



Reirradiation in Patients with Locoregional Recurrence or a Second Primary Neoplasm within a Previously Irradiated Area after Salvage Surgery with Reconstruction Using Pedicled Flaps and Flaps with Microsurgical Anastomosis

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Abstract

A salvage surgery is, if possible, a treatment of choice for recurrences following radiotherapy or second primary neoplasms within a previously irradiated area. A complementary radiotherapy to an area of the post tumor removal site with a necessary margin of healthy tissues after a salvage surgery is possible, although it involves a high risk of early and late toxicity. Nine patients operated using pedicled flaps or with creation of vascular microanastomoses for a recurrence or a second primary neoplasm within a previously irradiated location underwent a reirradiation. A survival of a few years in 6 patients, including a symptom-free survival in 3 patients, was achieved. The treatment toxicity was acceptable, although in one case, a necrosis of the mandible requiring surgical treatment occurred. Centers performing reirradiations must have a team of experts experienced in complex planning of radiotherapy or radiochemotherapy possess modern technical facilities and be able to carry out a complex treatment for complications related to undesirable effects of radiotherapy retreatments.

Keywords: Head and Neck Cancer; Recurrence and Second Primary; Salvage Surgery; Reirradiation

Introduction

Local and regional recurrences are the main cause of failures after a radiotherapy or chemoradiotherapy in patients who have cancer of head and neck organs. For this reason, the percentage of deaths exceeds 50% [1-7]. The percentage of patients with cancer of head and neck organs following radiotherapy or chemoradiotherapy, in whom a second primary neoplasm within an irradiated area may manifest it, is estimated to be 25% [8]. A salvage surgery is the management method of choice in case of treatment failure, recurrence or second primary neoplasm [9-12]. However, only 20% to 25% of patients are qualified for such a type of surgical procedure [13].

The prognosis of patients with a recurrence or second primary neoplasm within a previously irradiated area is unfavourable. As mentioned before, a salvage surgery is the most frequently used treatment in those cases, which makes it possible to achieve locoregional control in about 15% of patients [17]. For many years attempts have been made to use reirradiations in patients who have cancer of head and neck organs with local and regional recurrences and in case of second primary neoplasm within an area previously treated with radiotherapy [4,15-27]. In this case, therapeutic decisions are the resultant of the possibilities of locoregional control and the risk of severe undesirable effects of a radiotherapy which result from an accumulation of the doses of first and second irradiation. Many factors, such as the general condition (taking into account the performance grade and tumor-dependent complaints), burden of pathological conditions from the scope of internal medicine, operability of a recurrence/second primary neoplasm, dose amount within the irradiated volume and analysis of doses delivered to adjacent tissues (including critical organs), volume of a recurrence/second primary neoplasm, time counted from the first irradiation and expected toxicity based upon an analysis of undesirable effects during a primary treatment

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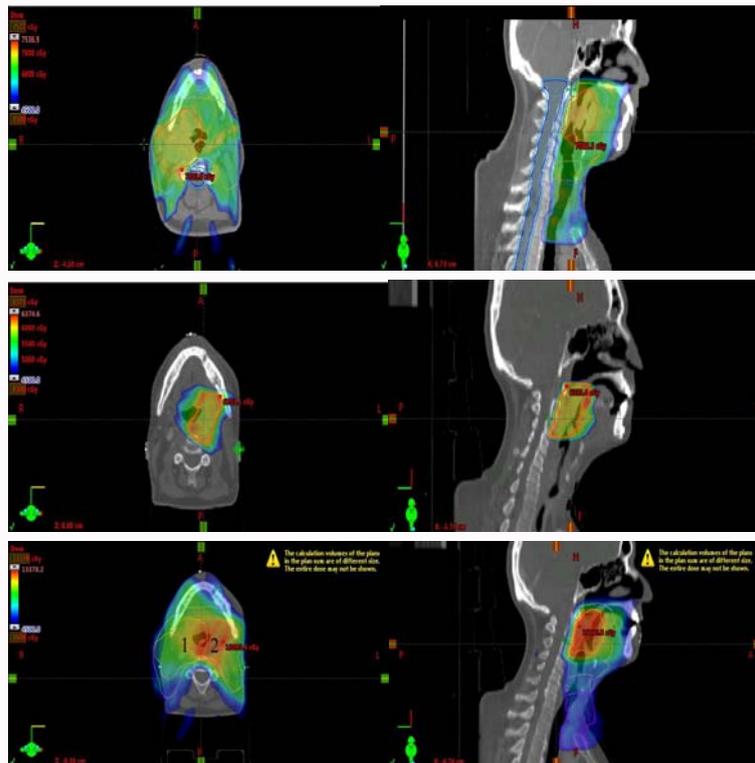


Figure 1: Compilation of the first radiotherapy treatment and retreatment after salvage surgery.

