Review Article

Re-irradiation with stereotactic body radiation therapy (SBRT)

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Abstract: Stereotactic body radiation therapy (SBRT) is a potential treatment option for patients who develop a relapse within or marginal to a previously irradiated volume, but it seems underused because of sparse knowledge on the efficacy and morbidity related to the treatment. Normal tissues often recover some of the damage caused by the primary radiotherapy with time, but the kinetics of recovery is not clearly described in the literature. There is a growing number of publications on SBRT reirradiation, but the literature consists mainly of retrospective cohort studies. The aim of the present paper is to review studies on SBRT reirradiation in various regions where some studies have been published such as the head and neck, lung, liver, pancreas, prostate and spine. Based on the retrospective nature of the literature, the guide-lines provided by this guideline are relatively weak. In some organ systems, some advice on constraints related to reirradiated volumes and doses may be given.

Keywords: Stereotactic body radiation therapy (SBRT); re-irradiation; radiation tolerance

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Background

A second course of radiotherapy (re-irradiation) is relatively rarely used as salvage after primary radiotherapy. In most cases, we tend to use surgery, cryotherapy or alternative local ablation methods to treat the recurrent tumor. The reason being that there is a lack of knowledge on efficacy and morbidity related to the use of irradiation. The concern about potential severe long-term normal tissue reaction results in underuse of re-irradiation.

Stereotactic body radiotherapy (SBRT) spares volumes of normal tissues because of its high precision and use of tight margins and it may therefore potentially have an advantage to conventional radiotherapy in re-irradiation of relapsing tumors. Traditionally, SBRT is given with few large doses but novel efficient techniques allow use of increased numbers of fractions thus combining the volume sparing and the fractionation effect on the normal tissues.

It is important to make a distinction between local or marginal recurrences where the re-irradiation volume overlaps totally or considerably with the primary treated volume and distant recurrences where there is no or only minor overlap between the volumes. In both situations, the possibilities for a second course of radiotherapy depends on the primary doses and volumes and the dose needed to control the relapse. With a local relapse, we account on recovery of normal tissue effects of the primary radiation therapy whereas we do not need to account for recovery of normal tissue from prior radiotherapy in the distant relapse situation. The recovery differs considerably from organ to organ. Early reacting organs such as mucosa recovers fast and almost completely, whereas some late reacting tissues such as kidney do not recover at all. Despite partial recovery, the late effects are still cumulative.

Finally, the tolerance to re-irradiation is dependent on the functional unit structure of the organ at risk; organs with functional units in parallel such as peripheral lung, liver and kidney are volume dependent and may tolerate small-volume re-irradiation well. Organs with serial functional unit structures such as spinal cord, airways and bowel exhibit less volume effect and they have higher risks of damage if the recovery after the initial treatment is incomplete.

A clinical consideration on re-irradiation should always include the patients' age and co-morbidities. Elderly patients and patients with severe co-morbidity may not tolerate re-treatment and specific co-morbidities such as chronic obstructive pulmonary disorders and interstitial lung disease or hepatitis/cirrhosis may reduce the tolerability of re-irradiation considerably.

The knowledge on the extent and the kinetics of normal tissue recovery from prior radiotherapy is incomplete, but the number of publications is increasing in the field and we are becoming aware of the potential benefits and possibilities in SBRT re-irradiation. The evolving literature also reveals a risk of toxicity and there is an increasing awareness of constraints in volumes and doses applied in planning of SBRT re-irradiation. The present paper summarizes the knowledge and provides recommendations on selection of patients for SBRT re-irradiation.

Methods

The present review is restricted to topics with sufficient literature and the focus is primarily on re-irradiation of non-brain sites such as head and neck, lung, liver, pancreas, prostate and spine. It is based on a Med-lines search that included the search terms ["SBRT" or "SABR" or "stereotactic"] combined with ["reirradiation" or "retreatment"] combined with ["head and neck" or "spine" or "lung" or "liver" or hepatocellular carcinoma" or "pancreas" or "pancreatic" or "prostate" or "prostatic"] on February 2017. Back-tracking through reference lists and existing reviews were supplementary to the Med-line search. This resulted in a total of 213 papers on head and neck (n=78), lung (n=46), spinal (n=49), liver (n=12), pancreas (n=8) and prostate (n=20). Only original studies were included and duplets were excluded. As a general concept, only studies with more than 25 patients were included. In case of SBRT for recurrences in the head and neck region, there were larger studies available and the limit was set to 50 patients per study and where patient numbers were limited (liver and pancreas), smaller studies were allowed.

