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Adjuvant radiotherapy post microvascular reconstructive surgery (MRS) for patients with locally advanced head and neck cancer – when and how?

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For many decades palliation (radiotherapy, chemotherapy or symptomatic treatment) was the only therapeutic solution for locally very advanced head and neck cancer. In the mid 70s, H. Buncke carried out pioneering microvascular reconstructive surgery (MRS) as a radical treatment. Since that time, the MRS has been accepted around the world as a successful radical therapy, not only for head and neck (H&N) cancers. A part of the H&N cancers need however post-MRS radiotherapy (RT). Based on the 20 year experience of the Institute of Oncology in Gliwice with MRS (about 2500 patients), D. Bula has defined local recurrence risk factors. Dutch studies convincingly documented the prognostic value of the estimated molecular profiles of the resected margins as additional risk factors. The use of conventional 2.0 Gy/fraction post-MRS-RT result in a high risk of the inserted reconstructive flap necrosis or rejection. Therefore, a novel IMRT-VMAT technique with 50 Gy given in 1.5–1.6 Gy/fraction has been designed which allows to almost eliminate the flap from the irradiated volume and therefore minimizes recurrence and/or flap rejection to almost zero. The present paper shows objectively selected a cluster of patients being the candidate to post-MRS safe and effective VMAT radiotherapy.

Key words: advanced head and neck cancer, microvascular reconstructive surgery, criteria for post-op. VMAT radiotherapy

When and why did MRS begin?

Worldwide, nearly 600 000 patients are annually diagnosed with squamous cell head and neck cancer and about 60% of them have locally very advanced disease with or without infiltration (destruction) of local bone structures [T4N0(+)]. Locoregional recurrence are the predominant most failure resulted from uncontrolled microdisease. For decades, palliative radiotherapy or symptomatic pain release therapy have been used as the only solution. As the result overall survival (OS) was only estimated but not the cure rate, because it has never been achieved [1, 2]. Generally, 5-year OS was low, on average about 10–15% (fig. 1, bottom survival curves) which raised to about 30–35% after radiotherapy combined with concurrent chemotherapy (usually single agent – cisplatin). The rate of patients with symptomatic therapy, mainly painkillers, has still remained pretty high and patients quality of life was usually very poor. Patients with advanced tumors, often accompanied with pathologic bone (mandible or maxilla) infiltration and local necrotic lesions had no chance to be cured.

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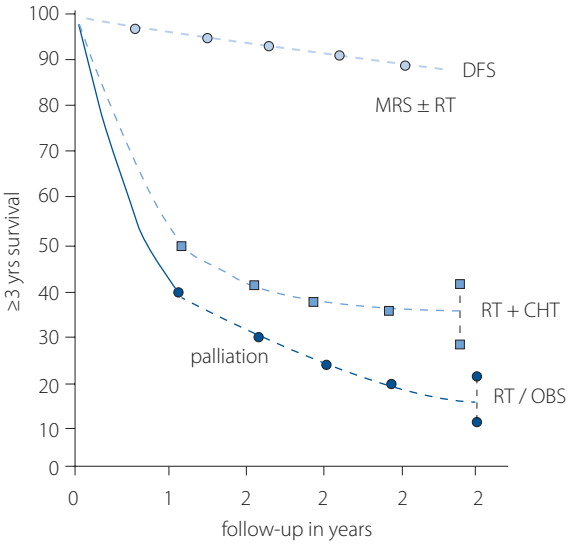

Figure 1. Survival after palliative radiotherapy (RT) or chemoradiation (RT + CHT) compared with disease-free survival (DFS) after microvascular reconstructive surgery (MRS) with or without adjuvant RT

Incidentally, large tumor regression after palliative chemoradiation led to radicalization of therapeutic procedures (surgery), which sometimes (rarely) resulted in local tumor control, however with a high risk of local recurrence. Therefore, the overall rate of local tumor control with disease-free survival was very low (a few percent) and lasted not longer than 2–3 years. For the majority of very advanced head and neck (H&N) cancer patients prognosis was not optimistic and although palliative therapy resulted in prolonged survival, their quality of life became worse and worse and was accompanied with increasing pain and deteriorating speech, in addition to problems swallowing and eating. Such poor perspectives for palliative therapeutic options lasted for many decades till the 70s.