RT: Radiotherapy; ST: Second Treatment; PMF: Radical pectoralis Major Flap; RFF: Radical Forearm Flap (Chinese flap); ALTF: Anterolateral Thigh Flap; Rec: Recurrence

should be taken into account in calculations of potential benefits and risks.

The use of reirradiation makes it possible to achieve a long-term symptom-free survival in 40% to 60% of patients who underwent this treatment. A few reports, including only one phase III trial, indicate possible benefits but at the price of high toxicity. This heterogenous in respect of the used surgical procedure clinical material gives no room for reliable assessments. The paper attempts to make a preliminary assessment of the effectiveness of radiotherapy retreatment after a salvage surgery in which the reirradiation following resection of a cancer recurrence or second primary neoplasm within the previously irradiated volume and the defect reconstruction using pedicled flaps or flaps with creation of microsurgical anastomoses are innovative elements. This paper also makes it possible to observe the evolution of postradiation reactions and to assess the functioning of flaps transposed. The aim of the study is also to assess the effectiveness of an irradiation of a volume limited to the postoperative surgical site with a minimal necessary margin.

Aim of Study

An evaluation of the possibilities of performing radiotherapy retreatments following salvage surgery in patients with recurrences/second primary neoplasms within previously irradiated areas with a tissue defect reconstruction using pedicled musculocutaneous flaps and free flaps with microsurgical creation of vascular anastomoses in terms of an increase of the time to progression and an evaluation of early toxicity.

The aim of the study is also to assess the effectiveness of an irradiation of a volume limited to a postoperative surgical site with a

minimal necessary margin.

Methods and Materials

The task of carrying out a radiotherapy retreatment in patients with locoregional recurrences and/or second primary neoplasms within a previously irradiated area of the oral cavity and oral pharynx after a salvage surgery, including a reconstruction using pedicled flaps and free flaps with microsurgical creation of vascular anastomoses, has been accomplished. During the period between 2014 and 2016, nine patients were retreated with an irradiation. The patients qualified for a radiotherapy retreatment had a WHO performance scale grade of 0-1. Table 1 shows the patients characteristics and treatment outcome (Table 1).

After the salvage surgery, the patients were irradiated using the IMRT technique and the irradiated volume was limited to the postoperative surgical site filled with a flap with a small necessary margin depending on the grade of histopathological completeness assessed by postoperative microscopy. The resection was microscopically nonradical (R1) in all the patients analysed. The physical and biological doses delivered to critical organs were subject to a particularly thorough analysis. Co-60 was used in one patient initially treated with an irradiation 25 years ago and the planned treatment was carried out using a 2D technique. In this case, it was possible only to estimate the dose delivered to the tumor and critical organs before planned retreatment. The other patients were treated with three-dimensional conformal radiotherapy, mostly IMRT. During the radiotherapy retreatments, a radical total dose of 60-66 Gy in conventional 2Gy/day fractions was given. The planning of a retreatment consisted in implementing the plan after the surgical treatment and in combining this plan with the plan of first irradiation

Table 1: The patient clinical characteristics and treatment outcome.

no	Age at 1-st RT	Primary Treatment			Second Treatment						
		Histology/ Localisation	1 st RT dose cGy/year	Other Therapy	year of 2nd diagnos	Histology/ Localisation	Time RT-ST	Salvage surgery and reconstruction	2 st RT dose cGy/year	outcome from ST - year alive	outcome
1	25	chondrosarcoma maxillary sinus both	6480/1989	surgery	2014	oropharyngeal cancer	25	PMF	6000/2014	3 year alive	no rec.
2	54	skin face cancer	5000/2010	surgery	2014	skin face cancer	4	RFF	6600/2014	3 year alive	no rec.
3	51	oropharyngeal cancer	6600/2003	-	2014	tongue cancer	11	PMF	6000/2014	3 year alive	no rec.
4	48	parotid gland adenoid cystic cancer	6000/2005	surgery	2015	parotid bed adenoid cystic cancer	10	PMF	6000/2015	2 year alive	with rec.
5	55	parotid gland acinic cell cancer	6600/2012	surgery	2014	local rec. with sphenoid sinus progresion	2	Advanced Flap	6600/2014	3 year alive	with rec.
6	56	maxillary sinus cancer left	6000/2010	surgery	2014	lymph nodes metastases	1	PMF	6000/2015	death after ST	with progression
7	69	skin face cancer	6550/2012	surgery	2012	local rec.	3	ALTF	6000/2015	1 year alive	with rec.
8	61	oropharyngeal cancer	7000/2008	-	2014	oropharyngeal cancer	6	Advanced Flap	600/2014	1 year death	no rec.
9	56	oropharyngeal cancer left	6750/2009	chemotherapy	2015	PMF	6	PMF	6000/2015	1 year death	no rec.

