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Prognostic value and importance of surgery combined with postoperative radiotherapy for oral and oropharyngeal cancer

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Aims. The aim of this paper is to evaluate the efficacy of surgery for patients with oral cavity or oropharyngeal cancer, and is impact on the final results of treatment combined with postoperative radiotherapy. Furthermore, predictive and prognostic value of clinical and histopatological postoperative factors were analysed, and estimation of clinical applicability of modified scale for risk of postoperative local and/or nodal recurrence according to Peters was checked.
Material and methods. Material includes 218 cases of the advanced oral cavity or oropharyngeal cancer All data were subdivided into 4 groups depending on treatment strategy. For the analysis of the treatment efficacy (overall and disease-free survival) many predictive and prognostic factors have been considered. Despite of multivariate logistic regression analysis of these factors, the risk of local recurrence was related to the results of combined treatment based on the modified numerical risk scale adapted from Peters. The risk value is the sum of scores given to individual prognostic factors. Time interval between surgery and radiotherapy (TI) and overall treatment time (TTT) have been accounted for the analysis.
Results. Generally, optimal results were noted in the group B, where surgery has been combined with postoperative radiotherapy. In case of surgery combined with preoperative radiotherapy (group E) 5-year DFS was 30%, and in the case when radiotherapy was delayed and applied when recurrence after primary surgery has occurred, the 5-year DFS was not higher than 20%. Macro- and microscopic surgical radicalism has been found one of the most important and significant prognostic factors. For positive margins (m+) 5-year DFS significantly decreases to about 20%. Surgical macro- and microradicalism has an important impact ($p=0.013$) on the incidence of distant metastases. The scoring system for the recurrence was based on Peters scale. The sum of the risk scores (TRRl+n) for individual prognostic factors allow to allocate clinical data into four risk groups. Increase of TRRl+n by one point correlates with the decrease in 5-year DFS by about 3%. The TRRl+n factor has been found the most powerful and independent prognostic and predictive factor.
Conclusions. 1. For patients with oral cavity or pharyngeal cancer, macro- and microscopically radical surgery is an effective treatment if combined with radiotherapy, and it provides a high probability of 5-year disease free survival and decreases the risk of distant metastases. 2. Presence and semi-quantitative value of well known clinical, surgical and pathological prognostic factors can be counted as a single numerical index of local failure, according to the modified Peters scale. The TRRl+n index is the most powerful, significant and independent predictor and prognostic factor.

Ocena wartości prognostycznej leczenia operacyjnego i jego miejsca w leczeniu skojarzonym z radioterapią u chorych na raka jamy ustnej i gardła

Cel. 1. Ocena skuteczności leczenia operacyjnego chorych na raka jamy ustnej lub gardła i jej wpływu na łączne wyniki leczenia skojarzonego z pooperacyjną radioterapią. 2. Zbadanie wartości predykcyjnej i prognostycznej klinicznych i histologicznych czynników pooperacyjnych oraz przydatności klinicznej zmodyfikowanej skali ryzyka wznowy.
Materiał i metodyka. Materiał obejmuje grupę 218 chorych na raka jamy ustnej lub gardła. Materiał podzielono na 4 grupy w zależności od taktyki leczenia. Oprócz wieloparametrowej analizy regresji logitowej licznych czynników prognostycznych i predykcyjnych, ryzyko wznowy określano w oparciu o zmodyfikowaną punktową skalę ryzyka wg Petersa. W analizie uwzględniono znaczenie prognostyczne czasu przerwy między leczeniem operacyjnym i radioterapią (TI) oraz całkowitego czasu skojarzonego leczenia.