In 1973, a significant breakthrough was initiated by Harry Buncke's pioneering work in which he transferred an island flap to reconstruct defect in the upper part of the feet. In the same year, Daniel and Taylor [3] repeated this reconstructive microvascular surgery. They, with many other pioneers [4–10] developed core principles of reconstructive microsurgery which are still pertinent today. This therapeutic procedure has quickly spread across US, European and Far South-East medical and oncology centers.

Microvascular reconstructive surgery (MRS) of locally advanced, not only head and neck cancers, should be considered as a milestone step because it has offered a radical outcome and long-term local tumor control, instead of the previous palliation and short-term survival. In the Institute of Oncology in Gliwice in 2000, the MRS has enriched methods and techniques of oncological surgery, and during the last 20 years about 2500 patients with advanced head and neck and other localization were successfully treated using the MRS. The overall 5-year disease-free survival rate increased to 88–90% (fig. 1, top curve) which clearly testifies to the tremendous improvements compared with previous results of palliative therapy. At the beginning of the MRS, the use of simple flaps gradually progressed into perforator, prefabricated, prelaminated, and chimeric flaps. Theoretically any tissue of any size from the body can be harvested using 135 different flaps, among which there are 65 types of free flaps. It allows the choice of a proper one for individual patient. Hidalgo et al. [11] pointed out that only seven free-flap donor sites are sufficient to solve 98% of microsurgical problems in oncology.

Although MRS has been a highly effective local therapy, there is still about 10–15% risk of local tumor recurrence and a few percent of postoperative local complications (flap necrosis). Thus, there is undoubtedly room for postoperative radiotherapy (RT), but it is still an open question whether all or only carefully selected patients need this RT as adjuvant therapy.

When should post-MRS radiotherapy should be applied?

Bula [12] analyzed the results of MRS in 119 patients with locally very advanced midface cancer, among which 85% were in stage T4N0(+) and in 63% of them four or more anatomical structures were involved. In 18 patients (10%), radicalism of surgical margins was defined as uncertain (very narrow margins?). One may ask what such uncertainty means. It is rather subjective than objective criterion for choosing post-op. RT. Using taxonomic statistics, the author established patient clusters with high and low risk of local recurrence. The cluster of patients with uncertain surgical margins, overweighed, with resection defect IIIA according Cordeiro scale [7, 8] and resected tumor size larger than 18 cm^2 strongly correlated with a high (about 90%) risk of local recurrence. On the contrary, cluster with radical margins (negative), normal weight, resection defect type IIA and a tumor size of about 4–8 cm^2 significantly ($p < 0.001$) correlated with almost no risk of local recurrence.

Therefore, patients from the first cluster likely seem to be candidates for postoperative RT. However, an important question arises as to whether the risk factor and parameters established by Bula can be considered as sufficient and adequate predictors for the post-MRS radiotherapy.

Studies of Nees et al. [13], Van Houten [14, 15] and Graveland [16], all from Vrije University Medical Center in Amsterdam (The Netherlands), have focused their studies on the molecular characteristics of minimal residual disease in surgical margins of head and neck cancer patients. Graveland [16] used two 5 µm sections from all surgical margins, which were histologically examined as to whether they were molecularly positive or negative. The specimens were used for immunohistochemical staining of the overexpression of the *p53* gene and *Ki-67* gene. A representative example of *p53* and *Ki-67*-positive fields is shown in the figure 2.

The *p53* and *Ki-67*-positive but histologically negative margins are the results of the cascade amplification of the EGFR,

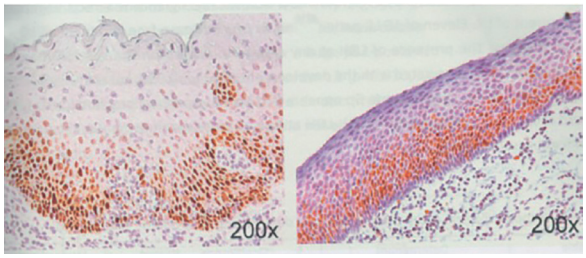

Figure 2. Example of immunohistochemical staining with: (A) a p53 positive field and (B) positive Ki-67 immunostaining [reprinted from Graveland et al. [16] with permission]

