Re-Treatment After Full-Course Radiotherapy: Is It a Viable Option?

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Re-irradiation of previously treated areas may become necessary for recurrent cancer, new primary tumours (common in head and neck cancer patients), or nodal and metastatic disease. Factors that should be taken into account in the decision to re-treat include: 1) previously treated volume (how much overlap is there with new treatment fields) and dose fractionation schedule; 2) which critical tissues or organs are at risk; 3) how much time has elapsed since first treatment; 4) whether there are any practical alternatives to re-irradiation? Rapidly proliferating tissues generally recover well from the initial radiotherapy and will tolerate re-irradiation to almost full doses. Some slowly proliferating tissues are also capable of partial proliferative and functional recovery, although this takes several months and some residual damage remains. Preclinical data demonstrate that re-irradiation with reduced doses is possible in lung and spinal cord after intervals of 3–6 months. Other slowly proliferating organs, e.g. the kidneys, do not appear to be capable of recovery, even after low, subtolerance doses. The largest clinical experience of re-irradiation is for head and neck cancers. A review of this literature reveals that the most frequent normal tissue complication seen is trismus (lockjaw), which occurs in 16 to 30% of re-treated cases, with lower incidences of soft tissue or bone necrosis and fibrosis. Myelitis is rarely reported, even in the re-treatment situation. In general the highest incidence of local control for the lowest incidence of serious complications is achieved for combinations of external beam and brachytherapy, and for small, well-differentiated, new primary tumours rather than recurrent disease. Re-treatment with total doses < 55 Gy gives very poor local control rates. Re-treatment schedules with curative intent require a high re-treatment dose, which is accompanied by an increased risk of normal tissue damage. To minimize serious complications, re-irradiation schedules require the best possible treatment planning (conformal therapy where possible). Hyperfractionation or a combination of external beam and brachytherapy could also be beneficial.

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Curative radiotherapy usually involves treating the normal tissue immediately surrounding the tumour to the limit of tolerance. A much larger volume will receive a lower dose because of shielding techniques or non-overlapping fields. Unfortunately, a significant number of patients subsequently relapse or develop nodal disease or new tumours within the previously irradiated region. Second tumours are particularly common among head and neck cancer patients where it has been estimated that up to 30% of patients will develop new primary tumours within 10 years (1, 2). Decisions regarding re-treatment options for these patients are complex and depend critically on the degree of overlap of treatment fields, the extent to which normal tissues in the re-treatment field have regenerated after the first treatment (proliferative recovery) and on the extent of residual or latent damage present after regeneration. Other important factors are whether there are distant metastases, or only local disease and whether the patient is to be re-treated with curative intent or palliatively. The risk of serious normal tissue damage after re-irradiation is obviously much greater than after the initial treatment, particularly for high total doses aimed at cure. These risks have to be weighed against the morbidity that would result from no re-treatment or from any alternative means of treatment. Curative surgery in a previously heavily irradiated area is usually not feasible. For some small localized tumours (either recurrent or new primary) in sites such as the oral cavity photodynamic therapy may, however, offer an alternative re-treatment possibility with less risk of severe morbidity than re-irradiation or surgical resection (3).

This paper gives a brief review of experimental data on re-irradiation tolerance for various normal tissues (for more details see 4, 5). A summary of clinical data for re-irradiation in the head and neck region is also given. This site was chosen because there is a substantial body of clinical experience and literature that allows some general conclusions to be made. For other sites, the data tend to be anecdotal or from retrospective analyses of studies with small numbers of patients. In order to compare data on

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different normal tissues using various fractionation schedules, results of published studies have been expressed in terms of biologically effective dose (BED) using linear quadratic concepts (6, 7): $BED_t = nd\ (1 + d/\alpha/\beta)$, where n = number of fractions, d = dose/fraction.

The BEDs for a defined level of tissue damage (BED_t) were calculated and both initial and retreatment doses are expressed as a percentage of BED_t.