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An abbreviated Ph.D. thesis

Wyniki. Generalnie najkorzystniejsze wyniki uzyskano w Gr. B, w której leczenie chirurgiczne uzupełniała pooperacyjna radioterapia. W przypadku radioterapii, poprzedzającej leczenie operacyjne (Gr. E), 5-letnie DFS wynosiło 30%, a w sytuacji, gdy RT stosowano dopiero po wystąpieniu wznowy pooperacyjnej (Gr. C i D), 5-letnie DFS nie przekraczało 20%. Jednym z najbardziej istotnych czynników prognostycznych okazała się makro- i mikroskopowa radykalność leczenia operacyjnego. Chirurgiczna radykalność makro- i mikroskopowa miała znamienny wpływ na częstość przerzutów odległych. W badaniach własnych posłużono się zmodyfikowaną punktową skalą ryzyka wznowy wg Petersa. Suma punktów ryzyka pRWm+w decydowała o uporządkowaniu materiału w 4 grupy według osiągniętego ryzyka niepowodzenia. Wzrost pRWm+w o 1 punkt wiązał się z obniżeniem szansy 5-letniego przeżycia bezobjawowego średnio o około 3%. Wskaźnik pRWm+w okazał się najsilniejszym i niezależnym czynnikiem prognostycznym. Oprócz tego czynnika, również czas przerwy między operacją i uzupełniającą radioterapią (TI) okazał się silnym i znamiennym czynnikiem prognostycznym.
Wnioski. U chorych na zaawansowanego raka jamy ustnej lub gardła radykalne makro- i mikroskopowo leczenie operacyjne jest skutecznym elementem taktyki leczenia skojarzonego, obciążonej niskim ryzykiem powikłań i stwarza wysoką szansę 5-letniego przeżycia bezobjawowego oraz obniża ryzyko wystąpienia przerzutów odległych. Obecność i pólilościowy udział uznanych czynników klinicznych, operacyjnych i histopatologicznych można wyrazić w formie wskaźnika ryzyka wznowy wg zmodyfikowanej skali Petersa. Wskaźnik ten wykazuje najsilniejszą, samodzielną i znamienną wartość predykcyjną i prognostyczną.

Key words: wartość predykcyjna i prognostyczna, punktowa skala ryzyka, suma punktów ryzyka
Słowa kluczowe: predictive and prognostic value, numerical risk scale, the sum of risk scores

Introduction

Cancers of head and neck belong to the group of the most clinically and histologically heterogeneous tumours, and thus optimal treatment strategy is still widely discussed. The use of specific treatment modality is usually based on well recognised prognostic criteria, i.e., tumour histology, grade and stage. The choice of surgery and/or radiotherapy is crucial, because the first therapeutic decision is critical for treatment outcome [1-4].

There is an increasing interest on tumour biology and kinetics of growth to define a new prognostic factors which could be useful predictors for optimal treatment schedules and its sequence [5]. It seems urgent to established significant power and hierarchy of prognostic factors and parameters gathered during and as the result of first treatment method which could be used as a guideline for the optimal choice of the second one, if combined treatment is planned.

In combined treatment it is an important obligation for surgeon to consider many numerical and rank factors in order to ensure radical effect of surgical treatment. In 1993 Peters et al. [6, 7] have set up in order the most important prognostic factors, and they proposed a rank scale for local and nodal recurrence risk as a basic rationale criteria for postoperative radiotherapy. There are only a few and fragmentary studies in this field, and its mainly concentrate on a single prognostic factor [7-10]. This situation motivates the present study, which the aim is to evaluate the efficacy of surgery of oral cavity and oropharyngeal cancers and to analyse its impact on overall results of treatment combined with postoperative radiotherapy. An important point of interest is to establish clinical applicability of the Peters` rank system for the risk of locoregional recurrence.

Material and methods

The group of 218 consequentive patients with oral cavity and oropharyngeal cancer treated with surgery in the Institute Of Oncology in Gliwice in 1986-1991 were included into the study. There were 75 females and thus male to female ratio was 3:1. Patient`s age was in the range of 27-83 years, and the average was 54 years. Primary tongue cancer was in 30% of cases, tonsil cancer in 27%, oral cancer was in 30% of cases and other localisation in 27%. All three levels of pharynx were involved in 30 cases (14%). In 82% of cases it was squamous cell cancer, in 8% transitional cell cancer, in 5% anaplastic cancer and in 4% adenocarcioma. In two cases malignant tumour was diagnosed, however histological type has not been established. Histological grade has been defined in 176 cases (81%), G I in 63%, G II in 13,5% and G III in 4,5% of cases. Patient`s characteristic in relation to TNM stage is presented in Table I.