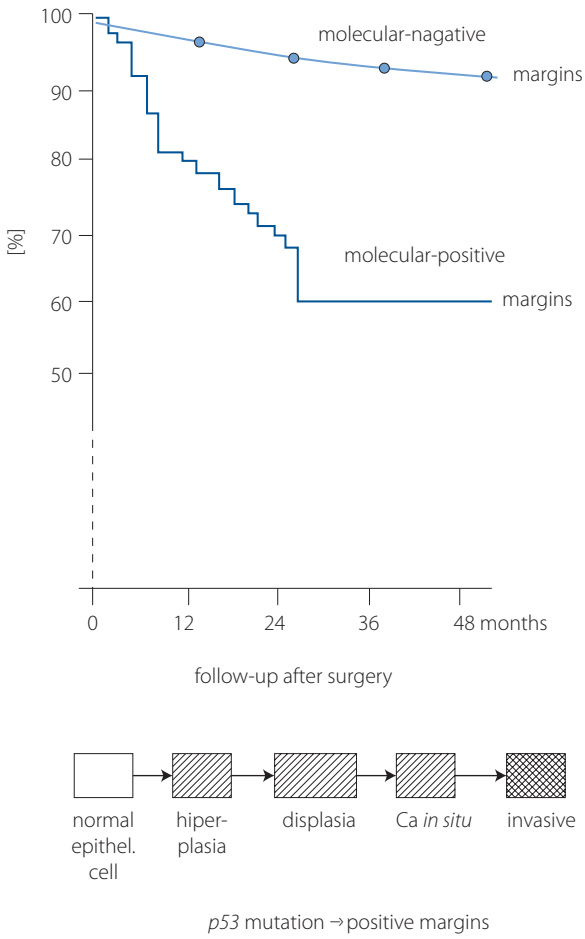

Figure 3. Local recurrence-free survival in relation to the molecular margin status (reprinted from Van Houten et al. Clin Cancer Res 2006; 6: 3803–3816, with permission)

cyclin D1, cathepsin D, Cox-2, 9 p51, 3p, 17p 13, 11q 11 genes with LOH (loss of heterozygosity) which lead to gradual alteration of normal epithelial cells through hyperplasia and dysplasia to cancer cells (fig. 3, bottom part), clinically occurring as local recurrence of the primary tumor, although it has incorrectly been diagnosed the second primary tumor (SPT). Such local recurrences (LR) develop from preneoplastic fields consisting of genetically altered normal mucosa cells that were not completely excised and they occur very early, during the first 10 months of the follow-up [13]. The results of the studies of Van Houten et al. [14, 15] have convincingly shown that cases with histologically negative but molecularly (*p53*, *Ki-67*, HPV) positive margins result in a significant ($p < 0.017$) decrease of the 5-year disease-free survival by about 30%, compared with cases with both molecular and histological negative margins (fig. 3).

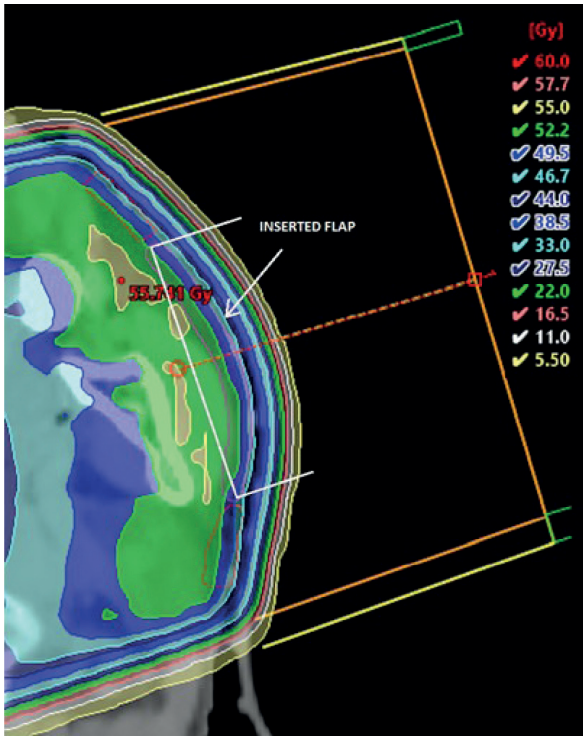

Figure 4. Simple a single- or two field post-MRS stationary irradiation using 30 fractions of 2.0 Gy

Results of the Dutch studies clearly encourage to supplement surgical margins with molecular staining as a significant predictor of high risk of local recurrence after the MRS, which is more precise of the LR than the "uncertain margins" defined by Bula [12]. Together with the high risk cluster factors defined by this author, they could increase the precision of individual selection of high LR risk patients to post-MRS radiotherapy.

