Review Article

Repeat Radiation for Local Recurrence of Head and Neck Tumors and in Prostate Cancer

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Summary

Background: Recent advances in diagnostic methods and in radiotherapy now increasingly enable repeat radiotherapy with curative intent for the treatment of previously irradiated lesions. In this review, we present data on oncological outcomes and on acute and late sequelae, as far as these are currently known, in patients with head and neck tumors (HNT) or prostate cancer (PCa) who underwent repeat radiotherapy after prior radiotherapy with curative intent.

Methods: This review is based on clinical series with over 20 patients that were published between May 1998 and April 2018 (HNT) or between October 1998 and October 2018 (PCa) and were retrieved by a search in the PubMed database.

Results: Most of the clinical series retrieved were retrospective and uncontrolled. There were 16 studies that included 2678 patients with recurrent head and neck tumors, and 8 that included 245 patients with recurrent prostate cancer. In patients with squamous cell carcinoma of the head and neck, intensity-modulated radiotherapy (IMRT) and stereotactic body radiotherapy (SBRT) yielded three-year survival rates of 47–57% but also produced substantial acute and late adverse effects. Most of the studies concerning recurrent PCa involved small patient groups. In these studies, repeat radiotherapy with SBRT yielded tumor control rates of 40–80% after 11–24 months of follow-up, with only mild acute toxicity.

Conclusion: Although no comparative studies are available, it seems that modern external beam radiotherapy techniques can be used for repeat radiotherapy of locally recurrent head and neck tumors with curative intent after careful patient selection. Repeat radiotherapy of PCa must still be considered experimental, but initial results from small-scale trials are encouraging. The long-term adverse effects cannot yet be assessed. Patients should be selected by an interdisciplinary tumor board. This type of treatment is generally carried out in a specialized center.

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The goal of any tumor treatment carried out with curative intent is permanent tumor control with minimal long-term impairment of quality of life. In the past, patients who had been treated once with radiotherapy could not be so treated a second time, because the high-dose region could not be configured precisely enough, and the surrounding healthy tissue was therefore at risk of a radiation overdose. Recent advances in radiotherapeutic methods now make it possible to consider radiotherapy in properly selected cases (*Table 1, Box*) (1–3). These advances include:

- Intensity-modulated radiotherapy (IMRT), a radiotherapeutic technique with a highly homogeneous dose distribution.
- Volumetric arc therapy (VMAT) and helical tomotherapy (HT), two types of IMRT that can be applied uninterruptedly while the linear accelerator is rotated around the patient.
- Stereotactic radiosurgery/stereotactic body radiotherapy (SRS/SBRT), which can be performed with various systems, including the Gamma Knife and the CyberKnife.
- Particle therapy, e.g., with protons.

When the CyberKnife is used, components of the apparatus that control the position of the patient, navigation of the radiation source, and beam-shaping now make it possible to irradiate tumors with very narrow safety margins.

These advances in radiotherapeutic techniques have been accompanied by advances in radiologic diagnostic methods, including computed tomography (CT) and magnetic resonance imaging (MRI), sometimes coupled with positron emission tomography (PET-CT or PET-MRI). As a result, it is now easier to identify recurrences after a first course of radiotherapy, and this, in turn, makes it easier to select suitable patients for repeat radiotherapy (4). In general, the indications for repeat radiotherapy and the outcome that can be expected from it are judged according to the following criteria:

- The patient's general condition
- The type and intensity of prior treatment
- The location and size of the recurrent tumor
- The degree of infiltration of neighboring structures
- The presence or absence of metastases.

Head and neck tumors (HNT) recur in 40–50% of cases after primary radiotherapy with curative intent. Rescue surgery is the treatment of first choice. If this is not possible, but the recurrence is still locally confined,

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BOX

Decision-making criteria in favor of repeat radiotherapy with curative intent

- Good general condition of the patient (ECOG 0 – 1)
- Small local recurrent tumor, radiographically well circumscribed (head and neck tumors; includes lymph node recurrence)
- Clean surgical margins (grade R0 or R1 resection) not achievable, or the operation would be physically mutilating or impair bodily function
- The patient's desires
- More than 6 months since initial radiotherapy
- Documentation of the initial radiotherapy is available for evaluation
- Radiation reserve capacity in surrounding normal tissue
- Interdisciplinary recommendation

then repeat radiotherapy, possibly in combination with systemic chemotherapy, may give the patient with a recurrent or new tumor in a previously irradiated area a second chance at curative treatment (5). For patients with recurrent prostate cancer (PCa) after radiotherapy with curative intent, for older patients with marked comorbidity, and for patients with distant metastases, systemic drug treatment (hormonal or anti-hormonal therapy) without radiotherapy is an option for long-term palliative treatment (6).