(Figure 1).

In this way, it was possible to assess the doses in a common volume, i.e. a volume initially irradiated and planned to be subjected to a retreatment, and the doses delivered to critical organs. The common volume for the primary treatment and retreatment in the dose range of 80-140 Gy was 870.2-3.3 cm³. Due to the expected toxicity, the beginning of radiotherapy retreatment was preceded by the creation of the possibility of an alimentation with food and fluids, including a PEG placement.

This material containing small numbers and heterogenous in respect of used surgical procedure clinical gives no room for a full evaluation. The reirradiation after a resection of cancer recurrence and defect reconstruction using pedicled flaps or flaps with creation of microsurgical anastomoses, which made it possible to observe the evolution of postradiation reactions and to assess the functioning of flaps transposed, were innovative elements in the study.

Results

In 2014 and 2015, ten patients, three women and seven men who met the qualification criteria were qualified for a radiotherapy retreatment. One female patient has resigned from the proposed treatment after a previously declared consent and preparation of treatment plan. In 2016, two patients who underwent salvage surgeries were qualified for a retreatment. These patients have resigned from a treatment with irradiation. Finally, 6 late recurrences and 3 cases of second primary neoplasms within a previously irradiated area were diagnosed during the diagnostic examinations. The patients underwent a salvage surgery before the radiotherapy. Postoperatively, the postoperative surgical site with a small margin has been irradiated. A dose of 60 Gy in 30 fractions was delivered to 7 patients, 66 Gy in 33 fractions to one patient and 66 Gy in 30 fractions to another patient. The common volume for the primary treatment and retreatment within the dose range of 80-140 Gy was 870.2-3.3 cm³. Two patients died without a progression. A pneumonia was the direct cause of death of one of these patients and the cause of death of the other patient is unknown. One patient died because of a progression. Three patients are alive with a progression, including two patients with a local progression and one patient with a dissemination

into the lungs and local progression, and the other three patients are alive without clinical or radiological features of a recurrence. During the radiotherapy and after its completion, all the patients were under a strict observation. The total biological doses delivered to the spinal cord did not exceed 5250 cGy. The doses delivered to the mandible did not exceed on average 8200 cGy. WHO grade III postradiation reactions occurred in 4 patients. During the 6th month of observation after the retreatment, a necrosis of the mandible requiring surgical treatment occurred in one patient. During the primary radiotherapy and radiotherapy retreatment, the mandible of this patient with a volume of 91.6 cm³ received on average 8014.7 cGy (minimal dose of 486.4 cGy, maximal dose of 12695.1 cGy). Apart from that, no significantly higher early toxicity was found in comparison to the course of treatment in radically irradiated for the first time patients. The late reactions require a longer observation time.

Discussion

The reirradiation is not a new strategy for the treatment of patients with recurrences or a second primary neoplasm. However, due to the high risk of complications patients are qualified only sporadically for this type of treatment. In all the cases of reirradiation, the accumulation of total dose exceeds doses considered to be maximal and it is extremely difficult to plan a treatment within the limits of critical organ tolerance doses. The technical progress of the recent years and dissemination of conformal techniques of radiotherapy, and in particular the use of modulated intensity beam irradiation (Intensity Modulated Radiation Therapy (IMRT)), make it possible to minimize hazards related to exceeding critical organ tolerance doses, however, the risk of complications remains high depending on total doses accumulation in any event. Intense early postradiation reactions occur in about 80% of patients within 6 months from starting reirradiation [18]. The acute treatment toxicity related mortality is high and amounts to 8% [18-21]. In case of qualification for radiotherapy retreatment, the expected intensification of early and late undesirable effects forces a strict selection of patients. The volume of a tumor or postoperative surgical site with a flap and the time counted from first irradiation play an important role in this respect. These two factors have a key importance as regards the prognosis and have to be taken into account during qualifications. The negative

impact of large tumor volumes and the short time counted from first irradiation [21,23,24] on the prognosis was confirmed in many reports. Giving suboptimal doses during a radiotherapy retreatment is also an unfavourable factor. A long time counted from first irradiation, small reirradiated volume, combination of radiotherapy retreatment and chemotherapy, radical doses given by means of 3D conformal techniques, including IMRT [4,22,23,25-27], are prognostic factors related to better prognoses.

