Reirradiation in head and neck cancers

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Salvage surgery is the mainstay of treatment for recurrences or secondary primary tumors in areas that were irradiated earlier. However, locoregional recurrence remains the main cause of death after surgery. Adjuvant reirradiation dramatically reduces locoregional recurrences but the risk–benefit ratio seems to be advantageous mostly for residual microscopic disease. In contrast, the rate of distant metastasis among reirradiated patients indicates that the local treatment alone is not sufficient. Full-dose exclusive chemo-reirradiation (over 60 Gy) can cure a subset of patients when surgery is not feasible. However, reirradiation is associated with a significant rate of severe toxicity and should, therefore, be compared with chemotherapy in randomized trials. Accrual may be difficult because of selection biases such as tumor volume, small volumes (largest axis less than 3–4 cm) being more likely to be irradiated. In addition, patients in poor general condition with severe comorbidities, organ dysfunction, or incomplete healing after salvage surgery, are unlikely to benefit from reirradiation. Noteworthy volumes to be reirradiated must be established between the head and neck surgeon and the radiation oncologist: the definition of the clinical target volume should be taken into account, the natural history of recurrent tumors, especially with regard to extension modalities, and the absence of strict correlation between imaging and histological real extension. This is even more critical with the advent of new irradiation techniques. Chemotherapy associations and new radiosensitizing agents are also under investigation. Comparison between reirradiation modalities is difficult because most trials are phase 2 mono-institutional trials. As selection of patients is a key issue, only phase 3 multiinstitutional trials can provide definitive results.
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Introduction

After initial treatment with radiotherapy or chemoradiotherapy, treatment of locoregional failures or second primary tumors in an earlier irradiated area is a challenge. When the recurrence is resectable, salvage surgery is the first option, if feasible. However, salvage surgery has poor results, especially for locoregionally advanced diseases: there is an important risk of locoregional failure after surgery, but some patients can be cured. For unresectable tumors, systemic chemotherapy is the standard treatment. Despite new regimens, which increase the response rates [1], survival remains poor and chemotherapy is only a palliative treatment.

Chemo-reirradiation has brought a new hope to unresectable patients. Growing evidence from different institutions has confirmed that this approach is feasible and can cure a subset of patients [2]. Furthermore, chemo-reirradiation can be associated with salvage surgery.

Biological and histological features of recurrent tumors and consequences of the reirradiation technique

Excepted for marginal recurrences, which could be explained by an initial geometrical miss, most central recurrences after definitive radiotherapy deal with biological mechanisms of tumor radioresistance: hypoxia at the center of the tumor, an important fraction of cells being in S phase, active repopulation during interfraction interval. But it has also been shown that recurrence of the tumor selects radioresistant cells: cells derived from the earlier irradiated tumors seemed to be more resistant to the radiation than the cells from untreated tumors [3]. The genetic mechanisms underlying this resistance are under investigation, including the overexpression of the genes involved in specific pathways [4]. For clinicians, this means that new schemes of radiotherapy had to be found to circumvent the intrinsic cell resistance. The use of concomitant chemotherapy, targeted agents, altered fractionation, dose escalation with intensity-modulated radiation therapy (IMRT) or stereotactic radiotherapy, and combination of these modalities could be effective against intrinsic cell radioresistance.

Recurrent tumors also have specific histological features compared with 'de-novo' tumors [5]. The recurrence is often present as numerous tumor foci in the fibrous tissue. These foci are usually multicentric and can invade surrounding tissues far from the initial tumor. There is a high percentage of undifferentiated and dissociated tumor

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cells in the vicinity of the tumor foci, and also a high percentage of perineural infiltration. As small foci and isolated tumor cells cannot be detected by computed tomography scan, MRI, or PET scan, there is a major risk to underestimate the real extension of a recurrent tumor in irradiated areas. After reirradiation, treatment failures are either entirely within the tumor gross volume or are distant failures [6]. The potential radioresistance and the patterns of invasion are strong arguments for high doses of reirradiation with sufficient margins around the recurrent tumor gross volume. A minimum of 2 cm is chosen in most trials, except where a 2-cm margin would fringe on spinal cord tolerance [7]. A low rate of regional or mucosal out-of-field marginal failures has also been reported with narrow margins, but it can be explained by the definition of out-of-field recurrence and also the high competing rate of in-field recurrences and distant metastasis [8].