Advances in PET and MRI (3-tesla MRI, PSMA [prostate-specific membrane antigen]-PET-CT/-MRI) now make it possible for recurrences to be diagnosed and locally delimited, with the simultaneous exclusion of metastatic disease (4). Rescue or salvage prostatectomy after prior radiotherapy with curative intent is still the standard treatment, despite the lack of comparative evidence, but it carries a high morbidity (7).

With regard to repeat radiotherapy (employing a wide variety of techniques) for patients with recurrent HNT, only a few prospective trials, but a large number of retrospective case analyses have been published in recent years, some of them from single institutions. As for re-irradiation in patients with recurrent PCa, our current knowledge is derived mostly from retrospective analyses of small patient cohorts. These two malignant entities in two very different regions of the body are characterized by different courses of treatment and spectra of potential side effects. Nonetheless, the data presented here provide an initial overview of the range of non-invasive treatment options that are increasingly being applied with curative intent in patients who have previously undergone high-dose radiotherapy. It must be pointed out that

these results may not be generalizable because of the lack of randomization in these mainly retrospectively evaluated, small-scale case series. There is an urgent need for the potential of these techniques to be assessed in controlled trials.

Methods

A literature search was carried out in PubMed. The evaluation included only original publications that appeared from May 1998 to April 2018 (HNT) or from October 1998 to October 2018 (PCa), and that included patients treated with repeat radiotherapy, with curative intent, by means of modern techniques (IMRT, VMAT, SBRT, particle therapy for HNT; SBRT for PCa), for local or regional recurrences or for new tumors of the head and neck, or of the prostate, that were within the field of initial radiotherapy (≥ 40 Gy). Publications were only considered if they were available in full text in either English or German. Review articles, studies without survival data, studies involving repeat radiotherapy combined with rescue surgery or other local treatments, and studies in which repeat radiotherapy was mainly performed with outdated techniques, such as tele-cobalt, 2D-RT, or 3D-conformal RT (3D-CRT), as well as studies involving brachytherapy, were excluded. In addition, the reference lists of the included studies were checked for additional publications. The studies were evaluated for:

- Patient numbers
- Tumor location
- Radiotherapeutic technique
- Basic data on repeat radiotherapy, including total dose (TD)
- Fractions (Fx) and single doses (SD)
- Systemic therapy.

The median duration of follow-up and the rates of progression-free and/or overall survival at 1, 2, 3, and 5 years were assessed, to the extent that the relevant data were available. Acute and late sequelae were analyzed and categorized according to the Common Terminology Criteria for Adverse Events (CTCAE: grade 3, serious; grade 4, life-threatening; grade 5, fatal) (*eMethods*).

Head and neck tumors

The overall survival at 1 and 2 years was 56% and 35–51% after IMRT (8), 31–84% and 13–58% after SBRT, and 62–68% and 30–42% after particle therapy (8–17). In a prospective phase II study of CyberKnife-SBRT plus cetuximab, the overall survival at 1 year was 47% (3). With SBRT alone, the median overall survival in a phase I study was only 6 months (95% confidence interval: 5–8 months) (18). The long-term survival rates after IMRT were 47–57% at 3 years (19–21), 19% at 5 years without simultaneous chemotherapy, and 23% at 5 years with simultaneous chemotherapy, with a median follow-up interval of 39 months (22).