PRECLINICAL DATA

Skin and other rapid turnover mucosal tissues

Published data for acute skin reactions (desquamation) in rodents demonstrate a very good recovery from the initial damage. All studies show that the skin can be re-irradiated with 90 to 100% of a full tolerance dose (BED_t) within 2 months after the initial (full tolerance) dose (e.g. 8–11). The extent and time-course of recovery is consistent with the known time-scale for proliferative response of basal layer epithelial cells after irradiation (12). Some experiments have, however, demonstrated that repeated large single doses (at 6- or 9-week intervals) progressively reduced re-treatment tolerance for mouse tail necrosis, consistent with some reduction in stem cell density of the epidermis (13, 14).

There are less data available for late skin damage after re-irradiation but some rodent results suggest a poorer re-treatment tolerance than for acute reactions (8). Re-irradiation studies on pig dermal tissue, however, demonstrated good re-treatment tolerance ($> 90\%$ BED_t) for a late dermal necrosis end point (15). The initial radiation doses used in the pig dermal necrosis studies did not cause acute epithelial desquamation, in contrast to the late skin deformity studies in rodents. This may imply that re-treatment tolerance for late skin deformity is only compromised where these reactions are consequential to a severe acute reaction rather than representing a true late response with separate aetiology (15, 16).

Re-irradiation tolerance for acute damage in other rapidly dividing mucosal tissues, such as intestine, are in general agreement with results for skin (17).

Bladder

Studies in mice have demonstrated that re-irradiation tolerance for late bladder damage (increased urination frequency and reduced bladder compliance) is independent of the interval between treatments (2 weeks to 9 months). The latency before expression of functional damage was, however, much shorter for re-irradiation intervals of 9 months (18).

Normal untreated bladder epithelium has a very slow cell turnover time (> 200 days) but it is capable of rapid proliferation in response to injury (19). Despite evidence for extensive epithelial proliferation at 6 to 9 months after bladder irradiation, no recovery from late functional bladder damage or increased re-treatment tolerance has been seen over this period (18, 20, 21). Compensatory proliferation in the bladder seems to precipitate expression of latent damage rather than reducing the level of damage. This might imply that epithelial damage, although involved in the initial urination frequency response, is not the major determinant of persistent damage after bladder irradiation.

Lung

Experimental studies in mice demonstrate very good recovery and re-irradiation tolerance in the lung for the end point of lethal pneumonitis (22, 23). Mice given initial doses equivalent to 30 to 50% of BED_t could be re-irradiated with doses equivalent to 100% BED_t at 4 to 8 weeks. Recovery was slower after higher initial doses and after initial doses in excess of 70% BED_t some residual damage remained at 6 months. This recovery and tolerance of previously irradiated lung to re-irradiation probably only applies to the acute pneumonitis phase of damage and not to the late phase of damage associated with increased collagen deposition and fibrosis (24). Indeed, many of the mice that survived the pneumonitis phase of damage after re-irradiation in the study by Terry et al. subsequently died of lung fibrosis (23).

The time-course for recovery and re-irradiation tolerance in the mouse lung (pneumonitis phase) coincides with the increased proliferation which occurs in type II pneumocytes at 2 to 8 weeks after irradiation (25, 26). Re-treatment after high doses leads to an earlier onset of pneumonitis. This is consistent with the target cell population (type II pneumocytes) being nearer to a critical level of cell depletion and requiring longer for repopulation.

Spinal cord

There is considerable experimental evidence demonstrating that significant recovery and increased re-irradiation tolerance does occur in the spinal cord within 6 months of irradiation, despite its slow proliferation rate. Analysis of data from studies on rat or guinea pig spinal cord demonstrates that re-irradiation tolerance is inversely related to the size of the initial dose and it increases over the 2 to 26-week period after irradiation. However, some residual damage remains from the first irradiation and the maximum total dose (i.e. initial plus re-treatment dose) that could be given in the rat was about 140% of the BED_t for 50% paralysis (27–33).

The findings from rodent studies are corroborated by results from a study of re-irradiation tolerance of monkey spinal cord (34). At 2 years after an initial treatment of 20×2.2 Gy, equivalent to about 60% of the BED_t for a 50% incidence of paralysis (76 Gy in 2.2 Gy fractions), these monkeys were re-treated with a further 18 to 30 fractions of 2.2 Gy. Only 1/21 and 1/6 monkeys developed paralysis in the top two dose groups (cumulative initial plus re-treatment doses of 101 and 110 Gy or 133 to 148%

BED_t, respectively). Animals re-irradiated with lower doses did not develop paralysis. More recent unpublished data (K. Ang, pers. comm.) show a similar response for monkeys retreated after a 1-year interval rather than 2 years. These data indicate that total cumulative doses (initial plus re-treatment) of about 140% BED_t can be given for re-irradiation of monkey cord at intervals ≥ 1 year.