Tab. I. Characteristics of the TNM stage

Stage (TNM)	Number pts.	%
T1-2 N0-1	130	60
T3-4 N0-1	38	17
T1-2 N2-3	28	13
T3-4 N2-3	14	6
TX N0-3	6	3
TX NX	3	1

Treatment methods

All cases were subdivided into 5 subgroups according to the methods of treatment:

(A) surgery alone – 8 cases (4%); (B) surgery with postoperative radiotherapy – 143 cases (66%); (C, D) surgery with delayed radiotherapy for postoperative local recurrence with or without salvage surgery – 20cases (9%) and (E) surgery with preoperative radiotherapy – 47 cases (21%). Macroscopically radical surgery was performed in 131 cases (60%), non radical was in 45 cases (21%) and in the remaining 42 cases (19%)surgical radicalism was not clearly documented. Neck nodes excision was performed in 111 cases and it was radical in 57% of them.

Radiotherapy was delivered using gamma 60 Co or 6-10 MeV photons. Total dose of 50-70 Gy (64% of them received total dose in the range of 65-70 Gy) was conventionally fractionated with one daily fraction of 2.0-2.5 Gy in overall treatment ti-

me (OTT) of 4-7 weeks. Time interval between surgery and radiotherapy (TI) was not longer than 7 weeks only in 33% of cases, in 42% TI was 8-14 weeks. Total combined treatment time (TTT = OTT + TI + 1) was also introduced as a prognostic factor, and in 36% of cases it was shorter than 14 weeks, in 47% it was in the range of 15-25 weeks and in the remaining TTT was longer than 25 weeks.

Rank scoring system for loco-regional risk was proposed by Peters et al. in 1993. It was modified and adapted for the present analysis. This system includes two risk scales, one for local recurrence (Tab. II) and the second for nodal recurrence (Tab. III). The first one (RRl), with the range of 0-12 risk points, includes macro- and microscopic margins, its width, vessel invasion and tumour grading. The second one (RRn) with the range of 0-9 risk points takes into account number of positive nodes related to the number of excised nodes, type of excision, extracapsular invasion and grading. This system was modified by giving higher points to positive macroscopic margins and to extracapsular invasion. Moreover, total risk score (TRRl+n) has been introduced, which is the sum of RRl and RRn being in the range of 0-21 points.

Tab. II. Modified rank scale for local recurrence [according to Peters, 6, 7]

Risk factors	Characteristics	Scale
Macroscopic Margin	(-)	0
	one or more (+)	3
Histopatological Margin	(-)	0
	one (+)	2
	>one or unknown (+)	3
Margin width	>5 mm	0
	<5 mm or unknown	2
Vessel invasion	(-)	0
	(+)	2
Histological grade	1-2	0
	3	2

Tab. III. Modified rank scale for nodal recurrence [according to Peters, 6, 7]

Risk factors	Characteristic	Scale
No. of metastatic nodes	crille excision – 1 (+) / > 10	1
	crille excision – 1 (+) / < 10	2
	1 (+) – no. of excised nodes unknown	2
	selective lymphadenectomy	
	1 (+)	2
	> 1 (+)	3
Extracapsular invasion	(-)	0
	(+)	3
Histological grade	1-2	0
	3	3

Results

In the group of 218 cases overall 5-year actuarial disease-free survival of 35% has been noted. There was significant correlation between T stage and 5-year DFS. The