The rate of serious acute side effects (CTCAE grade 3) ranged, depending on the location and size of the

TABLE 1

Available types and techniques of radiotherapy for the re-irradiation of head and neck tumors and prostate cancer

	Type of radiation	Radiotherapeutic technique	Apparatus	Applicability
Brachytherapy ^{*1}	Gamma rays	HDR PDR LDR	Afterloading method Permanently implanted seeds	Interstitial therapy with rigid needles, catheters, or tubes Permanent implantation
Teletherapy ^{*2}	Photons	IMRT VMAT SBRT	Linear accelerator, tomotherapy Linear accelerator Linear accelerator adapted for stereotaxy CyberKnife	Postoperatively, as radiotherapy alone or in combination with systemic treatment SBRT by means of a specially adapted linear accelerator or CyberKnife enables the treatment of smaller tumors with markedly shorter treatment times
Teletherapy	Electrons	2D	Linear accelerator	Useful for superficial tumors, alone or in combination with photons
Teletherapy	Protons, carbon ions, etc.	PBT IMPT	Cyclotron, synchrotron	As radiotherapy alone or in combination with systemic treatment

^{*1} **Brachytherapy** is radiotherapy from the interior of a tumor (brachy = "near"). In a first step, access to the interior of the tumor is gained by the best possible route, as determined by the anatomical location of the tumor and surrounding structures. This can be done, for example, with a hollow needle, a catheter, or a tube. In a second step, a small capsule containing radioactive material is introduced into the tumor by this access route under computer guidance, in order to irradiate the tumor from within with a dose profile that has been precisely calculated in advance. The advantage of this technique is that the healthy tissue surrounding the tumor need not be irradiated by radiation beams directed at the tumor from outside. Its main disadvantage is its limited applicability to large tumors. It is, therefore, also used to provide a local increase of radiation dose (a local boost) after large-volume external beam radiotherapy.

^{*2} **Teletherapy** comprises all radiotherapeutic techniques in which the patient is irradiated from outside (tele = "far"). Most radiotherapeutic techniques are of this type, regardless of whether they employ photons or protons, and regardless of the particular physical method used (e.g., IMRT or VMAT). The advantage of the wide variety of teletherapeutic techniques is that every patient can be treated with the one that is most suitable for him or her, whether the tumor is superficial or deep, large or small, mobile or stationary. Specialized techniques, such as stereotaxy or proton-beam therapy, are generally available only in large centers and specialized institutes.

Ir192, iridium-192; HDR, high dose-rate; PDR, pulsed dose-rate; LDR, low dose-rate; 2D-RT, two-dimensional radiotherapy; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated RT; VMAT, volumetrically modulated arc therapy; SBRT, stereotactic body radiotherapy; PBT, proton-beam therapy; IMPT, intensity-modulated proton therapy

recurrent tumor, from 0% to 39% (Table 2). These mainly consisted of mucositis, hemorrhage, dermatitis, and dysphagia. Acute side effects of grades 4 and 5 after either IMRT or SBRT were encountered in 5% and 0.5% of all patients, respectively. In retrospective studies of IMRT, grade 3 late morbidity was either not reported at all or reported in up to 74% of all cases (20). This very wide range is explained by the inhomogeneity of the patient cohorts. Likewise, severe or life-threatening late morbidity of either grade 3 or grade 4 was reported either not at all or in up to 24% of cases after IMRT, in 61% after IMRT / 3D-CRT, and in 0–46% after particle therapy (8, 21). The main types of late complication were hemorrhage, dysphagia, soft-tissue fibrosis, and osteoradionecrosis (ORN). Fatal complications of therapy (grade 5) were mainly due to arterial hemorrhage and the carotid blowout syndrome (CBO), which arose in 0–10% of the treated patients (3, 8, 11, 15, 20). There was also a single fatal hemorrhage (1.6%) in the prospective Phase II study of CyberKnife-SBRT (3). In five of the eight studies in which fatalities were recorded, SBRT was used for repeat radiotherapy (3, 8, 9, 11, 12, 15, 16, 20). In a single IMRT study that included only 38 patients, in which hyperfractionated radiotherapy with two single doses of 1.2 Gy per day was given up to a median overall dose of 64.8 Gy, 8% of the patients died of epistaxis (20). A detailed overview of

survival and toxicity in the studies of repeat radiotherapy for head and neck tumors is provided in Table 2. In 11 studies, 24–100% were treated with chemotherapy or cetuximab immunotherapy in addition to radiotherapy. A systematic analysis of the efficacy of the individual substances was not possible. Repeat radiotherapy was given in combination with systemic treatment whenever this was clinically feasible, with the aim of reinforcing the local effect of radiotherapy while improving systemic control (22).