Head and neck

Surgical resection is the preferred salvage therapy for smaller recurrent or new primary cancers in the head and neck region if the patient has previously received full course radiotherapy to the tumor site. Many patients are inoperable for technical or medical reasons. Conventional radiotherapy or palliative chemotherapy is the only options for most of the patients. Overall, irradiation with conventional fractionation with or without chemotherapy for recurrent squamous cell carcinoma has resulted in modest rates of local control (1,2), however, somewhat better for patients with recurrent naso-pharyngeal cancer (3). Randomized studies in conventional radiation therapy have pointed at the importance of high radiation dose and addition of chemotherapy, but they have also demonstrated that the patients carry a poor prognosis and high risk of acute and late toxicities (4). The most feared late complications in re-irradiation of the head and neck are radiation myelopathy, carotid blowout syndrome, mandibular and soft tissue necrosis, fistula, mucosal ulceration, laryngeal edema or stenosis, dysphagia and trismus.

With SBRT, it is intended to deliver a high biological dose to a confined and precisely defined target with the aim to achieve the best local control with the least risk of severe morbidity. There is now a growing evidence on the effect of SBRT to recurrences of squamous cell carcinoma in the head and neck region. Local control seems favorable with SBRT and cetuximab in a phase II study with a 1-year local overall progression free survival of 60% (5). However, the median progression free survival and survival were only 7 and 10 months, respectively. Similar favorable local control and modest median survival of 12 months were found in a phase II study on SBRT combined with cetuximab by Lartigau *et al.* (6).

Even with treatment of a relatively small volume, the risk of morbidity is still prominent. In one of the largest studies published, Ling et al retreated 291 patients with recurrent head and neck cancer who all had received previous external radiotherapy with a combination of SBRT and cetuximab (only squamous cell type) (7). The risk of grade ≥3 late morbidity varied considerably between re-irradiation sites, being most pronounced in the oropharynx and larynx where 50% of patients suffered severe morbidity whereas fewer (20%) experienced severe morbidity in treatment of recurrent neck nodes. In addition to site, high re-irradiation dose (≥44 Gy) was related to increased risk of late morbidity.

In additional studies on recurrent head and neck cancer, the 2-year loco-regional control rates were 28–30% and overall survival rates 24–41%, respectively (8,9). Complete surgical resection of the recurrence before SBRT, nasopharynx origin and interval of longer than 2 years between treatment of primary and recurrence were prognostic factors related to survival.

A study by Yamazaki included patients treated with

SBRT, IMRT and proton therapy for recurrent head and neck cancer (10). Local control rates were 67% in patients treated with protons and photons, respectively. Survival rates were 68% and 54% and not statistically different between the two modalities. Proton patients experienced more toxicity, but they also received higher biological doses than photon patients did.

In an analysis of late effects in patients retreated with Cyberknife radiotherapy for head and neck cancer, 17% developed carotid blowout which was fatal in most of the patients (11). The risk was highest with recurrent tumor encasing the carotid artery and when the carotid artery receives the full prescription dose. Carotid blowout may also occur, but most likely with a lower frequency, after conventional fractionated reirradiation. In a review of more than 1,500 patients, the serious complication was observed in only 1.3% of patients treated with conventional radiotherapy and concurrent chemotherapy did not increase the risk (12).

A survey of current practices performed in highly experienced centers using SBRT for head and neck cancers revealed heterogeneous practice of SBRT (13). SBRT was the preferred radiation technique for treatment of 10–100% of recurrent head and neck cancer cases. Most centers required a minimum of 6 months progression free interval between treatment of the primary and the recurrent cancer. Relative contraindications for re-irradiation were connective tissue disorders, skin ulcer, tumor overlying a blood vessel, or encasing the carotid artery, and proximity to the brachial plexus, optic pathways, brain or cavernous sinus. Most centers used systemic therapy along with SBRT as a boost after conventional radiotherapy or as the definitive treatment of the recurrence.

It seems justified to conclude that SBRT provides favorable long-term local control of recurrent head and neck cancer when administrated with concomitant systemic antineoplastic therapy. Progression free survival and overall survival are modest and the treatment is related to a risk of severe morbidity. SBRT should be provided with caution, the patients should be carefully selected, the progression free interval should be 6 month or longer and dose and fractionation should be conservative. Conventional fractionated radiotherapy should be preferred when the recurrent tumor encases the carotid artery.