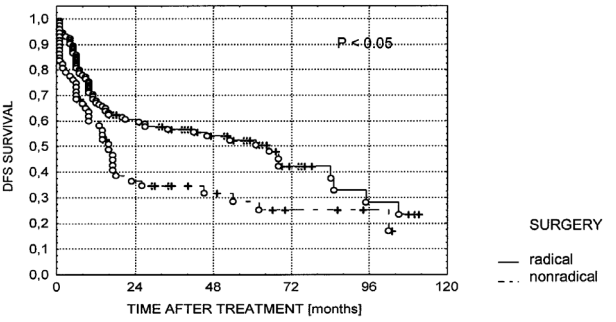

Fig. 1. Actuarial disease-free survival (DFS) depending on macroscopical results of surgery

increase from T1 to T4 stage corresponded with decreasing of 5-year DFS from 70% to 25%. Nodal stage increasing from N0 to N3 also resulted in 28% decrease in 5--year DFS, however this tendency was no statistically significant. Generally, an increase in T (T1 – T4) and N (N0 – N3) stage leads to 3-fold decrement in DFS.

In the group B, C and D including all together 163 cases (75%), surgery was the primary but not the only treatment modality. Actuarial 5-year DFS was significantly higher when surgery was combined with radiotherapy (B), than in cases (C, D) in which RT was delayed until local recurrence occurred (20%). For the group E with preoperative RT 5-year DFS was not higher than 30%.

The results show that macroscopically radical surgery produces on average 44% 5-year DFS (Fig. 1), which is significantly 2 times higher than the results of non radical surgery (21% 5-year DFS). Similar tendency was noted for histologically negative margins (Fig. 2) as compared with positive margins (55% vs. 32% 5-year DFS). This difference was highly significant (p=0.005). Also interval between surgery and radiotherapy (TI) and total combined treatment time (TTT) showed significant power as prognostic factors (p=0.01 and p=0.009). The longer TI or TTT the lower 5-year DFS has been noted. This reverse correlation was the most evident for cases with postoperative microscopically negative margins.

Overall failure rate was 50% (108 of 218 cases) including 26% of local and 11% of nodal recurrences. Among 19% of distant metastases, 7% developed together with local recurrence (Tab. IV). In group E with preoperative radiotherapy the incidence of loco-regio-

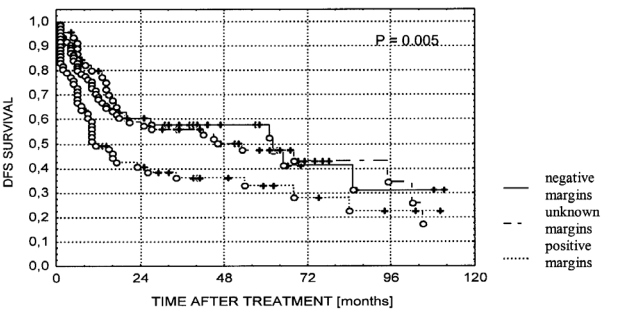

Fig. 2. Actuarial disease-free survival (DFS) depending on surgical margins histology

Tab. IV. Failure type and rate depending on treatment methods

Treatment methods	No. pts.	Local recur.	Nodal recur.	Distant meta.	Failure overall
A. Surg. alone	8	1 – 13%	0 – 0%	3 – 37% (1)	3 – 37%
B. Surg. – RT	143	29 – 20%	11 – 8%	18 – 13% (5)	53 – 37%
C. Surg. – rec. – RT	14	3 – 21%	2 – 14%	4 – 29% (3)	6 – 43%
D. Surg.- rec. – surg. – RT	6	2 – 30%	1 – 17%	1 – 17%	4 – 67%
E. Surg. – RT.	47	23 – 49%	10 – 21%	16 – 34% (7)	4 – 89%
Significance		p <0.0001	p <0.001	p <0.0005	p <0.0001
Overall	218	57 – 26%	24 – 11%	42- 19%	108 – 50%
Aa				(16 -7%)	

() – No. of cases with distant meta together with local recurrence

nal recurrences and distant metastases was about 2-3 times higher than in group B with postoperative RT (p=0.0001). When the RT was delayed until local recurrence occurred after surgery as primary treatment (group C, D) the incidence of all types of failure was higher than in the group B.

