ANALYSIS OF APPLICATION AND RESULTS OF HIGH DOSE RATE BRACHYTHERAPY IN THE TREATMENT OF BASE OF TONGUE CANCER

Ph.D. thesis

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INTRODUCTION

Approximately 30% of tumours of the oropharynx are base of tongue cancers. In 2002, 228 new cases were registered and 251 patients died of this disease in Hungary. Base of tongue cancer extends rapidly to the surrounding structures and has great metastatic capacity. No optimal treatment of this condition has yet been found. In the non-surgical treatment of these tumours, the „organ preserving” modalities have become more and more important, because they provide – beside the practically complete retaining of speech and swallow functions as well as good cosmetic results – a high locoregional tumour control. At present radiotherapy is the most important means of this kind of treatment. Local dose escalation is an important factor in increasing local tumour control with irradiation, and brachytherapy (BT) is a possible choice for this purpose. Low dose rate (LDR) BT has been applied for a long time in the treatment of base of tongue tumours, but no detailed analysis can be found in the literature about the application and efficacy of high dose rate (HDR) BT.

I have chosen the investigation of the role of HDR BT in the radiotherapy of base tongue cancer as the subject of my dissertation, because the bad prognosis and high mortality of this disease call for the development and application of a more effective treatment.

AIMS

1. Analysis of application and efficacy of external radiotherapy and boost HDR BT in the treatment of base of tongue tumour.
2. Comparison of the results and side-effects to the exclusively percutaneous irradiation and the LDR series known from the literature.

3. Studying the role of postoperative irradiation of T1-2N0 cancer of the base of tongue after tumour excision.

4. Comparison of the use of rigid needles vs. flexible applicators in the treatment of HDR after-loading (AL) brachytherapy of the base of tongue cancer.

5. Quantitative, computerized comparison of the traditional, X-ray film operated planning with computer tomography (CT) guided planning in the BT of cancer of the base of tongue.

6. Analysis by means of modelling of percutaneous boost irradiation of base of tongue cancer and its comparison with brachytherapy from the point of view of dose exposure of the surrounding normal tissues.

7. Analysis of prognostic factors influencing local and locoregional tumour control as well as overall survival in patients treated with definitive radiotherapy.

**MATERIAL AND METHOD**

In 1992 a study was initiated at the department of radiotherapy of the National Institute of Oncology to investigate HDR BT in the treatment of base of tongue tumours. The dissertation analyses the therapeutic data of 77 patients with base of tongue cancer (T1-4N0-3M0) treated between January 1992 and June 2000. Side effects (acute and chronic) were classified on the basis of the recommendation of RTOG/EORTC.

From the point of view of the treatment type patients were classified into three groups:
A. Exclusively percutaneous irradiation (n = 40)
B. External radiotherapy and boost brachytherapy (n = 30)
C. Surgery and postoperative irradiation (n = 7)

**Exclusively percutaneous irradiation (group A)**

In the 40 patients treated without boost brachytherapy the medical status contraindicating general anaesthesia, lack of cooperation, or refusal of BT were the reasons for not using interstitial irradiation. The dose varied between 60-72 Gy to the primary tumour.

**External radiotherapy and boost brachytherapy (group B)**

Thirty patients, in whom there was no contraindication of interstitial radiotherapy and who accepted this treatment method, belonged to the second group. In all cases BT followed percutaneous irradiation. On average 60 Gy was delivered, which reached the therapeutic level as a result of summation with the BT dose (mean 18 Gy; range, 12-30 Gy). Interstitial BT was carried out with a microSelectron HDR after-loading unit (Nucletron B.V., The Netherlands) using an Ir-192 source with 370 GBq (10 Ci) initial activity. Flexible plastic tubes (20 patients) mostly with fractionated treatment (3-5 Gy per fraction) and rigid steel needles (10 patients) generally with one fraction (6-12 Gy per fraction) were applied.

**Surgery and postoperative irradiation (group C)**

Tumours (7 cases) which did not reach the axis of the base of the tongue (tumour size: T1-small T2N0) were excised. Four patients underwent elective, unilateral neck dissection beside the local surgery. The mean dose of sole BT of the tumour bed was 28 Gy (range, 24 to 30 Gy) given with flexible catheters and 4 to
5 Gy per fraction. Elective bilateral neck irradiation up to a total dose of 50 Gy was delivered to patients without neck dissection.