Prostate cancer

The median age at the time of diagnosis of the recurrence or of repeat radiotherapy was 68.8 to 71.6 years, while the median follow-up ranged from 11.7 to 24 months (23, 24). 74% of the patients had received high-dose definitive radiotherapy with 3D-CRT or IMRT as their primary treatment. In 23% of the patients, the prostate gland was resected first (and the seminal vesicle and lymph nodes in addition, in some cases), followed by adjuvant radiotherapy of the prostatic bed, or by rescue (salvage) radiotherapy in the setting of a biochemical recurrence. 3% of the patients were primarily treated with LDR brachytherapy, combined telebrachytherapy, or high-dose stereotaxy. The suspicion of recurrence (PSA recurrence, according to the definition of the American Society for Radiation Oncology

TABLE 2

Studies on head and neck tumors

First author / study	N	Re-RT technique ± systemic treatment	Median re-RT dose	Median follow-up (months)	Overall survival	Toxicity, ≥ grade 3 (CTCAE)	Predictors of better outcomes
Prospective							
Lartigau (3)	60	CK-SBRT with cetuximab	36 Gy, 6 Fx of 6 Gy each	11.4	1 year: 47.5% Median: 11.8 months	Cutaneous: 68% Grade 5: 1.6% bleeding Grade 3: 8% mucositis, dysphagia, induration, skin fibrosis	–
Yamazaki (8)	25/31	CK-SBRT No Cht	44 Gy, 5 Fx Dose escalation: total dose: 25, 32, 36, 40, 44 Gy	–	Median: 6 months	No DLT	–
Retrospective							
Vargo (9)	1186	IMRT ± Cht	>60 Gy	39	5 years: 19.4% 22.7% with Cht		OS: age <65 years Charlson Comorbidity Index <6, early stage on diagnosis, >1 year without recurrence, re-RCT better than re-RT alone
Yamazaki (12)	42	IMRT 64% SBRT 29%, 3D-CRT 3% with Cht	51 Gy 40–60 Gy (1.1–1.4 Gy 2 Fx/d)	36	3 years: 49% IMRT 57% other 37% n. s.	No acute grade 3 Late grade 3: 39% with IMRT, 31% with SBRT (not significantly different) No late grade 4	
Davis (10)	38	IMRT 92.1% ICT	64.8 Gy (1.2 Gy 2 Fx/d), 60 Gy or 50 Gy	47.8	3 years: 47.2%	Late grade 3: 73.7% Grade 5: 8% fatal epistaxis	OS and PFS: tumor coverage with the dose (GTV D95, median dose), patient age
Shikama (11)	27	IMRT 55% 3D-CRT 45% 35.5% simultaneous Cht, 6.5% ICT, 13% other	60 Gy	20.6	3 years: 48.5% Median: 24.8 mo	Acute grade 3: 29% Late grade 3 and 4: 61% No ORN and no CBO	
Rwigema (14)	176	IMRT CK-SBRT Particles	60 Gy, 20 Fx 32 Gy, 5 Fx 57.6 Gy (RBE) 16 Fx		1 year: Overall 56.3% Photons 54.1% Particles 67.9% 2 years: Overall 38.9% IMRT 51% CK 55%; n. s.	≥ grade 3: 27% 24% with photons, 46% particles – 9.7% of the patients receiving particle therapy had grade 5 toxicity	OS: NPC More grade ≥ 3 toxicity in younger patients with large PTV
Cvek (13)	414	IMRT 52% SBRT 48% ± Cht	60 Gy 5 Gy, 1–5 Fx up to 40 Gy	28 24 n. s.	2 years: IMRT 35.4% SBRT 16.3% p < 0.001 Median: IMRT 13.3 months SBRT 7.8 months	Acute ≥ grade 4: IMRT 5.1 vs. SBRT 0.5% Same late toxicity	OS: in RPA class II (n = 353) GTV >25 mL, IMRT better than SBRT Modern re-RT has low toxicity
Chang (22)	34	Protons, weekly Cht	n. a.	25	1 year: 62% 2 years: 42%	No patients with grade 5	
Kodani (16)	69	CT-SBRT Linac-SBRT 47.8% cetuximab	40.9 Gy	9.7	1 year: 30.6% 2 years: 13.3% Median: 12.6 months	Grade 1–2: 88.7%	
Yazici (15)	28	SBRT 3D-CRT	SBRT 30 Gy, 1–7 Fx 3DCRT 45 Gy, 10–30 Fx	7.3	2 years: 21.7%	Grade 2–3: 7.1% Grade 5: 10.7%	
Heron (18)	381	CK-SBRT	30 Gy, 5 Gy		1 year: 37.5%	CBO 8.4%	
Hayashi (17)	40	SBRT 24% Cht	48 Gy, 16 Fx, 2 Fx/d	n. a.	1 year: 33% 2 year: 29%	Grade 3 acute 37% mucositis, ORN 10% no CBO no late Grade 3–4	OS and LC: good general condition, small GTV