It is unclear to what extent the increase in total tolerance observed for spinal cord re-irradiation is related to proliferation in the putative target cells (oligodendrocytes and endothelial cells). Mature glial cells and endothelial cells have very slow turnover times but can be stimulated into increased proliferative activity by irradiation. The main proliferative burst for glial cells occurs at about 20 weeks (35, 36), which is too late to explain increasing re-irradiation tolerance from 8 weeks after initial treatment. An early, transient increase in glial cell proliferation does occur at 3 weeks (36). This may be related to the early regenerative phase that has been identified in glial progenitor cells after irradiation of the rat optic nerve (37). However, recent data suggest that it is vascular mediated (endothelial cells) rather than parenchymal (glial cells) damage which is responsible for white matter necrosis after irradiation (Van der Kogel unpublished 1998). The precise influence of stimulated proliferation of glial cells for regeneration of spinal cord after irradiation therefore remains unclear.

Kidney

Progressive, dose-dependent development of renal radiation damage, without apparent recovery, has been clearly demonstrated after single dose or fractionated irradiation of rodent kidneys (38–40). This is entirely consistent with clinical observations of slowly progressive renal damage that can occur over periods of 5 to 10 years after irradiation (41, 42). Based on the known profiles for development of renal damage, it is obvious that re-irradiation after large initial doses is unlikely to be feasible. It is, however, less obvious what the situation would be after low, subtolerance renal irradiation.

Owing to the slowly progressive nature of renal damage, the absence of measurable dysfunction at the time of re-irradiation cannot be interpreted as a sign that there is no latent or residual injury. Re-irradiation studies in mice demonstrate that either single dose or fractionated doses which are below the threshold required to produce measurable functional damage significantly reduce the tolerance to re-treatment at 6 months (5, 38, 43, 44). Initial doses of $\geq 25\%$ BED_t lead to a marked loss of tolerance for re-irradiation at 6 months relative to 2 weeks. The total cumulative doses (initial plus re-treatment doses) which could be given in the 6-month re-treatment groups were, in some cases, as low as 50 to 60% of the total doses which could be given in a single treatment course (no re-treatment). This is consistent with there being continuous progression of occult renal damage in the interval between treatments with no recovery from the initial damage.

A single report of re-irradiation of the rat heart (45) indicates that the heart responds in a similar way to the kidney; i.e. decreasing re-irradiation tolerance with increasing time from the initial irradiation, indicative of progression of damage rather than recovery.

CLINICAL DATA

A number of factors should be borne in mind when attempting to draw conclusions from clinical re-irradiation data. The reports to date are all based on retrospective analyses of very heterogeneous populations of patients treated over long periods (more than 20 years in many cases). Radiotherapy techniques have evolved considerably over this time and for patients irradiated before about 1970 the dose distributions are not comparable with modern day radiotherapy. In addition, the complications reported in the published series were almost never scored according to standardized criteria and are therefore unlikely to be comparable between (or even within one) series. Most reports include patients re-treated with a wide range of doses (sometimes with palliative intent) and irradiation techniques.

Any assessment of the severity of normal tissue damage after re-irradiation must take into account the level of morbidity that would have occurred without re-treatment. Obviously, patients who require re-treatment for second or recurrent cancers represent a special 'high-risk' group and it is unlikely to be possible to achieve a cure without some normal tissue toxicity. The boundaries for 'acceptable damage' are therefore different for the re-treatment situation than for initial treatments.

Head and neck re-irradiation

The published literature for series of head and neck cancer patients where the major component of re-treatment was with external beam irradiation is summarized in Table 1. The study by Fu et al. (46) reports on a series of 42 patients re-treated between 1940 and 1974 for recurrent nasopharyngeal carcinoma in the primary site ($n = 36$) or neck nodes ($n = 6$). The majority received a combination of external beam radiotherapy and intracavitary radium or cobalt beads (three of these patients also received concurrent chemotherapy). Others were treated with intracavitary irradiation alone or in combination with electrodesiccation, or surgery. The actuarial 5-year survival rate, after first recurrence, for the whole group was 41% (this includes patients who were re-treated more than once) with a clear trend for worse survival in cases where the recurrence occurred within one year of initial treatment. Local soft tissue or bone necrosis developed in 9 patients (21%).