Lung

High local control and low morbidity rates are observed after SBRT of peripheral lung cancers (14), but in central cases the risk of morbidity is much higher (15). This has led to use of SBRT in treatment of recurrent peripheral lung cancers and metastases arising after previous thoracic radiotherapy, in cases where there is a complete separation between the primary and the recurrent volumes and in cases where there is an overlap between the two volumes.

A retrospective analysis from the MD Anderson was carried out in patients treated with after SBRT of recurrent lung tumors who previously had received radiotherapy for stage I–II (44%) or III–IV (56%) non-small cell lung cancer (16). The local control rate was 92%, but 2-year progression free- and overall survival rates were only 26% and 59%, respectively. Thirty-three percent of the patients experienced grade 3 and none grade 4–5 toxicities; fifty percent had symptomatic pneumonitis. All grade 3 pneumonitis was observed in patients treated for out-of-field relapse and none among in-field relapse patients. Thirty-one percent developed chest wall pain. In contrary to pneumonitis, pain was considerably more prevalent in patients treated for in-field relapse.

Other studies also found favorable 1-year local control rates of 77–95% after treatment of recurrences of primary lung cancer or metastases to the lungs (17-20). The studies are all retrospective and include patients with varying extend of infield and outfield recurrences. They generally report only moderate toxicity, however, one patient treated for a central located tumor developed an aorta-esophageal fistula and died from fatal bleeding (17).

At University of Pittsburg, they retreated patients with recurrences after primary surgical resection and I^{125} vicryl mesh brachytherapy of non-small lung cancer (21). With high biological SBRT doses, they achieved a 1-year local control rate of 84% and 2-years progression free survival rate of 32%, respectively. Only one grade 3 esophageal stricture following a centrally located recurrence was observed in a patient who previously was treated with radiofrequency ablation as well as brachytherapy.

Relatively low doses (30 Gy in 5–6 fractions) were used for reirradiation of centrally located non-small cell lung cancer in Italy (22). The low doses resulted in a 1-year local control rate of 86% and overall survival rates at 1 and 2 years of 59% and 29%, respectively. Five patients experienced grade ≥4 pneumonitis; among these, one died (grade 5). Another patient died from fatal hemorrhage. In Sweden, they used high biological doses for SBRT re-irradiation of 32 tumors in 29 patients where 11 tumors were central and the remaining 21 were peripheral (23).

Treatment of peripheral tumors resulted in five grade 3 morbidities, mostly dyspnea, and no grade 4–5 toxicities. In contrast, 12 grade ≥3 toxicities were observed after treatment of central tumors; among these were three deaths from fatal hemorrhage.

High local control rates can be achieved after SBRT of primary lung cancer and metastases that has previously been treated with radiation therapy. It is safe to re-irradiate peripheral lung tumors in patients with sufficient lung function, but there is a high risk for severe complication, especially fatal hemorrhage, when retreating central tumors with SBRT. Fatal toxicity may occur even with use of low SBRT doses.

Liver

One of the major challenges in SBRT of liver tumors and especially hepatocellular carcinoma is the relatively low radiation tolerance of the liver (24). Hepatocellular carcinoma is often secondary to chronic hepatitis and extensive cirrhosis and these conditions predispose for radiation induced liver disease (RILD). The degree of cirrhosis may be graded according to the Child-Pugh (C-P) classification system. With C-P class B and C, the liver is vulnerable and due to a low reserve capacity, it tends to decompensate after a radiation trauma.

There are only few papers on re-irradiation for hepatocellular carcinoma and no papers on retreatment of liver metastases. Two studies on re-irradiation includes patients treated with SBRT as well as conventional fractionated radiotherapy for recurrent hepatocellular carcinoma (25,26). A study from Korea retreated 43 patients after a progression free interval of 14 months from the primary radiotherapy (26); twenty-four patients were treated with palliative doses. The authors found partial response in 63% and complete response in 19% of the cases. High radiation dose was related to a high chance of response. Median overall survival time was 11 months and prognostic factors related to survival were C-P class and tumor stage. Only two patients developed grade 3 morbidity in terms of duodenal ulcer and pneumonitis. In a second study from Taiwan, 36 patients received SBRT re-irradiated after a median progression free interval of 1 months (25). Surprisingly, thirteen patients developed RILD. Four were transient and nine were lethal and resulted in death after 3–5 months. Only high C-P score predicted development of RILD. Patients with RILD had a poor prognosis with a median survival of 6 months, whereas those without RILD survived 29 months. Presence of portal vein thrombosis and development of RILD was related to poor survival.