Interesting impact of radical surgery on distant metastases – free survival was noted (Fig. 3). Macro- and microscopically radical surgery combined with postoperative RT provides 5-year distant meta-free survival 20%

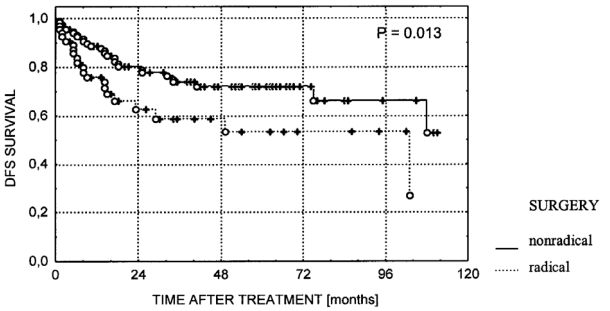

Figure 3. Actuarial distant metastases-free survival depending on surgical outcome

higher (p=0.01) than in case of non radical surgery (72% vs. 52%).

Multivariate regression analysis shows highly significant and independent prognostic power for the total score for loco-regional recurrence risk.

For practical reason scores were subdivided into two main groups – low risk with TRRl+n (<10 points) and high risk with TRRl+n (>10 points). An increase of TRRl+n from less than 4 points to more than 10 points generally caused (a) a significant and dramatic decrease in 5-year DFS from 62%, (b) an increase of locoregional recurrence risk from 28% to 41% and (c) 2-fold increase of distant metastases risk from 10% to 21% (Tab. V). Generally, surgical and histological risk factors which cause the increase of TRRl+n from less than 4 points to more than 10 points significantly correlate with 2-fold higher risk of single or more failure types.

Figure 5 shows that with the increasing TRRl+n from 1 to >15 points 5-year DFS decreases from 58% to 18% what gives about 3% decrease in the DFS per one point increase in the TRRl+n. The best prognosis (75% 5-year DFS) can be expected for TRRl+n not higher than 4 points and surgery – radiotherapy interval (TI) shorter than 10 days. For TRRl+n above 15 points and TI extended to 60 days the 5-years DFS decreases by about 50% (to 27%).

Discussion

Squamous cell cancers of head and neck represent one of the most clinically and histologically heterogeneous group of tumours. Even within the same histologic type, stage and grade there is a large heterogeneity with respect to tumour biology, kinetics of growth and the risk of dissemination to regional nodes and tissues. For early stages (T1-2 N0) surgery is still primary choice of highly effective treatment strategy. In combination with brachytherapy 90% long-term local control can be achieved [4, 11].

Large group of advanced tumours (T3-4 N0 and T1--4 N2-3) is the main candidate to combined treatment.

Tab. V. Loco-regional control depending on value of total recurrence risk point (TRRl+n) according to Peters [6, 7]

Treatment outcome	Risk group Gr. I (N=39) 1 – 4 points	Gr. II (N=101) 5 – 9 points	Gr. III (N=68) 10 – 14 points	Gr. IV (N=10) 15 – 20 points	P value
Local control (>5 yrs.)	24 – 62%	31 – 31%	11 – 56%	4 – 40%	0.00001
Local failure	0 – 0%	6 – 6%	9 – 13%	3 – 20%	0.005
Local recurrence	9 – 23%	27 – 27%	21 – 31%	0 – 0%	0.05
Nodal recurrence	2 – 5%	11 – 11%	9 – 13%	2 – 20%	0.01
Distant metastases	4 – 10%	23 – 23%	14 – 21%	1 – 10%	0.05
Uncertain data	-	3 – 2%	4 – 6%	-	
Failure overall	15 – 38%	67 – 66%	53 – 78%	6 – 60%	0.0001