For the same reasons, tumor clinical infiltration, which guides the surgeon during salvage surgery, goes far beyond the real extent of recurrent tumors. Frozen sections during salvage surgery are difficult to interpret. Assessing margins after complete examination of the surgical specimen is also difficult in earlier irradiated patients. After salvage surgery on infiltrative tumors, recurrence at the primary site is the main cause of death, even if definitive margin analysis of surgical specimen is negative [9]. In contrast, positive nodes are rarely found when neck dissection is performed [10]. This strongly argues for treating microscopic diseases around the surgical bed without treating the neck. Reirradiation fields have to be discussed for each case with the surgeon: large flaps are usually used in salvage surgery. Surgeons and radiotherapists have to define together what to reirradiate around these large flaps (for example, base of skull, infratemporal fossa, mediastinal area, etc.).

Chemo-reirradiation for unresectable tumors

Type of chemotherapy associated with reirradiation

Small series of reirradiation in head and neck squamous cell carcinoma have been reported in the 1980s: using a classical technique and without concomitant chemotherapy, clinical responses with an acceptable rate of severe complications could be obtained, and some patients achieved durable tumor control [11,12].

In 1996, the Chicago team published a series of 45 patients with daily 2-Gy fraction, associated with 5-fluorouracil (5-FU) and hydroxyurea, delivered in a split course until 60 Gy, with a 14-day cycle composed of 5 days of treatment followed by 9 days of rest. The 2-, 3-, and 5-year actuarial survival was 22, 17.5, and 14.6%, respectively. Fatal treatment-related complications were observed in five (11%) out of 45 patients [13]. These results were confirmed at Gustave Roussy Institute in a series of 169 patients, with 102 out of 169 patients treated with the 5-FU–hydroxyurea protocol [14]. The Radiation Therapy Oncology Group (RTOG 96-10) used the same association for 86 patients. Radiotherapy was delivered in 1.5 Gy (twice daily) fractions and similar results were obtained [15].

The same scheme of split course reirradiation with 5-FU–hydroxyurea protocol was tested in different series with a third radiosensitizing agent (cisplatinum, paclitaxel, or gencitabine). Salama *et al.* [6] compared five different protocols in 115 patients, including 49 patients who had undergone surgical resection. The series reported by Chmura *et al.* [16] (41 patients), Brockstein *et al.* [17] (54 patients), also used split reirradiation with paclitaxel in association with 5-FU–hydroxyurea. These series showed that a third agent could presumably increase the local control rates.

Using split-course reirradiation (twice daily) and concurrent cisplatin–paclitaxel in 105 patients, RTOG 9911 also observed an increase in the overall survival (OS) compared with RTOG 96-10 (25.9 vs. 16.9 at 2 years) [7,18]. These series show that other associations of radiosensitizing agents could be more efficient than the initial 5-FU–hydroxyurea association, but a better selection of patients or better irradiation techniques over time could also explain the increase in the survival.

Modalities of reirradiation

All series showed that reirradiation total dose was an important prognostic factor. The advent of IMRT, offering highly conformational tumor coverage with better protection of normal tissue, may lead to improvement in the locoregional control and in the reduction in late complications. Lee *et al.* [18] reported a series of 105 patients, with various tumor sites including 21 nasopharyngeal sites, 18 paranasal sinuses, and six parotids. There were also 36 post-salvage surgery patients. The majority of patients (91/105) received radiotherapy once a day, and 75 received concomitant chemotherapy, platinum-based chemotherapy in most of the cases. In 74 (70%) out of 105 patients, reirradiation used IMRT. Patients treated by IMRT had superior 2-year locoregional control compared with those treated by non-IMRT techniques (52 vs. 20%). The acute and late grades 3 and 4 toxicity rates compared favorably to the historical controls. Similar results on 78 patients treated with IMRT were reported by Sulman *et al.* [19] at MD Anderson Cancer Center, with 64%, 2-year locoregional control.