*Traditional and CT based planning*

Before interstitial treatment traditional planning with the use of X-ray films (n = 27) or CT based planning (n = 10) was applied. Quantitative analysis was performed in a modell study to compare and evaluate the plans made by these two methods. For the analysis cumulative dose-volume histogram characterestic of implantation geometry was used. In case of CT based planning the histogram characterizes the target volume. Dose non-uniformity ratio (DNR) was applied for the homogeneity of distribution. DNR is equal to the quotient of the 150 % dose volume (V_{150}) and the prescribed 100 % (V_{100}) reference dose volume. Dose distribution is optimal from the point of homogeneity, when DNR is minimal. During CT based planning, beside DNR, also the coverage of the target volume with the reference dose was studied. The coverage index (CI) shows the ratio of the target volume receiving a dose equal to or greater than the prescribed dose.

*Modelling percutaneous boost irradiation*

In 10 patients the conformal plans made for boost external irradiation and interstitial brachytherapy using the same CT images were compared from the aspect of the dose exposure of critical organs (mandible, parotid gland, spinal cord). Dose exposure was calculated by means of dose-volume histogram.

*Statistics*

The probability of survival was estimated using the Kaplan-Meier method. Fisher-exact test and log-rank test were applied
to compare differences in the probability of events and in survival, retrospective. Uni- and multivariate Cox proportional hazards analysis was used to evaluate prognostic factors with respect to LTC, LRTC and OS. The relative risk (RR) and the 95 % confidence interval (95 % CI) were calculated from the regression coefficient. A p-value of ? 0.05 was considered to represent statistical significance.

RESULTS

Exclusively percutaneous irradiation
The median follow-up time for surviving patients treated with exclusively external radiotherapy (n = 40) was 57 months (range, 20-100). The first control after irradiation showed a rate of 55 % for complete remission locally (Table 1). The 5-year rate of LTC, LRTC and OS, calculated by Kaplan-Meier method was 36 %, 34 % and 26 % (Table 2), the LTC according to tumour size (T1-T4) was 100 %, 67 %, 45 % and 18 %, respectively. Grade 1 mucositis occurred at a negligible rate, but grade 2-3 reaction was characteristic for most patients. Serious mucositis (grade 4) developed in 5 %.

External radiotherapy and boost brachytherapy
The median follow-up time for surviving patients treated with boost BT (n = 30) was 52 months (range, 16-108). The first control after irradiation showed the rate of complete remission to be 80 % locally (Table 1). The 5-year rate of LTC, LRTC and OS, calculated by Kaplan-Meier method was 60 %, 52 % and 46 % (Table 2), the LTC according to tumour size (there was no T1) was 100 %, 73 % and 48 %, respectively. Serious mucositis (grade 4) developed in 10 %. Osteoradionecrosis occurred in one patient. Grade 2-3 reactions were more frequent in patients
treated with a single high dose (12 Gy), than in those receiving several smaller doses per fraction, but the difference was not significant (p = 0.0653).

**Table 1**
Results of exclusively percutaenous irradiation and external radiotherapy + boost brachytherapy*

<table>
<thead>
<tr>
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<th>n (%)</th>
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<tr>
<td><strong>Complete remission</strong>¹</td>
<td></td>
</tr>
<tr>
<td><strong>Group A</strong></td>
<td>22/40 (55 %)</td>
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<tr>
<td><strong>Group B</strong></td>
<td>24/30 (80 %)</td>
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* 8 weeks after completing therapy; ¹ the difference is significant (p = 0.0257); n = number of patients; Group A = exclusively percutaneous irradiation; Group B = external radiotherapy and boost brachytherapy

**Table 2**
Probability of 5-year local and locoregional tumour control and overall survival in patients treated with different methods

<table>
<thead>
<tr>
<th></th>
<th>LTC (%)</th>
<th>p-value</th>
<th>LRTC (%)</th>
<th>p-value</th>
<th>OS (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group A</strong></td>
<td>36</td>
<td>0.0188</td>
<td>34</td>
<td>0.0753</td>
<td>26</td>
<td>0.0545</td>
</tr>
<tr>
<td><strong>Group B</strong></td>
<td>60</td>
<td></td>
<td>52</td>
<td></td>
<td>46</td>
<td></td>
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LTC = local tumour control; LRTC = locoregional tumour control; OS = overall survival; Group A = exclusively percutaneous irradiation; Group B = external radiotherapy and boost brachytherapy

**Surgery and postoperative irradiation**

All seven patients treated by tumour excision (partly also by neck dissection) followed by interstitial HDR brachytherapy or percutaneous irradiation plus BT of the tumour bed were found
progression-free locoregionally after a follow-up period of 47 months (range, 27-78 months). Distant metastases were not detected either. Moderate mucositis confined to the implanted region occurred in all patients.