Skolyszewski et al. (47) report on a series of 20 head and neck cancer patients re-irradiated with cobalt-60 gamma rays between 1968 and 1974. The overall 3-year survival was 70% with 50% of patients disease free at this time. Four patients developed soft tissue necrosis, two with additional bone necrosis. There was a trend for better tumour control for recurrences occurring more than one year after initial treatment and for re-treatment doses of > 50 Gy, but the number of patients is small.

Yan et al. (48) report on large series of nasopharyngeal cancer patients (n = 219) re-irradiated between 1958 and 1976. Distant metastases had already developed in 57 of these patients at the time of re-treatment; the remaining 162 were re-treated with curative intent. Most of these patients were re-irradiated with cobalt-60 (± supplementary x-rays) but some were re-irradiated with 25–35 MeV electrons. The overall 5-year survival for the whole group was 18% but for patients with recurrences confined to the head and neck region the 5-year survival was 23% with 14% free of disease. Survival was better in patients who recurred > 3 years after initial treatment (38% vs. 21%), and for re-treatment doses > 50 Gy. The incidence of complications in the re-treated series (patients who survived for more than 5 years) was compared with a series of 210 patients who received only one course of radiotherapy over the same period. Radiation myelitis increased from 9 to 12% in the re-treated series. Bone and soft tissue necroses were not increased but subcutaneous fibrosis increased from 9 to 16% and trismus increased from 11 to 29% in the re-treated series.

The study by Langlois et al. (49) reports on 35 patients re-irradiated between 1973 and 1981 for relapse or a second tumour in the head and neck region. Re-irradiation was with cobalt-60 or electron beam therapy and surgery preceded irradiation in 12 cases. The actuarial survival rate was 19% at 2 years. Delayed necrosis and bleeding were seen in 13 patients, usually as a result of lysis of residual tumour. A multivariate analysis revealed that re-irradiation doses > 60 Gy were associated with better local control (55 vs. 8%). Intervals of > 1 year between first and second irradiation were also associated with longer survival. Failure to achieve local control at 3 months and re-irradiation doses < 60 Gy to large tumours treated palliatively were associated with increased complications.

Wang (50) reported on a series of 51 patients irradiated for recurrent nasopharyngeal cancer between 1950 and 1981. The early-stage tumours (T1/T2) were re-irradiated with a combination of 4 MV external beam radiotherapy (EBRT) and intracavitary irradiation (cesium-137). Patients with larger lesions received EBRT only. The actuarial 5-year survival for the patients treated with doses ≥ 60 Gy (n = 38, mostly T1/T2) was 45%, compared with no 5-year survivors in the group treated with < 60 Gy (more than half of these were T3/T4 tumours). Survival was also better for recurrences occurring more than 2 years after initial treatment (66% vs. 13% 5-year survival). There were only three moderate or serious complications (6%) noted in this series.

Table 1

Re-irradiation of head and neck: EBRT ± brachytherapy

Reference	Site/No. of patients		Re-treatment dose (Gy)	L.C.[1] (%)	Survival[1] (%)	Complications (%)
Fu et al. 1975 (46)	NP/	42	12-63 ± IC	26/3 yr	41*	21
Skolyszewski et al. 1980 (47)	All/	20	34 – 75	50	70/3 yr	20
Yan et al. 1983 (48)	NP/	219	< 50 – > 50	11	18	> 29[2]
Langlois et al. 1985 (49)	All/	35	30-79 Gy	24/2 yr	19/2 yr*	37
Wang 1987 (50)	NP/	51	< 50 – > 60 ± IC boost	NS	0 < 60 Gy 45 > 60 Gy	6
Wang & McIntyre 1993 (51)	L/	20	60 – 70	61*	93*	5
Emami et al. 1987(52)	All except NP/	52	< 50	11	17	28
		36	> 50	25		
Levendag et al. 1992(53)	All/	55	18 – 84 EB	29	20*	7
		18	35 – 95 (inc. IC)	50	20	17
Pryzant et al. 1992 (55)	NP/	53	28 – 99 (incl. IC)	35*	21*	17*
Stevens et al. 1994 (56)	All/	100	19 – 77 ± IC	32	17*,[3] 37*,[4]	9
Lee et al. 1997(57)	NP/	654	7.5 – 70 ± IC	23/5 yr* 32/5 yr	16/5 yr*	48*