The sparse literature on SBRT re-irradiation of hepatocellular carcinoma points at a poor prognosis for patients with recurrent hepatocellular carcinoma. High C-P score and portal vein thrombosis predict for poor survival after re-irradiation. Selection and dose prescription should be conservative because of the high risk of RILD in these patients. There is no available literature on SBRT retreatment of metastases.

Pancreas

Salvage surgery is only possible in very few selected cases and SBRT has been considered as an option for patients presenting with a local progression after primary surgery or radiation therapy. Gastrointestinal toxicity limits the use of re-irradiation.

A retrospective study of 23 patients treated for locally recurrent pancreatic cancer was analyzed at Stanford University (27). Of these, 12 were treated for a recurrent retroperitoneal tumor after surgical resection and postoperative radiotherapy and the remaining 11 after definitive radiotherapy. In both groups, patients had received some type of systemic antineoplastic therapy. SBRT resulted in excellent local control of the recurrent cancer with freedom from local failure of 81% at 1 year. A large proportion of patients suffered from pain prior to therapy and 57% experienced improvement of pain at follow-up. Six patients (26%) developed grade 2–3 toxicity, one with a gastric fistula and another with a bleeding gastric ulcer. Nine patients received SBRT as a single fraction of 25 Gy and the remaining 14 patients with a dose of 5×5 Gy. No statistical differences in local control or morbidity were observed between the two groups.

A study from Harvard contained 30 patients treated with SBRT with a dose of 24–36 Gy in 5 fractions for recurrence of pancreas cancer (28). All had received prior radiation therapy to the abdomen, 9 with SBRT. Local control rate at 1 year was 78% and 7% developed grade 3 bowel obstruction as a late effect.

Eighteen patients received SBRT re-irradiation in a joint study from John Hopkins and Stanford (29). Fifteen had previously undergone resection in combination with chemo-radiation. The SBRT dose was 20–27 Gy in 5 fractions. Freedom from local progression was 62% and the pain response rate was 57%. As the only serious side effect, one patient developed small bowel obstruction. A Chinese study

evaluated 24 patients treated with SBRT for recurrent pancreatic adenocarcinoma in abdominal lymph nodes or the pancreatic stump after surgery with 5–8 fractions of 6–10 Gy per fraction (30). The 1-year local control rate was 83% and 78% experienced a pain response shortly after SBRT. No severe toxicity was observed that could be related to SBRT.

In all three studies, the overall survival after SBRT re-irradiation was poor. Median survival ranged 9–12 months. All three studies found a palliative effect of SBRT, which favors use of SBRT for re-irradiation. However, selection as well as doses and volumes should be conservative because of the risk of severe bowel toxicity.

Prostate

Prostate cancer patients treated with radiation therapy have a relatively high risk of PSA relapse. It will often be due to local recurrence in the prostate gland, but it is related to an increased risk of death (31). Salvage treatments at time of PSA relapse include salvage prostatectomy, cryotherapy, high intensive focused ultrasound (HIFU) or radiotherapy (32). However, salvage prostatectomy is infrequently used (33), primarily because of the relatively high risk of severe morbidity in terms of incontinence, urethral stricture and rectal injury. Brachytherapy is due to its sharp dose fall-off the most frequently used radiation modality and a growing number of publications within high dose rate (HDR) brachytherapy demonstrates the safety of focused re-irradiation of the prostate (34).

So far, there are only two French reports on SBRT for local prostate cancer recurrence after previous full course radiotherapy. A study from Tours included patients who previously had full course radiotherapy or prostatectomy followed by postoperative radiotherapy (35). The patients received 5×7.25 Gy to the prostate or the prostatic bed. With a mean follow-up time of 12 months, the biochemical recurrence-free survival (bRFS) was 83%. Only few grade 1 and one grade 2 acute genito-urinary (GU) morbidities were noted. In the second study from Nice, 18 patients received SBRT re-irradiation (36). With a follow-up of 15 months, the 1-year b-RFS was close to 60%. One patient experienced a grade 4 GU toxicity based on a necrosis of the prostate complicated by local infection and sepsis. Before the event, the patients had numerous urethral instrumentations through the urethra.