First author / study	N	Re-RT technique ± systemic treatment	Median re-RT dose	Median follow-up (months)	Overall survival	Toxicity, ≥ grade 3 (CTCAE)	Predictors of better outcomes
Karam (19)	62	CK-SBRT 33 % cetuximab	35 Gy	12.3	1 year: 61.9% 2 years: 23.4% median: 16.2 mo	Well tolerated No patients with grades 4 or 5	LRC: with >50 Gy in 5 Fx & GTV <25 mL SBRT is feasible and safely performable with minimal toxicity
Chan (20)	75	CK-SBRT no Cht	DFS I: 30 Gy, 3–5 Fx DFS II: 30 Gy, 4–6 Fx CBO: 36.5 Gy No CBO: 34.7 Gy	I: 11 II: 23	1 year: I: 42% II: 84% 2 years: I: 23% II: 38% Median: 14 months I: 11 months II: 23 months	CBO: n = 11, I: 1 of 7 (16%) II: Grade 5: 8%, 2/4 (50%) alive CBO 14.7% > Grade 2: 16% dysphagia	
Kakria (21)	21	CK-SBRT No Cht	30 Gy, 5 Fx every day	–	1 year: 71% 2 years: 58.3% Median: 62 months	Late: 28.6% Grade 5: 2/6 (10%) massive hemorrhages 5 and 28 months after SBRT	OS: GTV <15 mL

CBO, carotid blowout; Cht, chemotherapy; CK, CyberKnife; 3D-CRT, 3D conformal radiotherapy; CTCAE, Common Terminology Criteria for Adverse Events; DFS, dose fractionation scheme; DLT, dose-limiting toxicity; Fx, fraction; GTV, gross tumor volume; ICT, induction chemotherapy; IMRT, intensity-modulated radiotherapy; LC, local control; LRC, locoregional control; NPC, nasopharyngeal carcinoma; n. a., not available; n. s., not significant; ORN, osteoradionecrosis; OS, overall survival; PFS, progression-free survival; PTV, planned target volume; RBE, relative biological effectiveness; Re-RT, repeat radiotherapy; Re-RCT, repeat radiochemotherapy; RPA, recursive partitioning analysis; SBRT, stereotactic body radiotherapy

[ASRO]: nadir + 2 ng/mL. [PSA, prostate specific antigen]), was confirmed by biopsy in some of the studies and, in others, by pelvic MRI or whole-body PET-CT. In most of the studies on recurrent disease, patients with metastases were excluded.

Nonetheless, Jereczek-Fossa et al. deliberately included patients with lymphatic and distant oligometastatic disease (25). In six studies, repeat radiotherapy was performed with CyberKnife-SBRT. Only one study involved treatment with VERO, a linear accelerator with micro multi-leaf collimators (MLC) that has stereotactic capability. In the series of Fuller et al., the median prostatic volume before repeat radiotherapy was 21.7 mL (23). Highly variable dose schedules were applied, depending on the initial treatment volume and the overall dose of the primary treatment. Mbeutcha et al. administered treatment on 5 consecutive days in a single week (26). The scheme most commonly applied to treat recurrences involved 5 single doses of 6–7 Gy each, given at 48-hour intervals. In most cases, marker-based, image-guided radiotherapy (“tracking”) was performed after the implantation of 3–4 gold fiducial markers into the prostate or the macroscopic tumor recurrence. Often, in patients with intraprostatic recurrences, the entire prostate gland was re-irradiated. Mbeutcha et al. were the only group who treated only the recurrent lesion within the prostatic gland (26).