Methods and technique of post-MRS radiotherapy

Traditionally, the beam(s) of a single-or-two-field stationary irradiation of post-reconstructive area cover(s) both the inserted flap (block of healthy tissues) and the block of normal tissues surrounding the flap (fig. 4). It sounds illogical to include the flap into the irradiated area because it is a locus of minor resistance (*locus minoris resistantiae*) of normal tissue island. Although the risk of the LR may decrease, on the other hand, the uncreased risk of the post irradiation flap necrosis and/or rejection significantly increases, after conventional 2.0 Gy fractionated radiotherapy.

Modern linear accelerators offer the use of a variety of intensity modulated RT (IMRT) techniques with non-uniform dose distribution using multileaf collimators (MLC). One such

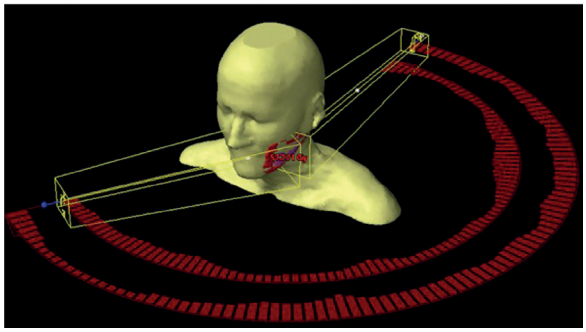

Figure 5. Example of VMAT radiotherapy technique with a single arc dose planning

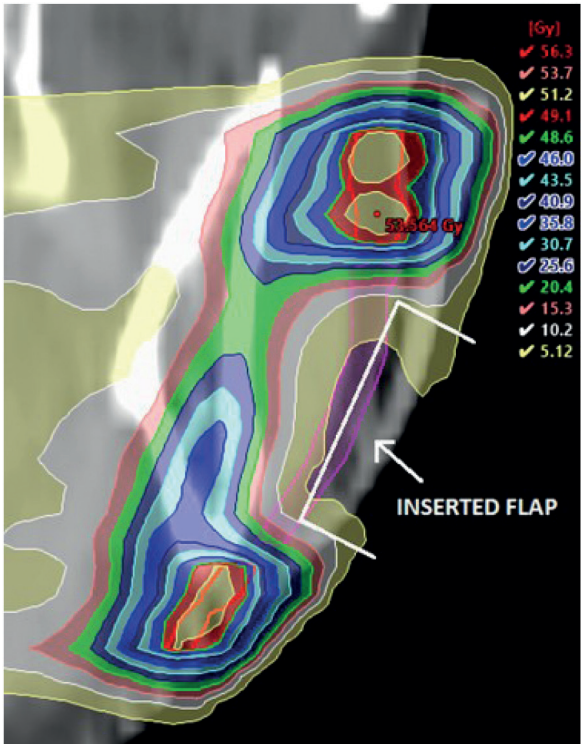

Figure 6. Example of vertical VMAT dose distribution of 50 ± 5 Gy in 30–31 fractions within the ring of normal tissues surrounding the inserted flap and sharp dose fraction gradient to above ≤0.35 Gy per fraction deposited in the periphery of the flap tissue

sophisticated technique is volumetric-modulated arc therapy (VMAT), which produces satisfactory dose distribution (fig. 5) to optimize the field shapes and beam intensities using a number of gantry angles. A significant advantage of the VMAT delivery is a reduction of the overall treatment time compared with conventional IMRT. For post-MRS adjuvant radiotherapy, the VMAT technique seems to be an optimal solution. This technique allows to plan the highest dose deposited in a ring of normal tissues surrounding the inserted flap likely containing microlesions of normal cells with potential genetic progression into cancer cells, and a sharp dose gradient dose to almost zero within the inserted flap (fig. 6). An important point of such dose planning is that the dose per fraction should be not higher than 1.5–1.6 Gy which results in of dose per fraction reduced to 0.35 Gy within margins of the inserted flap. It allows to minimize or even eliminate the risk of the flap necrosis or rejection.

Summarizing, the recurrence risks factors defined by Bula [12] supplemented by an estimation of the molecular status of the respective margins increase the objective selection of patients as proper candidates to post-MRS adjuvant radiotherapy. The choice of the VMAT technique with the GTV_S (ring of normal tissues surrounding the inserted reconstructive flap) total dose of about 50 Gy in 1.5–1.6 Gy dose per fraction seems to be the optimal solution for post-MRS radiotherapy as it likely lowers (even to zero) the risk of the inserted flap necrosis or rejection, and provides long term disease-free survival of patients with locally advanced head and neck cancer.

Conflict of interest: none declared

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