The two retrospective cohort studies report favorable morbidity profiles of SBRT re-irradiation of the prostate, but the studies are small and the follow-up is short. Both studies indicate that the risk is on the GU side effects rather than GI effects. Careful selection of patients without preexisting GU morbidity and tight constraints to the urethra and the bladder neck to limit the risk of GU morbidity seem important. Longer follow-up is needed to conclude on the effect of SBRT re-irradiation on disease control.

Spine

Many patients referred for spine SBRT have previously had conventional radiotherapy. Relapsing metastases after primary spinal CRT or SBRT are painful and related to high risk of loss of ambulatory function. Conventional radiotherapy may relive pain, but the effect on preservation of motor function is limited.

A large multicenter database study by the Elekta Spine Study Consortium analyzed re-irradiation SBRT in 215 patients treated for 247 spinal targets (37). The typical initial radiation dose was 30 Gy in 10 fractions and median re-irradiation SBRT dose was 18 Gy in one fraction, sixty percent as a single fraction. The free interval between primary irradiation and retreatment was 14 months. The 1-year local control and survival rates were 83% and 48%, respectively. Performance status was the only prognostic factor related to survival and single-fraction SBRT the only factor related to local control. No patients developed myelopathy.

In retrospective cohort studies, re-irradiation of spinal metastases is related to a high probability of local control ranging 66–96% and pain response of 48–76%, respectively (38-43). The free interval between primary treatment and re-treatment, presence of epidural disease and the distance between the target and the thecal sac >1 mm are considered related to better local control. The overall survival ranges 45–76% at 1 year after re-irradiation and depends on performance status and the free interval.

Myelopathy with weakness or loss of motor function and changes on MRI is very infrequent after SBRT (44). Sahgal *et al.* reviewed dose-volume data of published cases of myelopathy following SBRT re-irradiation; five myelopathy cases were compared to 14 non-myelopathy cases (45). The total biological effective dose (tBED) from the primary conventional and the re-irradiation course was considerably higher in myelopathy patients than in the non-myelopathy patients. They concluded that re-irradiation SBRT can be safely given with a $BED_{max\ 2/2}$ (normalized to 2-Gy equivalent dose assuming α/β 2 Gy) of 20–25 Gy, provided that the

free interval between the two courses exceeds 5 months, that the $tBED_{max\ 2/2}$ does not exceed 70 Gy and that the re-irradiation SBRT thecal sac $BED_{max\ 2/2}$ comprises less than 50% of the thecal sac $tBED_{max\ 2/2}$.

Vertebral compression fracture is another important spine SBRT complication. It may lead to chronic pain and should be avoided whenever possible. In primary spine SBRT, high prescription dose, single fraction and high spinal instability neoplastic score (SINS) are risk factors for development of vertebral compression fracture. The SINS comprises clinical and radiological characteristics related to vertebral instability and it guides the clinician to select patients at risk for fracture for surgical stabilization before SBRT. In the Elekta Spine Study Consortium database, 11% underwent surgical stabilization before SBRT and 5% developed a vertebral compression fracture after SBRT (37).

Re-irradiation SBRT may provide favorable local control and prevent progression in a large fraction of patients with spinal metastases and acceptable performance status. It provides valuable palliation in terms of pain and sustained ambulatory function. It is a safe procedure with low risk of myelopathy and vertebral compression fracture if the above-mentioned constraints are met.

Discussion

The level of evidence in retreatment after primary radiation therapy is low. There are a few randomized trials on conventional radiotherapy in re-irradiation of head and neck cancer. In SBRT, there are only two phase II study, both in head and neck cancer. All other studies on the use of SBRT are relative small retrospective cohort studies of heterogeneous patient groups. Due to the retrospective nature, the study materials vary considerably with respect to previous treatment, differences in dose and volumes of the primary radiation therapy. Additional therapies such as surgery and chemotherapy in conjunction to radiation therapy at recurrence differs substantially within and between the cohorts and the cohorts vary in age, gender and comorbidities. The retrospective data collection, the broad heterogeneity and the small patient numbers per study reduce the validity of the SBRT studies and a literature review within the field allows only weak recommendations. The clinician is therefore often left with the option to deliver highly individualized treatment where patient selection, target volume definition, prescription of doses and fractionation are at the clinicians own discretion and experience.