Hormonal treatment that was already being given was generally continued. The median PSA value at the time of repeat radiotherapy was 3.1–10 ng/mL (23, 27). The median interval from repeat radiotherapy to the PSA nadir was 6–7.5 months; the absolute value of the nadir was 0.38–1.0 ng/mL (26, 28).

Different primary endpoints were used in the survival analyses. In two articles, freedom from recurrence at 1 year, as judged by biochemical follow-up (PSA value), was reported in 80 and 83.3% of patients (27, 28). In two other articles, the rates of BNED (biologically no evidence of disease) at the time of follow-up were given as 41–82% (Table 3) (23, 29). After repeat SBRT, the median time to biochemical recurrence was 10–16.5 months (25, 28). No reliable differentiation of local, regional, and distant recurrences or metastases was possible, because not all of the authors carried out new imaging studies at the time of treatment failure. Zerini et al., in the 32 patients whom they evaluated, observed 4 local recurrences, 1 lymphonodular recurrence, and 7 cases of distant metastatic disease (29). The risk factors for biochemical failure (rising PSA) after repeat SBRT that were identified by Loi et al. were: advanced T stage (>T3a), high risk as defined by the National Comprehensive Cancer Network (NCCN), and continued antihormonal therapy (27).

Overview and limitations

Advances in imaging techniques and high-precision radiotherapy now make it possible for patients with local recurrences or second tumors in the head and neck region to undergo repeat percutaneous radiotherapy with modern techniques, with curative intent. Because of the lack of data from controlled studies, patients must be selected by interdisciplinary tumor boards in consideration of all of the relevant potential benefits and risks.

In carefully selected patients, long-term progression-free survival and a fairly long new

TABLE 3

Relevant studies of patients with locoregional recurrences after definitive radiotherapy for prostate cancer

First author	Year	Journal	Data acquisition	Number of patients	Technique	Median follow-up duration	Freedom from biochemical recurrence at 1 year (BRFS)	Biologically no evidence of disease at the time of assessment (BNED)
Jerezek-Fossa (25)	2012	Int J Radiat Oncol Biol Phys	Retrospective	34	CyberKnife	16.9 months		56%
Zerini (29)	2015	British Journal of Radiology	Retrospective	32	CyberKnife, Vero, μ MLC-Linac	21.3 months		40.6%
Fuller (23)	2015	Practical Radiation Oncology	Prospective	29	CyberKnife	24 months		82%
Janoray (24)	2016	Cancer Radiothérapie	Retrospective	21	CyberKnife	11.7 months	83.3%	
Mbeutcha (26)	2017	Radiation Oncology	Retrospective	18	CyberKnife	14.5 months		55.6%
Leroy (30)	2017	Radiation Oncology	Retrospective	23	CyberKnife	22 months	(54% at 2 years)	/
Loi (27)	2018	Clinical Oncology	Retrospective	50	CyberKnife	21.3 months		54%
Miszczuk (28)	2018	Technol Cnccr Res Treat	Retrospective	38	CyberKnife	14.4 months	/	/

TABLE 4

Acute and late genito-urinary (GU) and gastrointestinal (GI) adverse effects, to the extent that these were reported and their timing was specified (number of patients affected, or, in the study of Miszczuk et al., percentage of patients affected)

