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COMPARISON OF CONVENTIONAL AND SPLIT-COURSE RADIOTHERAPY AS PRIMARY TREATMENT IN CARCINOMA OF THE LARYNX

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Abstract

Based on our experience with conventional, daily irradiation, a split-course radiation schedule was introduced in 1978. The schedule, which was based on Cohen's models for squamous cell carcinoma and vascular damage respectively, predicted an improved tumour control and a reduced rate of late complications, e.g. late oedema, if the conventional, daily treatment was replaced by a split-course schedule. The schedule has later been abandoned, but the experience gained from split-course treatment at various dose levels has been analysed and the results compared with those obtained by conventional radiation. The data allowed construction of dose-response curves and estimation of iso-effect doses. Split-course treatment was associated with a significantly reduced therapeutic ratio because, disappointingly, it did not improve tumour control, and the severity of late complications grew. No late complications were avoided by introducing a 3-week pause in the radiation therapy regimen, nor was the tumour response improved despite a 12-Gy increase in total dose. This indicates a significant repopulation corresponding to more than 0.5 Gy/day, equivalent to an up to 100-fold increase of the number of clonogenic tumour cells during the pause—an increase that occurred despite the decrease, clinically, of the tumours during this period.

Key words: Therapeutic radiology; laryngeal cancer, comparison conventional vs split-course, tumour control, oedema, fistulas.

Radiotherapy is the primary treatment of laryngeal carcinoma in Denmark. A detailed analysis of 308 patients treated to 57 or 60 Gy totally with conventional, daily irradiation in the period of August 1963 through August 1972 (9) showed that the local control rate probability and the degree of late oedema could usefully be described by the cell population kinetic model proposed by COHEN (4, 5, 9). Thus, a close agreement between the observed and the expected local control for squamous cell carcinoma was found. Although the model does not prescribe any special relationship for late oedema, the model for late effects in the vascular stroma was found to correlate well with this function. With this experience a working hypothesis was proposed from which it was possible to predict the frequency of local recurrence and late oedema. A theoretically optimal split-course schedule was calculated from the extrapolated data, which predicted an improvement in local control rates from 74 to 87% and a drop in late complications from 6% to less than 1% (9). According to Cohen's model, this would occur if the treatment schedule was changed from 60 Gy (30 fractions over 6 weeks) to a split-course regimen with 40 Gy (20 fractions over 4 weeks) followed by a 3-week interval before ending the treatment with an additional 32 Gy (16 fractions over 3 1/2 weeks), i.e. a total dose of 72 Gy in 36 fractions over 10 1/2 weeks. Such a schedule was adopted at the Department of Radiotherapy and Oncology in January 1978. Due to an unexpected, high incidence of complications, the total dose was reduced to 68 Gy in January 1979 (9). This reduced schedule was used until October 1979 when the Danish Head and Neck Cancer Study (DAHANCA) protocol 2 was launched (13). Only patients treated prior to the DAHANCA study are included in the present analysis. The split-course principle has later been abandoned, but the experience gained from split-course treatment at 2 dose levels is now available for a comparative analysis.

The aim of the present study was to provide a clinical, radiobiological analysis of parameters related to regeneration in tumours and late responding normal tissues, and to focus on the importance of overall treatment time. Pending a more detailed investigation a thorough evaluation of the hypothesis and the validity of Cohen's model is considered outside the scope of the present analysis.

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Table 1

Overview of treatment schedules

Radiotherapy schedule	Period
Daily radiation	
57 Gy/30 fr./6 wk	Aug 1963–June 1970
60 Gy/30 fr./6 wk	July 1970–Aug 1972
Split-course radiation	
40 Gy/20 fr./4 wk–3 wk–32 Gy/16 fr./3.5 wk	Jan–Dec 1978
40 Gy/20 fr./4 wk–3 wk–28 Gy/14 fr./3 wk	Jan–Oct 1979

Table 2

Frequency of local tumour control and late radiation morbidity

Schedule	Tumour control	Late oedema	Fistula
57 Gy daily rad.	63±3% (132/208)	2±1% (5/208)	23±6% (12/52)
60 Gy daily rad.	74±4% (72/97)	6±2% (6/97)	21±9% (4/19)
68 Gy split-course	61±8% (20/33)	24±7% (8/33)	75±21% (3/4)
72 Gy split-course	73±6% (43/59)	53±6% (31/59)	92±8% (12/13)

Frequency estimated with ±1 SD based on binomial distribution.