The advantage of SBRT is the sparing of normal tissue, which is of the highest importance in the recurrence scenario. On the other hand, SBRT is most often delivered with extreme hypofractionation. At the time when the SBRT concept was invented, the technique and resources determined the use of few large doses. Today, SBRT is still delivered with hypofractionation but now it is primarily explained by a belief of a biological advantage. However, in cases with a high risk of late effects or complications because of a radiosensitive organ at risk in the proximity of the target there is a rational for use of more fractions. This is often the case with SBRT in the re-irradiation scenario.

The relatively modest morbidity following SBRT re-irradiation as reported in the present review supports the findings of experimental studies where many normal tissues recover radiation-induced damage to a large extent. The protective effect of fractionation and the long-term recovery of damage in the spinal cord dated back to the 1970's in studies of rodent spinal cord (46-48) and it was later confirmed in studies on monkeys (49). Significant recovery was observed in the serially organized spinal cord starting 8 weeks after primary radiotherapy with recovery being proportional with the interval between primary irradiation and re-irradiation. Dose to the spinal cord at the primary irradiation was the second determinant of the degree of recovery. These experimental findings are in agreement with the low incidence of myelopathy after SBRT re-irradiation of the spine provided that the interval between primary radiotherapy and re-irradiation is longer than 5 months and that dose-volume constraints as mentioned above are met.

In parallel-organized tissues such as peripheral lung and liver, the reserve capacity is often considerable. Both in cases of overlap or non-overlap of the primary and relapsing targets, the reserve capacity may compensate for the loss of organ function. Imaging studies indicate that liver tissue receiving low and intermediate doses may recover to some extent during the first months after a primary SBRT (50). Whether similar processes occur in other organs is less clear. Experimental animal studies and functional imaging studies may provide with valuable information on the recovery kinetics and retreatment tolerance. They are therefore strongly warranted.

There is a potential for use of SBRT re-irradiation in a number of cases where cancer recur locally in the body after primary radiotherapy. The most prominent limitation in use of SBRT re-irradiation is the lack of knowledge about efficacy and tolerability of re-irradiation. Knowledge on

radiation tolerance may be achieved from experimental and to some extent from functional imaging studies, but the most valuable knowledge has to be derived from randomized studies (4). For some cancer types, it may not be possible to conduct large clinical trials due to small patient numbers. For other types, the numbers are sufficient for conduction of randomized clinical trials. Patients with local relapse after primary radiotherapy should be included in clinical trials with prospectively collection of morbidity data, preferentially in randomized trials that ensure that we obtain the needed evidence.

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Footnote

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References

1. Langer CJ, Harris J, Horwitz EM, et al. Phase II study of low-dose paclitaxel and cisplatin in combination with split-course concomitant twice-daily reirradiation in recurrent squamous cell carcinoma of the head and neck: results of Radiation Therapy Oncology Group Protocol 9911. J Clin Oncol 2007;25:4800-5.
2. Spencer SA, Harris J, Wheeler RH, et al. Final report of RTOG 9610, a multi-institutional trial of reirradiation and chemotherapy for unresectable recurrent squamous cell carcinoma of the head and neck. Head Neck 2008;30:281-8.
3. Kong L, Lu JJ. Reirradiation of locally recurrent nasopharyngeal cancer: history, advances, and promises for the future. Chin Clin Oncol 2016;5:26.
4. Nieder C, Langendijk JA, Guckenberger M, et al. Prospective randomized clinical studies involving reirradiation : Lessons learned. Strahlenther Onkol 2016;192:679-86.
5. Vargo JA, Ferris RL, Ohr J, et al. A prospective phase 2 trial of reirradiation with stereotactic body radiation therapy plus cetuximab in patients with previously irradiated recurrent squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 2015;91:480-8.
6. Lartigau EF, Tresch E, Thariat J, et al. Multi institutional phase II study of concomitant stereotactic reirradiation and cetuximab for recurrent head and neck cancer. Radiother Oncol 2013;109:281-5.
7. Ling DC, Vargo JA, Ferris RL, et al. Risk of Severe Toxicity According to Site of Recurrence in Patients Treated With Stereotactic Body Radiation Therapy for Recurrent Head and Neck Cancer. Int J Radiat Oncol Biol Phys 2016;95:973-80.
8. Kress MA, Sen N, Unger KR, et al. Safety and efficacy of hypofractionated stereotactic body reirradiation in head and neck cancer: Long-term follow-up of a large series. Head Neck 2015;37:1403-9.
9. Unger KR, Lominska CE, Deeken JF, et al. Fractionated stereotactic radiosurgery for reirradiation of head-and-neck cancer. Int J Radiat Oncol Biol Phys 2010;77:1411-9.
10. Yamazaki H, Ogita M, Himei K, et al. Carotid blowout syndrome in pharyngeal cancer patients treated by hypofractionated stereotactic re-irradiation using CyberKnife: A multi-institutional matched-cohort analysis. Radiother Oncol 2015;115:67-71.
11. Cengiz M, Özyigit, Yaziki G, et al. Salvage reirradiation with stereotactic body radiotherapy for locally recurrent head-and-neck tumors. Int J Radiat Oncol Biol Phys 2011;81:104-9.
12. McDonald MW, Moore MG, Johnstone PA. Risk of carotid blowout after reirradiation of the head and neck: a systematic review. Int J Radiat Oncol Biol Phys 2012;82:1083-9.
13. Karam I, Yao M, Heron DE, et al. Survey of current practices from the International Stereotactic Body Radiotherapy Consortium (ISBRTC) for head and neck cancers. Future Oncol 2017;13:603-13.
14. Kopek N, Paludan M, Petersen J, et al. Co-morbidity index predicts for mortality after stereotactic body radiotherapy for medically inoperable early-stage non-small cell lung cancer. Radiother Oncol 2009;93:402-7.
15. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 2006;24:4833-9.
16. Kelly P, Balter PA, Rebueno N, et al. Stereotactic body radiation therapy for patients with lung cancer previously treated with thoracic radiation. Int J Radiat Oncol Biol Phys 2010;78:1387-93.