First author / study	Toxicity criteria	GU acute Grade 1	GU acute Grade 2	GU acute Grade 3	GU late Grade 1	GU late Grade 2	GU late Grade 3	GU acute Grade 1	GU acute Grade 2	GU acute Grade 3	GU late Grade 1	GU late Grade 2	GU late Grade 3
Jerezek-Fossa (25)	RT OG/ EORTC	3 of 19	2 of 19	1 of 19	1 of 19	1 of 19	1 of 19	1 of 19	0	0	0	1 of 19	0
Zerini (29)	RT OG/ EORTC	6	2	0	7	1	0	3	2	0	5	0	0
Fuller (23)	Unknown	0	0	1	0	3	1	0	0	0	0	0	0
Janoray (24)	Unknown	0	0	0	1	0	0	2	0	0	0	0	0
Mbeutcha (26)	CTCAE 4	5	2	0	4	1	0	5	1	2	0	1	0
Leroy (30)	CTCAE 4	/	/	/	/	/	/	/	/	/	/	/	/
Loi (27)	Unknown	9	1	1	9	3	1	4	0	0	1	2	0
Miszczuk (28)	RT OG/ EORTC	18.50%	7.40%	3.70%	22.20%	16.70%	12.50%	7.40%	/	/	11.10%	/	/

RT OG, Radiation Therapy Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; CTCAE, Common Terminology Criteria for Adverse Events

tumor-free phase can be achieved. Especially in the head and neck area, however, the potentially severe acute and late sequelae of repeat radiotherapy must be taken into account in the decision of whether to treat the patient in this way. All such decisions should be made by an interdisciplinary tumor board. The comprehensive provision of all relevant information to the patient is a prerequisite for joint decision-making.

The treatment of head and neck recurrences with repeat radiotherapy employing modern techniques, i.e., IMRT, SBRT, or particle therapy, yields 1- and 2-year overall survival rates of 31–84% and 13–58%, respectively. 3-year survival in the IMRT studies that followed up patients for this length of time was 47–57%, and 5-year survival in one study was 19% without chemotherapy and 23% with chemotherapy (22). Predictors of longer survival were young age (≤ 65 years), good general condition, low comorbidity, and an interval of more than one year from the primary treatment to the recurrence (13, 14, 20, 22). In particular, when SBRT is used, a macroscopic recurrent tumor volume of less than 150 mL seems to predict longer survival and lesser toxicity (9, 14, 16). In any case, steps must be taken to minimize the toxicity of repeat radiotherapy to the surrounding tissues, in view of the high rates of serious and lethal side effects (74% and 11%, respectively). This can be accomplished without compromising efficacy by hyperfractionating IMRT into two doses of 1.1–1.4 Gy (each) per day, up to a total dose of 60–66 Gy. If normofractionation is used, the single doses should not exceed 1.8–2.0 Gy, and the overall dose should not exceed 50–66 Gy.

Strongly hypofractionated SBRT should be restricted to smaller target volumes (<25 mL) and non-critical soft tissue regions to avoid late sequelae including radiogenic skin ulceration, osteoradionecrosis, and, above all, blowout hemorrhage from arterial vessels. On the basis of a prospective, phase I dose-escalation trial with a median survival time of only 6 months, it appears that SBRT at a cumulative dose of 44 Gy, delivered in 5 fractions over 2 weeks, must be considered the absolute dose limit in this situation (18). The risk seems to be low if one limits the overall dose to 36 Gy and delivers it in six fractions of 6 Gy each every other day: this is associated with a 1-year overall survival of 47% (3).

No data have been published to date on potentially promising combinations of repeat radiotherapy with new drugs, such as checkpoint inhibitors. As in the primary situation, it seems that, in the head and neck region, repeat radiotherapy combined with systemic treatment yields a survival advantage. The combination should be with cisplatin or cetuximab (22). Even though high-grade comparative evidence is still lacking, repeat radiotherapy for head and neck tumors with curative intent can be considered an established form of treatment, albeit with a few caveats.

Key messages

- Carefully selected patients with inoperable local or locoregional recurrences of head and neck tumors that have already been treated with (even high-dose) radiotherapy can undergo retreatment with percutaneous high-precision radiotherapy with curative intent.
- Repeat radiotherapy for prostate cancer is experimental at present, but very small clinical series have yielded encouraging results.
- The necessary IMRT and stereotactic techniques are now available all over Germany.
- Repeat radiotherapy in the head and neck region causes serious adverse effects that are sometimes fatal. Repeat radiotherapy for prostate cancer has been found to cause less severe side effects over relatively short follow-up periods of up to 24 months. Its long-term side effects cannot yet be reliably assessed.
- Repeat radiotherapy should only be performed if recommended by an interdisciplinary tumor board. Comprehensive patient information is a further prerequisite.