**Comparison of traditional and CT based planning**

The average values of the reference dose volumes ($V_{100}$) were practically identical (33.9 vs. 33 cm$^3$). On the other hand, the average of the 150% dose volumes ($V_{150}$) was smaller with traditional planning than in conformal irradiation (14 vs. 17.8 cm$^3$). It follows that DNR characterizing dose homogeneity was smaller in the traditional plans (0.49 vs. 0.53), thus dose distribution was more homogeneous. The coverage of the target volume (CI) was however better in case of the conformal plans: on the average 87% of the target volume received the prescribed dose, whereas in the traditional plans only 78%.

**Comparison of percutaneous boost irradiation and interstitial brachytherapy**

The coverage of the target volume was better in plans made for external radiotherapy, because in almost all cases the entire volume received the prescribed dose. In plans made for brachytherapy 13% of the target volume proved to be low dose region. With percutaneous irradiation the maximal dose was on the average 9% higher than the prescribed dose, while dose homogeneity of the interstitial plans can be characterized with a DNR value of 0.53. Dose exposure of the critical organs however proved to be higher in external radiotherapy. Maximal dose of the mandible always exceeded the prescribed dose with an average of 6% in all cases. The parotid gland received 42% and 8% of the maximal dose with external radiotherapy and BT, respectively. In case of external radiotherapy an average of 1.9
cm$^3$ of the medulla received 10% of the prescribed dose, while with interstitial treatment exposure was not measurable in this organ.

Prognostic factors for local and locoregional tumour control and overall survival

In univariate analysis no boost ($p = 0.0449$) and larger tumour size ($p = 0.0043$) were negative predictors of local tumour control. Only tumour size was found to have a significant effect on LRTC ($p = 0.0125$). Smaller tumour size ($p = 0.0025$) and node negative status on the neck ($p = 0.0098$) influenced overall survival favourably. In multivariate analysis smaller tumour size (T1-2-3) had a positive influence on LTC ($p = 0.0042$) and on OS ($p = 0.0047$), boost brachytherapy on LTC ($p = 0.0444$), while absence of neck node metastasis on OS ($p = 0.0163$).

CONCLUSIONS

The results have proved boost HDR BT to be a suitable method for the radiotherapy of malignant tumours of the base of tongue. Compared with exclusively percutaneous irradiation boost treatment had a significantly more favourable effect in respect of local remission and LTC. The number of serious side-effects caused by irradiation was negligible.

Comparison of LDR and HDR brachytherapy showed no essential difference either in the results or in the side-effects.

For bypassing chronic side-effects delivering the dose of HDR BT in several fractions (maximum 6 Gy per fraction) seems to be appropriate. Further improvement of LRTC and survival can be expected from planned salvage surgery and concomitant chemotherapy. Multicentric, randomized studies could help to
find the exact role of HDR BT in the radiotherapy of carcinoma of base of the tongue.

Conclusion as regards the adequate therapy cannot be drawn from the treatment of four patients with early stage tumours of the base of tongue, treated with surgery and exclusively postoperative HDR brachytherapy. Combination of brachytherapy and percutaneous irradiation following tumour excision gave promising results (5-year survival) in the case of three patients.

Application of flexible plastic catheters in the brachytherapy of cancer of the base of tongue made fractionated therapy possible, which is more advantageous from the point of view of both radiation biology and physics.

CT and CT based planning is necessary in case of all patients for fixing the target volume and for improvement of the coverage with the reference dose.

Boost BT is more unfavourable from the point of view of dose homogeneity, but more advantageous in terms of radiation exposure to surrounding normal tissues than percutaneous irradiation.

Uni- and multivariate analysis of prognostic factors of tumours of the base of tongue showed that relatively smaller tumour size had a significant effect on LTC and OS, boost brachytherapy with external radiotherapy influenced LTC favourably, while the absence of neck node metastasis was linked to better OS.