Abbreviations: NP = nasopharynx; L = larynx; NS = not stated; EBRT = external beam radiotherapy; IC = intracavitary irradiation.
[1] Local control and survival rates are at 5 years unless specified otherwise.
* = Actuarial estimates.
[2] Complication rate for patients surviving = 5 yrs.
[3] Survival in patients with recurrent tumour.
[4] Survival in patients with new primary tumour.

A more recent publication from this group (51) reports on a series of 20 patients re-treated for recurrent laryngeal tumours (T1/T2) between 1958 and 1992. All patients received 60–70 Gy with cobalt-60 or 4 MV photons. The 5-year actuarial local control was 61% and the corresponding survival rate was 93%, including salvage laryngectomy for 5 patients. The only complication reported in this series was a prolonged wound healing time in one laryngectomy patient.

Emami et al. (52) report on a series of 99 patients treated for recurrent head and neck cancer between 1967 and 1985. All sites except the nasopharynx were included in the study. Eleven patients were re-treated with surgery alone but none survived 5 years. Of the remaining patients, 48 received surgery plus irradiation and 40 received irradiation only. Brachytherapy was occasionally used as a supplement to EBRT. Long-term survival was achieved in 17% of the group that received irradiation. Tumour control was better for the combination of radiotherapy and surgery than for radiotherapy alone (21% vs. 13%), for irradiation doses > 50 Gy (25% vs. 11%) and for tumours recurring at the primary site rather than in neck nodules (21% vs. 10%). Moderate or severe complications (fibrosis, trismus, fistula, stenosis and necrosis) were seen in 28% of the re-irradiated patients.

The study by Levendag et al. (53) reports on a total of 73 recurrent or new primary tumours in the head and neck region. Patients re-treated between 1970 and 1980 ($n = 55$) were given EBRT (4 MV photons) to a mean total dose of 46 Gy, some with additional chemotherapy, surgery, or both. Almost the entire patient group had recurrent tumour in the original site (54). From 1985 to 1988, 18 head and neck cancer patients were re-irradiated for recurrence ($n = 8$) or new primaries with brachytherapy alone (composite volume implants through afterloading catheters) or in combination with EBRT. The mean total dose to this group of patients was 62 Gy. Fourteen of this group received additional surgery, chemotherapy or hyperthermia. Local control was achieved in 29% of the patients retreated with EBRT alone and in 50% of those re-treated with brachytherapy $\pm$ EBRT. There was, however, no difference in 5-year actuarial survival rates for the two groups (20% in both cases). An interval of more than 2 years between initial and re-treatment was associated with better prognosis; 5-year survival of 40% compared with 10% for relapses within one year. The late complication rate for the whole group was 36%, with no obvious correlation between re-treatment dose and complication risk.

Pryzant et al. (55) reports on a series of 53 patients re-irradiated for recurrent or persistent nasopharyngeal carcinoma from 1954 to 1989. Before 1977 treatment was with megavoltage radiotherapy to a median dose of 57 Gy. This series was also separately reported (56). From 1977, 20–30 Gy EBRT was combined with 40–50 intracavitary cesium-137 in selected cases ($n = 9$). None of the patients had distant metastases at the time of re-treatment but half had local spread beyond the nasopharynx. Ten patients received additional chemotherapy and 8 had neck dissections. Overall 5-year actuarial local control and survival rates were 35% and 21%, respectively. Local control was higher in the small group treated from 1977 with a combination of EBRT and intracavitary cesium-137 (7 of the 9 patients had local control). The interval between initial and re-treatment did not correlate with survival time from re-treatment. Re-irradiation doses > 55 Gy were associated with better survival (39% vs. 8%) but not with better local control. The actuarial incidence of severe complications at 5 years was 17% for the whole group and this was related to the cumulative dose of EBRT; 5-year severe complication rates of 4% versus 39% for patients who received total cumulative doses (initial plus re-treatment) EBRT < 100 Gy or > 100 Gy. There were no severe complications in patients re-treated with a combination of EBRT and intracavitary cesium-137.