Compared with IMRT, stereotactic body radiation therapy allows a greater degree of precision in radiation delivery but with larger doses per fraction. It can minimize irradiation of nontarget adjacent tissues and allows for radiation dose escalation [20]. Image-guided radiotherapy has also been proposed as a means of overcoming potential set-up uncertainties and accounting for interfraction motion, which could increase the in-field control [21]. Further studies are needed to confirm these promising results.

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Trials investigating novel agents with reirradiation

New chemotherapy approaches have been investigated.

A multiinstitutional phase 2 trial tested the association of cisplatin and tirapazamine, a hypoxia selective topoisomerase-2 poison, combined with accelerated concomitant boost radiotherapy. In evaluable patients, there was a 28% rate of complete response, and a 2-year OS of 27% [22]. Furthermore, patients with hypoxic tumor fractions could be selected with high ^{18}F-misonidazole PET.

In a retrospective-matched cohort study, stereotactic body radiotherapy alone was compared with the same technique of reirradiation combined with weekly cetuximab infusion [23]. The 2-year OS rates for reirradiation and cetuximab–reirradiation were 21.1 and 53.3%, respectively. This survival advantage was obtained without significant increase in grades 3–4 toxicity and also observed in the subgroup that had received cetuximab therapy during their earlier therapeutic regimen.

As antivascular endothelial growth factor therapy can increase oxygenation and radiosensitivity, it was tested in a phase 1 trial in association with reirradiation, 5-FU, and hydroxyurea. Long-term survival was obtained in 13% of patients, without increasing the toxic effect [24].

Chemo-reirradiation after salvage surgery

In a retrospective series of 25 patients receiving concomitant 5-FU–hydroxyurea and reirradiation after salvage surgery [25], De Crevoisier *et al.* reported a 4-year survival rate of 43% in patients selected for histological gravity signs: positive surgical margin and/or lymph node involvement with capsular rupture. Late effects were osteoradionecrosis in 16%, and grades 2–3 cervical fibrosis in 40% of patients. Machtay *et al.* [26] reported a series of 16 patients with locally advanced recurrent tumors, treated with postoperative split reirradiation (twice daily) associated with cisplatinum and 5-FU for two cycles, and daily administration with amifostine. The 2- and 3-year actuarial OS was 81 and 63%, respectively, but incidence and severity of late effects were significant. In both the series, patients with macroscopic gross disease after surgery had early recurrence.

These results prompted the French groupe d'etude des tumeurs de la tête et du cou (GETTEC) and French groupe d oncologie radiotherapie des tumeurs de la tete et du cou (GORTEC) groups to launch a randomized trial to evaluate the efficacy of the 5-FU–hydroxyurea–reirradiation protocol, compared with the classical wait-and-see attitude [27]. Only patients in good general condition with locally advanced but completely resected tumors were included. In the wait-and-see arm, local failures after surgery could have benefited from the delayed reirradiation at the time of the recurrence. In the reirradiation arm, local recurrences were reduced by a factor of 2, which translated into a significant increase in disease-free survival. On account of toxic-related deaths, distant metastasis, and second primaries, there was no increase in OS. At 2 years there was a 39% grades 3–4 late toxicity in the reirradiation arm compared with 10% in the wait-and-see arm.

Selection of patients

All types of post-radiation side effects have been described with reirradiation. Acute toxicity can often be managed with prolonged hospitalization. Late toxicity remains the main problem for the surviving patients, because of its severity. Grades 3 and 4 cervical sclerosis is the most common late toxicity, and can be associated with osteoradionecrosis, trismus, cricopharyngeal dysfunction, and cervical contracture. Fatal strokes, carotid hemorrhage, major vessel or mucosal necrosis, and life-threatening edema have been reported in most large series.