Material and Methods

Ninety-two patients with histopathologically verified invasive squamous cell carcinoma of the larynx were treated with split-course radiotherapy between January 1978 and October 1979. All patients were treated with a curative intent using high voltage radiation with Cobalt-60. The material consisted of 70 (76%) glottic and 22 (24%) supraglottic tumours. The analysis was performed in December 1986, and no patients were lost for follow-up. The split-course irradiated patients were compared with 308 patients given continuous, daily radiation at 2 dose levels (57 or 60 Gy) as previously described in detail (10).

The radiation therapy technique, fractionation schedule, description of data, and analysis, as well as a detailed argumentation of using the split-course irradiation, have previously been published (9, 10). The radiation treatment given to the split-course treated patients was applied as described in these papers. The 4 different fractionation schedules are shown in Table 1.

The end-points in the present analysis were local tumour control, late oedema, and frequency of fistula in patients undergoing laryngectomy for recurrence. The data for these frequencies have previously been published for the continuously treated group (9, 10) and have been estimated similarly in split-course treated patients.The values given are the observed minimum frequencies (10). Dose-response curves are performed by logit-analysis (17).

Late oedema was defined as clinically significant, persistent oedema noted in the patient's records. Since oedema may precede local failure late oedema was excluded in patients with local recurrence within 18 months (10). In the split-course schedule late oedema was only observed in 3 patients with local failure and after latency periods of between 2 to 4.5 years.

Fistula-incidence was corrected for the use of metronidazole (given as a prophylactic to ward off anaerobic infection at the time of laryngectomy) which has been shown to strongly affect the results (20). Therefore, only patients who did not receive the prophylactic treatment were included.

Variations in total dose in both continuous and split-course treated patients allowed distinction of 4 groups of patients, viz. receiving either continuous or split-course irradiation at 2 different dose-levels (Table 2). The material in this table constitutes the basis for the present analysis.

The 4 treatment groups were comparable with regard to tumour localization (glottic, supraglottic), stage and T-classification, tumour volume, field size, and observation time.

Results

Both tumour control and late normal tissue damage showed a steep dose-response relationship. An increase of 3–4 Gy in both the conventional and the split-course schedules thus resulted in a significantly increased response, the magnitude of which is illustrated by the slope of the dose-response curves (Figs 1, 3 and 4).

Local tumour control. An increase of 3 and 4 Gy in the continuous and the split-course regimen brought about an 11% and a 13% increase in tumour control respectively.

This prominent dose-response relationship allowed construction of dose-response data based on a logit analysis

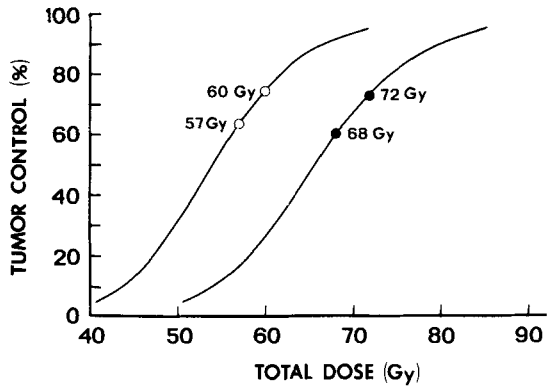

Fig. 1. Logit estimate of dose–response relationship for squamous cell carcinoma of the larynx treated with daily or split-course radiotherapy. ● Split-course; ○ continuous treatment.

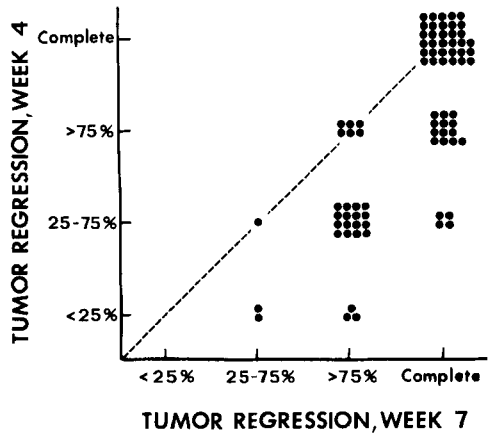

Fig. 2. Clinical evaluation of tumour response during a 3-week pause after 40 Gy in 4 weeks. All patients were evaluated immediately before and after the split interval (78 patients with evaluable tumours).