17. Kilburn JM, Kuremsky JG, Blackstock AW, et al. Thoracic re-irradiation using stereotactic body radiotherapy (SBRT) techniques as first or second course of treatment. Radiother Oncol 2014;110:505-10.
18. Liu H, Zhang X, Vinogradskiy YY, et al. Predicting radiation pneumonitis after stereotactic ablative radiation therapy in patients previously treated with conventional thoracic radiation therapy. Int J Radiat Oncol Biol Phys 2012;84:1017-23.
19. Patel NR, Lanciano R, Sura K, et al. Stereotactic body radiotherapy for re-irradiation of lung cancer recurrence with lower biological effective doses. J Radiat Oncol 2015;4:65-70.
20. Reyngold M, Wu AJ, McLane A, et al. Toxicity and outcomes of thoracic re-irradiation using stereotactic body radiation therapy (SBRT). Radiat Oncol 2013;8:99.
21. Gill BS, Clump DA, Burton SA, et al. Salvage stereotactic body radiotherapy for locally recurrent non-small cell lung cancer after sublobar resection and i(125) vicryl mesh brachytherapy. Front Oncol 2015;5:109.
22. Trovo M, Minatel E, Durofil E, et al. Stereotactic body radiation therapy for re-irradiation of persistent or recurrent non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2014;88:1114-9.
23. Peulen H, Karlsson K, Lindberg K, et al. Toxicity after reirradiation of pulmonary tumours with stereotactic body radiotherapy. Radiother Oncol 2011;101:260-6.
24. Dawson LA, Ten Haken RK. Partial volume tolerance of the liver to radiation. Semin Radiat Oncol 2005;15:279-83.
25. Huang Y, Chen SW, Fan CC, et al. Clinical parameters for predicting radiation-induced liver disease after intrahepatic reirradiation for hepatocellular carcinoma. Radiat Oncol 2016;11:89.
26. Seol SW, Yu JI, Park HC, et al. Treatment outcome of hepatic re-irradiation in patients with hepatocellular carcinoma. Radiat Oncol J 2015;33:276-83.
27. Koong AT, DAS; von Eyben, R; Pollom, EL; Chang, DT. Reirradiation with stereotactic body radiation therapy after prior conventional fractionation radiation for locally recurrent pancreatic adenocarcinoma. Advances in Radiation Oncology 2017;2:10.
28. Dagoglu N, Callery M, Moser J, et al. Stereotactic Body Radiotherapy (SBRT) Reirradiation for Recurrent Pancreas Cancer. J Cancer 2016;7:283-8.
29. Wild AT, Hiniker SM, Chang DT, et al. Re-irradiation with stereotactic body radiation therapy as a novel treatment option for isolated local recurrence of pancreatic cancer after multimodality therapy: experience from two institutions. J Gastrointest Oncol 2013;4:343-51.
30. Zeng XL, Wang HH, Meng MB, et al. Stereotactic body radiation therapy for patients with recurrent pancreatic adenocarcinoma at the abdominal lymph nodes or postoperative stump including pancreatic stump and other stump. Onco Targets Ther 2016;9:3985-92.
31. Agarwal PK, Sadetsky N, Konety BR, et al. Treatment failure after primary and salvage therapy for prostate cancer: likelihood, patterns of care, and outcomes. Cancer 2008;112:307-14.
32. Tetreault-Laflamme A, Crook J. Options for Salvage of Radiation Failures for Prostate Cancer. Semin Radiat Oncol 2017;27:67-78.
33. Chade DC, Eastham J, Graefen M, et al. Cancer control and functional outcomes of salvage radical prostatectomy for radiation-recurrent prostate cancer: a systematic review of the literature. Eur Urol 2012;61:961-71.
34. Yamada Y, Kollmeier MA, Pei X, et al. A Phase II study of salvage high-dose-rate brachytherapy for the treatment of locally recurrent prostate cancer after definitive external beam radiotherapy. Brachytherapy 2014;13:111-6.
35. Janoray G, Reynaud-Bougnoux A, Ruffier-Loubiere A, et al. Stereotactic body re-irradiation therapy for locally recurrent prostate cancer after external-beam radiation therapy: Initial report. Cancer Radiother 2016;20:275-81.
36. Mbeutcha A, Chauveinc L, Bondiau PY, et al. Salvage prostate re-irradiation using high-dose-rate brachytherapy or focal stereotactic body radiotherapy for local recurrence after definitive radiation therapy. Radiat Oncol 2017;12:49.
37. Hashmi A, Guckenberger M, Kersh R, et al. Re-irradiation stereotactic body radiotherapy for spinal metastases: a multi-institutional outcome analysis. J Neurosurg Spine 2016;25:646-53.
38. Chang UK, Cho WI, Kim MS, et al. Local tumor control after retreatment of spinal metastasis using stereotactic body radiotherapy; comparison with initial treatment group. Acta Oncol 2012;51:589-95.
39. Choi CY, Adler JR, Gibbs IC, et al. Stereotactic radiosurgery for treatment of spinal metastases recurring in close proximity to previously irradiated spinal cord. Int J Radiat Oncol Biol Phys 2010;78:499-506.
40. Damast S, Wright J, Bilsky M, et al. Impact of dose on local failure rates after image-guided reirradiation of recurrent paraspinal metastases. Int J Radiat Oncol Biol Phys 2011;81:819-26.
41. Mahadevan A, Floyd S, Wong E, et al. Stereotactic body radiotherapy reirradiation for recurrent epidural spinal metastases. Int J Radiat Oncol Biol Phys 2011;81:1500-5.

