangeli S, Jereczek-Fossa BA, Alongi F, Aristei C, Becherini C, Belgioia L, et al. Combination of novel systemic agents and radiotherapy for solid tumors - Part II: An AIRO (Italian association of radiotherapy and clinical oncology) overview focused on treatment toxicity. Crit Rev Oncol Hematol 2019;134:104–19. https://doi.org/10.1016/j.critrevonc.2018.11.006.
[21] Hendriks LEL, Schoenmaekers J, Zindler JD, Eekers DBP, Hoeben A, De Ruysscher DKM, et al. Safety of cranial radiotherapy concurrent with tyrosine kinase inhibitors in non-small cell lung cancer patients: A systematic review. Cancer Treat Rev 2015;41(7):634–45. https://doi.org/10.1016/j.ctrv.2015.05.005.
[22] Barney BM, Markovic SN, Laack NN, Miller RC, Sarkaria JN, Macdonald OK, et al. Increased bowel toxicity in patients treated with a vascular endothelial growth factor inhibitor (VEGFI) after stereotactic body radiation therapy (SBRT). Int J Radiat Oncol Biol Phys 2013;87(1):73–80. https://doi.org/10.1016/j.ijrobp.2013.05.012.
[23] Hecht M, Zimmer L, Loquai C, Weishaupt C, Gutzmer R, Schuster B, et al. Radiosensitization by BRAF inhibitor therapy-mechanism and frequency of toxicity in melanoma patients. Ann Oncol 2015;26(6):1238–44. https://doi.org/10.1093/annonc/mdv139.
[24] Hwang WL, Pike LRG, Royce TJ, Mahal BA, Loeffler JS. Safety of combining radiotherapy with immune-checkpoint inhibition. Nat Rev Clin Oncol 2018;15(8):477–94. https://doi.org/10.1038/s41571-018-0046-7.
[25] Martin AM, Cagney DN, Catalano PJ, Alexander BM, Redig AJ, Schoenfeld JD, et al. Immunotherapy and symptomatic radiation necrosis in patients with brain metastases treated with stereotactic radiation. JAMA Oncol 2018;4(8):1123. https://doi.org/10.1001/jamaoncol.2017.3993.
[26] Theelen WSME, Chen D, Verma V, Hobbs BP, Peulen HMU, Aerts JGJV, et al. Pembrolizumab with or without radiotherapy for metastatic non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Respiratory Med 2021;9(5):467–75. https://doi.org/10.1016/s2213-2600(20)30391-x.
[27] Kim JM, Miller JA, Kotecha R, Chao ST, Ahluwalia MS, Peereboom DM, et al. Stereotactic radiosurgery with concurrent HER2-directed therapy is associated with improved objective response for breast cancer brain metastasis. Neuro Oncol 2019;21(5):659–68. https://doi.org/10.1093/neuonc/noz006.
[28] Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol 2010;11(1):21–8. https://doi.org/10.1016/s1470-2045(09)70311-0.
[29] Lehrer EJ, Peterson J, Brown PD, Sheehan JP, Quiñones-Hinojosa A, Zaorsky NG, et al. Treatment of brain metastases with stereotactic radiosurgery and immune checkpoint inhibitors: An international meta-analysis of individual patient data. Radiother Oncol 2019;130:104–12. https://doi.org/10.1016/j.radonc.2018.08.025.
[30] Verhagen CVM, de Haan R, Hageman F, Oostendorp TPD, Carli ALE, O'Connor MJ, et al. Extent of radiosensitization by the PARP inhibitor olaparib depends on its dose, the radiation dose and the integrity of the homologous recombination pathway of tumor cells. Radiother Oncol 2015;116(3):358–65. https://doi.org/10.1016/j.radonc.2015.03.028.
[31] Lourenco LM, Jiang Y, Drobnitzky N, Green M, Cahill F, Patel A, et al. PARP inhibition combined with thoracic irradiation exacerbates esophageal and skin toxicity in C57BL6 mice. Int J Radiat Oncol Biol Phys 2018;100(3):767–75. https://doi.org/10.1016/j.ijrobp.2017.10.051.
[32] Jagsi R, Griffith KA, Bellon JR, Woodward WA, Horton JK, Ho A, et al. Concurrent veliparib with chest wall and nodal radiotherapy in patients with inflammatory or locoregionally recurrent breast cancer: the TBCRC 024 phase I multicenter study. J Clin Oncol 2018;36(13):1317–22. https://doi.org/10.1200/JCO.2017.77.2665.
[33] de Haan R, van den Heuvel MM, van Diessen J, Peulen HMU, van Werkhoven E, de Langen AJ, et al. Phase I and pharmacologic study of olaparib in combination with high-dose radiotherapy with and without concurrent cisplatin for non-small cell lung cancer. Clin Cancer Res 2021;27(5):1256–66. https://doi.org/10.1158/1078-0432.CCR-20-2551.
[34] Kroeze SGC, Fritz C, Basler L, Gkika E, Brunner TB, Grosu AL, et al. Combination of stereotactic radiotherapy and targeted therapy: patterns-of-care survey in German-speaking countriesKombination von stereotaktischer Strahlentherapie und zielgerichteter Therapie: Patterns-of-Care-Umfrage im deutschsprachigen Raum. Strahlenther Onkol 2019;195(3):199–206. https://doi.org/10.1007/s00066-018-01422-5.
[35] Sharma S, Hertan L, Jones J. Palliative radiotherapy: current status and future directions. Semin Oncol 2014;41(6):751–63. https://doi.org/10.1053/j.seminoncol.2014.09.021.

[36] Amin NP, Remick J, Agarwal M, Desai NA, Bergom C, Simone 2nd CB. Concurrent radiation and immunotherapy: survey of practice patterns in the United States. Am J Clin Oncol 2019;42:208–14. https://doi.org/10.1097/COC.0000000000000501.
[37] Kraus KM, Fischer JC, Borm KJ, Vogel MME, Pigorsch SU, Devečka M, et al. Evaluation of practical experiences of German speaking radiation oncologists in combining radiation therapy with checkpoint blockade. Sci Rep 2021;11(1). https://doi.org/10.1038/s41598-021-86863-2.
[38] Sha CM, Lehrer EJ, Hwang C, Trifiletti DM, Mackley HB, Drabick JJ, et al. Toxicity in combination immune checkpoint inhibitor and radiation therapy: a systematic review and meta-analysis. Radiother Oncol 2020;151:141–8. https://doi.org/10.1016/j.radonc.2020.07.035.