There are two main strategies of reirradiation which are the subject of studies and controversial debate. One of them is based upon an irradiation of a recurrence alone or combined with a chemotherapy following a radiotherapy/chemoradiotherapy or of a second primary neoplasm within a previously irradiated area. The other strategy includes a salvage surgery with a complementary reirradiation. In such cases, the possibility of using chemotherapy in the absence of surgical radicality (resection R2) or in the presence of unfavourable factors found during a postoperative microscopy, such as a lymph node capsule penetration by an infiltrating cancer, emboli present in vessels or infiltrations along vessels and nerves, is sometimes considered. A salvage surgery using pedicled flaps or flaps with creation of microsurgical anastomoses was performed in 9 patients treated at our center. In all the nine cases, the surgeries were microscopically nonradical due to the high-grade local progression, which was the reason of qualifications for a reirradiation, similarly to what happened in other studies [28,29]. According to our observations, 1/3 of patients are alive without progression, of which 2 patients 3 years and 1 patients 2 years. In some studies, a 5-year overall survival rate and a local control at a level exceeding 50% was achieved [30], however, a 2-year Overall Survival rate (OS) and a Progression-Free Survival (PFS) at a level of 30% to 40% is stated in the majority of the elaborations which is in line with our observations [31-34].

The results of many studies suggest that a reirradiation with a chemotherapy is related to the greatest therapeutic profit, but also to a high treatment toxicity. In the studies RTOG 96-10 and 96-11, 8% of treatment dependent deaths have been found and grade IV reactions occurred in 32% of patients [35,36]. Postradiation reactions, some of which were of WHO grade III, occurred in 4 of 9 our patients and a postradiation necrosis of the mandible requiring surgical treatment occurred in one patient. It seems that the toxicity level of a reirradiation after a surgery for LRR or SP using flaps is lower than that after a reirradiation alone which is usually combined with a chemotherapy and the results indicate benefits resulting from such a treatment strategy [27].

A qualification for an irradiation after a salvage surgery of patients with a recurrence or second primary neoplasm within the previously irradiated location first requires an assessment of the possibilities of performing surgical treatment and an analysis of the possibilities of performing a radiotherapy retreatment in a situation of doses overlapping and summing up in the whole reirradiated volume or its part is the second element. This complex form of therapy associated with a high toxicity requires a precise and thorough analysis of total biological doses within the volume defined for a retreatment and within critical organs. The difficulties in the inclusion of patients into this strategy are due to two reasons. Some patients resigned for the reason of the risk associated with the toxicity presented them. The second reason were the unfavourable results of analyses of doses which made it impossible to carry out radiotherapy retreatments. The number of patients in our elaboration is small, but it did not

differ substantially from the numbers analysed in other centers. Over an appreciably longer period between 1996 and 2011, 37 salvage surgeries after a primary radiotherapy with a reconstruction using musculocutaneous flaps, including 26 free flaps and 11 pedicled flaps, and afterwards radiotherapy retreatments were performed at the Memorial Sloan - Kattering Cancer Center [31]. In spite of that, it is the number of patients treated in the same way which makes it possible to explicitly assess the treatment strategy investigated.

Clinical Comments

A reirradiation in patients with recurrences following the primary radiotherapy or primary neoplasms within the previously irradiated location is possible and it creates an opportunity of a long-term survival of which a significant percentage is symptom-free. The treatment toxicity is high, but acceptable and lower than that of a reirradiation alone combined with a chemotherapy. Whichever strategy is accepted, when deciding on a radiotherapy retreatment the planned treatment should always be considered in terms of a maximal protection of critical organs using modern precise IMRT irradiation techniques. As suggested in the proposed criteria of qualification for reirradiations presented in 2011 by the American College of Radiology - Expert Panel on Head and Neck Cancer [37], a radiotherapy retreatment should be considered in case of a recurrence that does not qualify for a resection or after a nonradical (R1 - R2) salvage surgery within a previously irradiated area. The selection of patients for radiotherapy retreatments as well as the necessity to carry out the treatment in selected centers with a team of experts having experience in the complex planning of radiotherapy or radiochemotherapy which are equipped with modern technical facilities are of crucial relevance. The centers carrying out treatments must also be able to carry out complex treatments for complications related to undesirable effects of radiotherapy retreatments.

Author Statements

The qualification and treatment of patients was done on the basis of routine practice which means analyzing each case by a consilium consisting of a group of experienced radiotherapists, clinical oncologists and surgeons. In our institution only clinical trials are assessed by ethic committees.

We obtained consent for treatment from the patients. As explained above, the treatment was not done within clinical trial framework.

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