42. Sterzing F, Hauswald H, Uhl M, et al. Spinal cord sparing reirradiation with helical tomotherapy. Cancer 2010;116:3961-8.
43. Thibault I, Campbell M, Tseng CL, et al. Salvage Stereotactic Body Radiotherapy (SBRT) Following In-Field Failure of Initial SBRT for Spinal Metastases. Int J Radiat Oncol Biol Phys 2015;93:353-60.
44. Wong CS, Fehlings MG, Sahgal A. Pathobiology of radiation myelopathy and strategies to mitigate injury. Spinal Cord 2015;53:574-80.
45. Sahgal A, Ma L, Weinberg V, et al. Reirradiation human spinal cord tolerance for stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 2012;82:107-16.
46. Goffinet DR, Marsa GW, Brown JM. The effects of single and multifraction radiation courses on the mouse spinal cord. Radiology 1976;119:709-13.
47. Hornsey S, Myers R, Warren P. Residual injury in the spinal cord after treatment with X rays or neutrons. Br J Radiol 1982;55:516-9.
48. van der Kogel AJ, Sissingh HA, Zoetelief J. Effect of X rays and neutrons on repair and regeneration in the rat spinal cord. Int J Radiat Oncol Biol Phys 1982;8:2095-7.
49. Ang KK, Jiang GL, Feng Y, et al. Extent and kinetics of recovery of occult spinal cord injury. Int J Radiat Oncol Biol Phys 2001;50:1013-20.
50. Fode MF, Petersenb JB, Sørensen M, et al. 2-[18F]fluoro-2-deoxy-d-galactose positron emission tomography guided functional treatment planning of stereotactic body radiotherapy of liver tumours. Phys Imaging Radiat Oncol 2017;1:28-33.

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