This late toxicity explains why the selection of patients is a major issue in reirradiation, because it is associated with general conditions and particularly with the late toxicity of the first radiation. This has been shown by Tanvetyanon *et al.* [28] in a large series of 103 patients including 46 patients who underwent salvage surgery. Classic prognostic factors such as interval from earlier radiation, recurrent tumor stage, tumor bulk at reirradiation, and reirradiation dose were found to be independent prognostic factors. Significant comorbidity and baseline organ dysfunction were present in 36 and 37% of patients, respectively. The median overall and progression-free survival rates of patients with neither comorbidity nor organ dysfunction (41 patients) were 59.6 and 16.5 months, compared with 5.5 and 4.8, respectively, among the 13 patients with both comorbidity and organ dysfunction. Both parameters were also independent prognostic factors.

Conclusion

Reirradiation is an option for treating recurrent or secondary primary tumors in earlier irradiated areas. It has to be compared with other salvage treatments to guide indications in routine clinical practice.

(1) Salvage surgery is the reference treatment for recurrences or second primary tumors in already irradiated areas, if the recurrence can be macroscopically resected completely. In these cases and despite improvements in surgical techniques, locoregional recurrence remains the main cause of death after surgery. In an attempt to improve the results of salvage surgery, reirradiation after surgery has been compared with the reference attitude (wait and see) in a randomized trial. Reirradiation dramatically reduces locoregional recurrences but translation in terms of survival has not been shown. It is possible that a subset of patients with a higher risk (involved margins for example) could benefit more than other patients. It is also possible that the reirradiation technique in this trial was not optimal: association of targeted agent with hyper

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fractionation is currently under investigation in a phase 3 multiinstitutional trial. The rate of distant metastasis among reirradiated patients also indicates that a local treatment will never be sufficient. Local recurrences are often associated with distant metastasis, which are not detectable before salvage surgery.

(2) Reirradiation with concurrent chemo agent and/or targeted agent can cure a subset of recurrences or second primary tumors in already irradiated areas, even if salvage surgery is impossible. On account of its high toxicity, reirradiation should be compared in randomized trials with chemotherapy. RTOG initiated a trial (0421) randomizing patients to reirradiation or exclusive chemotherapy. This trial was closed because of lack of accrual. The GORTEC trial included 57 patients in a randomized trial comparing reirradiation and methotrexate (submitted for publication): all patients died in the two arms with a maximal follow-up of 5 years. Although four complete responses were achieved in reirradiation arm (none in chemotherapy arm), reirradiation did not improve OS compared with methotrexate (23 vs. 22% at 1 year, not significant). Accrual in this trial was difficult because small-volume recurrent tumors were not randomized and were directly treated with reirradiation in curative intent. This means that, for small-volume recurrences, clinicians decide to choose a potentially curative treatment despite its high toxicity.

(3) In reirradiation, selection of patients is the key issue with two main criteria. Only residual microscopic diseases after salvage surgery or small-volume macroscopic recurrences (for nonsurgically treated patients) have a reasonable chance to be cured with reirradiation. For large-volume recurrences, or when macroscopic disease is still present after salvage surgery, reirradiation is likely to bring only toxicity. In the series of patients treated with daily image guidance IMRT, the only parameter predictive of the in-field recurrence was the tumor volume Chen *et al.* [21] In routine practice the highest chance of cure is associated with tumor diameters less than 3 or 4 cm.

Patients in poor general condition with severe comorbidity or preexisting organ dysfunction, or incomplete healing after salvage surgery, will not benefit from reirradiation. For these patients the potential carcinological benefit will be outweighted by the severe toxicity of reirradiation including treatment-related deaths. Patients who do not fulfill these criteria can be treated with palliative chemotherapy, if feasible, or by supportive care.

(4) Many reirradiation techniques are under investigation, especially in three areas: chemotherapy associations, radiation delivery techniques, and new radiosensitizing agents. Comparison between reirradiation modalities is difficult because most trials are phase 2 monoinstitutional trials. As selection of patients is one of the most important issues, only phase 3 multiinstitutional trials could provide definitive results. The total dose of radiotherapy delivered in recurrent planning target volume (planning target volume = clinical target volumes + margins accounting for set-up uncertainties) is a prognostic factor in all series. As IMRT and tomotherapy can deliver high doses while sparing at-risk organs, these techniques are logically fitted to reirradiation. Definition of the clinical target volumes must be in accordance with the natural history of recurrent tumors, especially with regard to the extension modalities and the absence of strict correlation between imaging and histological real extension.

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