Stevens et al. (57) report on a total of 100 patients retreated between 1964 and 1991 for recurrent ($n = 85$) or new primary tumours ($n = 15$) of the head and neck. The patients in this series were selected on the basis of having only minimal radiation damage from the first course. Most patients were re-irradiated with EBRT only but additional interstitial or intracavity irradiation was given in 14 cases and 4 were treated with brachytherapy only. The actuarial 5-year survival was 37% for new primary cancers and 17% for recurrent disease. Local control was achieved in 60% and 27%, respectively. Re-irradiation doses of > 50 Gy to recurrent tumours were associated with better local control; 9/9 of the new primary tumours treated with ≥ 60 Gy were controlled versus 0/6 for doses < 60 Gy. There was a trend toward better local control for intervals of > 1 year before re-treatment. Severe complications occurred in 9 patients, including 4 fatal haemorrhages, with no obvious relationship between complication rate and total or re-treatment dose.

By far the largest group of re-irradiated head and neck cancer patients is reported by Lee et al. (58). In this series a total of 654 patients with recurrent undifferentiated or poorly differentiated nasopharyngeal carcinoma was re-irradiated from 1976 to 1992; 48 of these patients received a third course of radiotherapy for further recurrence. None of the patients had distant metastases at the time of re-treatment but 65% had disease extending outside the nasopharynx. Most were irradiated with EBRT only, to a median total dose of 46 Gy (range 7.5–70 Gy). The rest received median doses of 40 Gy by brachytherapy alone, or combined with 20 Gy EBRT. The 5-year actuarial local control and survival rates were 23% and 16%, respectively. Late complications developed in 26% of patients (including 2% fatal) with a 5-year actuarial risk of 48%. The most frequent complication was trismus (16%), followed by deafness (7%) but the most serious was temporal lobe

Table 2

Re-irradiation of head and neck cancers: ^{192}I brachytherapy alone

Author/Institute	Site/no. of patients	Re-treatment dose (Gy)	L.C. (%)	Survival[1] (%)	Complications (%)
Syed et al. 1978 (60)	All/64	45–60	48	44/2 yr	30
Mazeron et al. 1987 (59)	OP/70	50–71	69*	14	27
Langlois et al. 1988 (61)	T, OP/123	31–84	59*	24*	23
Fontanesi et al. (62)	All/23	39/60	91	26/1–3 yr	48
Pommier et al. 1997 (63)	P/14	39–60	64	21*	0

Abbreviations: T = tongue; OP = oropharynx; P = pharyngeal wall; NS = not stated.* = Actuarial estimate.[1] Five-year survival unless stated otherwise.

necrosis (3%). Only 1% of patients developed either soft tissue or bone necrosis. Extent of local recurrence was the most important prognostic factor, with 35% local control for stage T1 versus 11% for T3 recurrences. For the T1 recurrences, re-treatment with a combination of EBRT and brachytherapy gave the best local control, but this was not significant in a multivariate analysis of the whole group. Initial and re-treatment doses were recalculated in terms of Biological Effective Dose (BED) using α/β ratios of 10 Gy for tumour and 2 or 3 Gy for late damage. With this approach the initial treatment dose had no significant influence on tumour control ($p = 0.4$) but the re-treatment BED was significantly associated with local control probability ($p = 0.001$). The 5-year local control for T1/T2 recurrences treated with > 70 Gy BED_{10} was 40% compared with only 14% for BED_{10} of < 60 Gy. The initial treatment dose was significantly associated with the risk of late complications for an α/β ratio of either 2 or 3 Gy ($p = 0.003$). The re-treatment dose was also associated with the risk of late complications, but only when an α/β ratio of 2.0 Gy was assumed ($p = 0.054$); for an α/β ratio of 3.0, Gy this was no longer significant ($p = 0.086$).

There are several other reports of re-irradiation of recurrent or new primary head and neck cancers using brachytherapy alone (afterloading techniques with iridium-192) (Table 2). The initial local control rates were generally good, although 5-year survival was only 14 to 24%, (many of the patients died of intercurrent disease or distant metastases (59). Complication rates were similar to those reported in series that used EBRT for re-treatment, i.e. 23 to 48%.