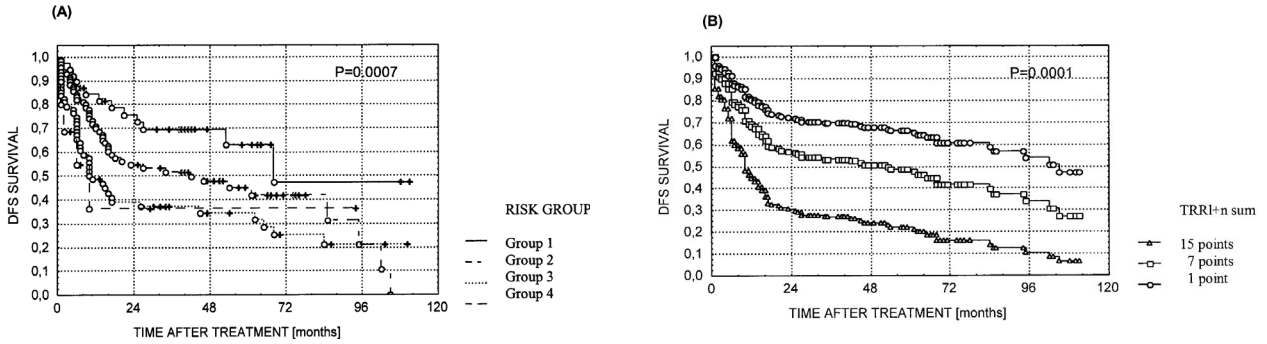

Figure 4. Actuarial disease -free survival depending on: (A) Group of the recurrence risk, (B) TRRI+n value

Preoperative radiotherapy (RT – SG) is aimed to control subclinical disease with the wide region of primary lesion and to produce tumour regression in order to increase a chance of radical surgery [1].

The present results showed however that the RT – SG treatment is less effective than surgery combined with postoperative radiotherapy (SG – RT) and the respective 5-year DFS were 30% and 39%. This rates decreased to only 20% when postoperative RT was delayed. Lower efficacy of the RT – SG was the result of higher incidence of loco-regional recurrence (49% vs. 20%) and about 3-fold difference in the incidence of distant metastases (34% vs. 13%) than for the SG – RT combination. This observations are supported by other authors [8, 12-15]. Similar tendency was observed by Regine et al. [16] who has noted 44% 5-year DFS after radical surgery. After combination of SG – RT the incidence of local recurrence decreased by 59%, and nodal recurrence and distant metastases by 62% compared with RT – SG. Strong [15] also documented higher efficacy of SG – RT than radiotherapy alone for both primary tumour and regional nodes with 50% reduction in recurrence rate if one neck level has been involved.

Present results likely suggest that in combination SG – RT surgery plays the major role. Furthermore microscopically radical operation may significantly decrease the risk of distant metastases and consequently leads to 20% improvement in the distant meta free survival compared with non-radical surgery. This gain was even higher if tumour stage was accounted for (82% 5-year DMFS for T1 compared with 58% for T2). Johnson et al. [17] also observed better results for radical surgery combined with postoperative RT. In the study of Zalefsky et al. [18] SG – RT for oral cavity cancer produced 50% 5-year DFS. Also Fletcher [19] has documented that radical SG – RT decreased local recurrence risk by about 50% and doubled 2-year survival rate.

There are only a few clinical prognostic factors which can be considered before treatment (localisation, stage, grade, growth kinetics). Majority of the most important factors are established intra- or postoperatively. Surgical margins are most often discussed as a major predictive factor for postoperative RT. Many authors point out that negative margins correlate with the reduction of recurrence risk after SG – RT by about 27-30%. The present results support these observations. Negative margins lead to 2-fold higher (58%) 5-year DFS than in the case of positive margins. Critical argument is that histological status of surgical margins is not a single and the most important prognostic factor and it seems better to consider a combination of factors than each one factor separately. In contrast to many authors who consider histological margins as important prognostic factor and predictor for postoperative RT, Peters et al. [6] have focused on extracapsular extension, documenting it as a major, independent and significant predictor for postoperative RT. Wang et al. [14] postulate however that N0 status correlates with 88% local control after SG – RT whereas more than 3 positive nodes in surgical specimen caused the decrease of local control to 49%. Bartelink and Cachin [1, 12] also support prognostic value of positive neck nodes.