In contrast, repeat radiotherapy for prostate cancer must still be considered experimental. The evidence available to date is derived from retrospective analyses of small, inhomogeneous patient cohorts without predefined inclusion or exclusion criteria.

The patient cohorts in most of the available studies on repeat radiation for prostate cancer were small and inhomogeneous, markedly limiting the informative value of these studies (31). Patients with pre-existing symptoms were excluded from the treatment. Even if the available data on side effects seem surprisingly favorable (*Table 4*), it must be pointed out once again that retrospective analysis is subject to the risk of under-reporting, and that the patient numbers were small and the follow-up intervals short (24 months at most). Thus, no reliable conclusion can be drawn about long-term side effects.

The results are still less clear, and cogent analysis still more difficult, because the patients were originally irradiated in different ways (teletherapy, brachytherapy, or combined tele-brachytherapy), and because they were given different types of systemic therapy, with or without androgen blockade, at the time of their repeat radiotherapy.

The rate of tumor control, i.e., lack of a PSA recurrence, at one year was approximately 20% in each of the studies, although 40–82% of the PCa patients were in complete PSA remission. The available studies yield no clear explanation why the tumor control rates are markedly worse than those for primary SBRT, despite the use of similar dose and volume strategies (32). Perhaps, in some patients, microscopic systemic dissemination may have been masked by continued anti-hormonal treatment, or else the choline PET-CT before repeat radiotherapy may not have been sensitive enough to

detect systemic metastatic disease. More advanced modalities of PET-CT and PET-MRI (3-tesla MRI, ⁶⁸Gallium- or ¹⁸F-PSMA PET-CT or -MRI) now enable more accurate detection of solitary local recurrences that are confined to the prostate, while simultaneously ruling out systemic metastases (33–35). If the apparent, surprisingly low rate of adverse effects can be confirmed in controlled long-term analyses, dose escalation in repeat radiotherapy for prostate cancer will become a valid consideration.

Conflict of interest statement

The authors state that no conflict of interest exists.

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► Supplementary material

eFigure, eBox:
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Supplementary material to:

Repeat Radiation for Local Recurrence of Head and Neck Tumors and in Prostate Cancer

by Arne Grün, Thomas Kuhnt, Thorsten Schlomm, Heidi Olze, Volker Budach, and Carmen Stromberger

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eBOX

Search strategy

pubmed – (“re-irradiation”[MeSH Terms] OR “re-irradiation” [All Fields] OR (“re” [All Fields] AND “irradiation” [All Fields]) OR “re irradiation” [All Fields]) AND (“Head Neck” [Journal] OR (“head” [All Fields] AND “and” [All Fields] AND “neck” [All Fields]) OR “head and neck” [All Fields])) AND (hasabstract [text] AND (“1998/05/01” [PDAT]: “2018/04/13” [PDAT]) AND (English [lang] OR German[lang])).

pubmed – (“re-irradiation” [MeSH Terms] OR “re-irradiation” [All Fields] OR (“re” [All Fields] AND “irradiation” [All Fields]) OR “re irradiation” [All Fields]) AND “prostate cancer” [All Fields])) AND (hasabstract [text] AND (“1998/10/01” [PDAT]: “2018/10/01” [PDAT]) AND (English [lang] OR German [lang])).

eFIGURE

Head and neck tumors: The search strategy yielded 197 studies. 16 studies, which included a total of 2678 patients, remained after the inclusion and exclusion criteria were applied. Among these patients, 85 were treated in two prospective trials and 2593 were treated in 14 retrospective studies. Most of the studies included recurrent or second tumors in multiple tumor sites (nasopharynx, oropharynx, hypopharynx, oral cavity, larynx, paranasal sinuses, cancer of unknown primary) as well as regional recurrences in the cervical lymph nodes.

Prostate cancer: The search yielded eight studies with a total of 245 patients satisfying the above inclusion criteria. All studies but one were retrospective, single-center analyses (25).

HNT, head and neck tumors; PCa, prostate cancer; re-RT, repeat radiotherapy; EBRT, external beam radiotherapy; BT, brachytherapy