Nisar Syed et al. (60) reported on 64 patients re-treated for persistent or recurrent head and neck carcinoma at intervals of at least 4 months after full tolerance EBRT. All patients were re-irradiated between 1974 and 1975. The interstitial re-irradiation doses ranged from 45 to 60 Gy, delivered in 3 to 5 days. The follow-up period was short (mean 24 months) but at least 44% of this poor-prognosis patient group achieved a minimum of 18 months' survival with local control. Nineteen of the patients (30%) developed necrosis in the implant area, and six of these later developed orocutaneous fistulas.

Mazeron et al. (58) report on a series of 70 patients re-treated between 1971 and 1980 for recurrent or new primary oropharyngeal cancer in previously irradiated sites. The total doses delivered by iridium implants were $50 - 71$ Gy in 4 to 7 days (mean 60 Gy). The overall survival rates were 36% and 14% for 2, and 5 years, respectively, with actuarial local controls of 72% and 69% at 2 and 5 years. Mucosal ulceration or necrosis developed in 27% patients, only one patient developed an oro-cutaneous fistula. There was no apparent correlation between re-treatment dose and complication rate. Langlois et al. (61) reported on a series of 123 patients re-treated between 1972 and 1984 for recurrence or new primary tumours of the tongue or oropharynx in previously irradiated areas. The total re-irradiation doses ranged from 31 to 84 Gy (mean 62 Gy), delivered in an average time of 12 days. Twelve patients received palliative treatment with doses of less than 40 Gy. The 2- and 5-year survival rates were 48% and 24%, respectively. Actuarial local control rates were 67% and 59% at 2 and 5 years, respectively. The best results were obtained for tumours of the mobile tongue and tonsila, with poorer local control for soft palate and base of tongue. Local control was also poorer for large tumours, re-treatments doses < 60 Gy and recurrent tumours. The incidence of mucosal necrosis was 23% but all were successfully managed medically. Necrosis correlated with previous surgery and site of re-irradiation (the highest incidences were seen for re-irradiation of the tongue)

The report by Fontanesi et al. (62) concerns a group of 23 patients re-irradiated between 1980 and 1986 for recurrent or new primary head and neck cancer. The re-irradiation doses ranged from 39 to 60 Gy at dose rates of 300–660 mGy/h. The follow-up times for these patients were short (4 to 34 months) but the local control rate was high (91%), and 6/23 patients were alive with no evidence of disease at > 1 year. Severe complications (mainly soft tissue necrosis and/or fistulas) were seen in 11/23 patients. Although the patient number was small, the authors concluded that complication rate was related to dose rate, with dose rates > 420 mGy/h associated with a more severe risk of necrosis. Dose rate did not seem to influence tumour control.

Pommier et al. (63) report on a small series of 14 patients re-irradiated with low dose-rate brachytherapy between 1982 and 1993 for posterior pharyngeal wall carcinomas. The median re-treatment dose was 55 Gy (39 to 60 Gy). Overall survival rates were 50% and 21% at 2 and 5 years, respectively (minimum follow-up of 4 years). Local failure occurred in 5 patients (36%). No serious complications were reported in this small series.

GENERAL CONCLUSIONS

The clinical literature on re-irradiation in the head and neck region represents a very heterogeneous group of patients. However, it is possible to make some general conclusions based on the larger published series. Taken as a whole the clinical literature indicates that long-term tumour control can be achieved in a significant number of patients, with 5-year survival in the order of 20 to 40%. Good prognostic factors for tumour control are 1) re-irradiation doses of > 50 Gy; 2) long interval between initial treatment and re-irradiation; 3) new primary tumours rather than recurrent disease; 4) well-differentiated tumours; 5) small tumours suitable for brachytherapy re-treatment. Moderate to severe late complications were seen more frequently in the re-treatment situation than expected from single-course treatments. Up to 20% incidences of soft tissue or bone necrosis were reported (or even higher when associated with lysis of residual tumour), with a high incidence of trismus also seen in some series. The late normal tissue complications tended to be associated with high initial doses rather than high re-treatment doses (this was significant in some series).

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