Parsons and Peters [6, 7, 13] were the first who proposed, so called, „total package time" which in the present paper is considered as total combined treatment time (TTT). Present analysis supports the conclusion of these authors that shortening the TI and OTT, and consequently the TTT would improve therapeutic gain of combined SG – RT. Parsons et al. [13] pointed out that it plays an important role especially in the case of more than 4 unfavourable prognostic factors. The TTT shorter than 90 days has corresponded with 60% chance of long-term local control, whereas for TTT longer than 100 days this chance decreased to only 14%. Peters et al. [6, 7] have proposed to begin postoperative radiotherapy as soon as possible even directly after wound healing. Present results closely correspond with these suggestions and the most significant impact of the TTT on treatment outcome was noted in the group with high risk of local recurrence (>10 points TRRI+n).

If a total „package time" has been checked as a clinically useful concept it seems that a „total risk factor package" could also be more practically convenient that each one factor considered separately. The present results support this suggestion. Among all individual factors the TRRI+n being the sum of rank values given to this factors has the highest, independent and significant prognostic power. For low risk group (TRRI+n <4 points) 5--year DFS was 62% and decreased to 19% for TRRI+n of more than 10 points which makes on average

3% decrease in DFS for each one point increase of TRRl+n. Own results are similar to these published by Peters although he has considered local tumour and node recurrence risk separately.

Present results allow to propose the following algorithm for combined SG – RT treatment for patients with cancer of oral cavity and oropharynx:

1. The choice of optimal combined treatment and its sequence for patients with head and neck cancer should be decided by the team of surgeon, pathologist, radiodiagnost and radiation oncologist before the start of treatment.
2. To predict the highest possible therapeutic gain of combined treatment it is important to estimate total risk points (TRRl+n) including all clinical, biological, surgical and pathological factors.
3. The TRRl+n equal zero (negative margins, no more than 1-2 positive neck nodes in the level close to primary lesion without extracapsular extension) allows to resign of radiotherapy after surgery, especially for elderly patients with long anamnesis.
4. For low recurrence risk (TRRl+n = 1 – 9 points) surgery should be combined with postoperative conventional radiotherapy within 10 weeks.
5. High recurrence risk (TRRl+n > 10 points) call for postoperative radiotherapy with short interval between surgery and RT and shorten overall treatment time (modified dose fractionation).
6. For borderline criteria to surgery it is important to consider preoperative radiotherapy, however as short as possible with immediate surgical treatment. Depending on the TRRl+n value postoperative RT should also be considered (sandwich therapy).
7. Surgery alone and „wait and see" policy with radiotherapy delayed until local recurrence occurred significantly decreases long-term disease-free survival.

Conclusions

For patients with advanced cancer of the oral cavity or oropharynx microscopically radical surgery combined with postoperative radiotherapy is highly effective treatment strategy providing on average 60% 5-year disease-free survival independent on TNM stage prior to treatment, 20% decrease in the risk of distant metastases and low (4%) risk of late complications.

Among well recognised positive prognostic factors at least 5 mm negative surgical margins, no extracapsular and vessel invasion, overall combined treatment time not longer than 9 weeks are the most favourable. However it is almost impossible to establish their hierarchy which may change depending on tumour and patient characteristics, surgeon experience and type of operation.

It seems clinically useful to replace individual factors by one numerical value of total recurrence risk point (TRRl+n) which reflect the number and prognostic power of unfavourable factors. The TRRl+n might be an important guideline for postoperative radiotherapy and its modifications if needed. Practical applicability of the TRRl+n scale should be checked in prospective study.

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