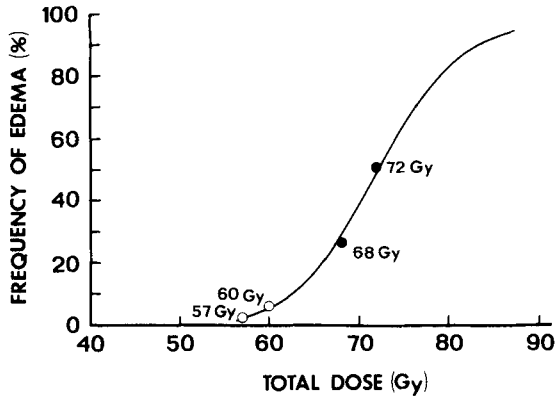

Fig. 3. Dose–response relationship for frequency of late oedema. The curve fits both data from continuous and split-course irradiation. ● Split-course; ○ continuous treatment.

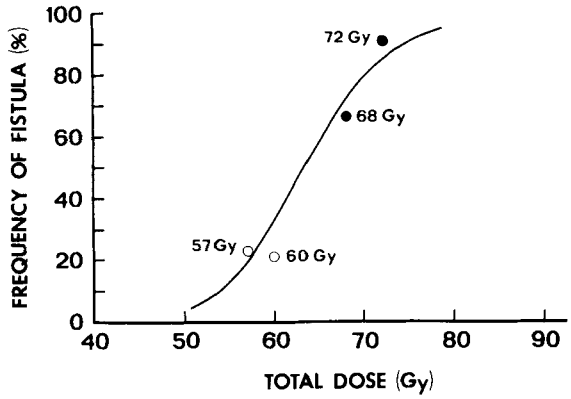

Fig. 4. Frequency of fistula in patients undergoing laryngectomy as a function of total dose and irradiation schedule. All data can be described by the same dose–response curve. ● Split-course; ○ continuous treatment.

(Fig. 1). The virtually identical shape of the 2 dose-response curves with a rightward shift of the split-course curve equivalent to approximately 12 Gy demonstrates the need for an increase in the total dose of this order to obtain equal effect by the 2 regimens. From Table 3, showing iso-effect values for 65% tumour control, it appears that TCD65 values are statistically significantly different (a difference of 12 Gy), corresponding to a ratio of 1.21. Identical tumour control in squamous cell carcinoma of the larynx thus requires a supplementary, approximately 20% increase in dose to compensate for a 3-week pause in the treatment.

Clinically, the extent of tumour regression during the 3-week interval was recorded in all patients (Fig. 2). Despite the increase in the number of clonogenic tumour cells during this 3-week interval, the tumours obviously regressed or, at least, they maintained their size, none showing any progression (Fig. 2).

Late normal tissue complications. The late radiation damage to normal tissue was primarily recorded as late oedema. The frequency of this kind of tissue damage rose from 2 to 6% in patients treated with daily radiation, depending on the size of the total dose administered, to a staggering 51% in patients having received a split-course treatment with a higher total dose (72 Gy). A logit analysis performed separately for the continuous and the split-course schedule showed that the latter did not statistically significantly shift the dose-response curves to the right. Thus, no significant difference was observed between the 2 estimated iso-effect levels at 5% and 35% respectively (Table 3). In fact, all 4 data points were best described by the same dose-response curve (Fig. 3), which indicates that no significant regeneration occurred during the 3-week interval.

Table 3 showed a non-significant, slight recovery ratio at the 5 and 35% level confirming the impression that no dose-sparing takes place with regard to late oedema.

The second late normal tissue end-point was fistula

Table 3

Isoeffect doses for local tumour control and late normal tissue damage in larynx carcinoma treated with continuous or split-course radiotherapy

Isoeffect end-point	Continuous radiation Gy	Split-course radiation Gy	Dose recovered Gy	Recovery ratio
65% Tumour control	57.4 (55.8–59.0)*	69.4 (65.8–73.3)	12.0	1.21+ (1.14–1.28)
5% Late oedema	59.3 (57.1–61.6)	62.6 (56.4–69.5)	3.3	1.06 (0.95–1.17)
35% Late oedema	66.9 (55.8–80.2)	69.6 (67.9–71.4)	2.7	1.04 (0.88–1.23)
22.5% Fistula	57–60	61.4 (44.2–85.2)	1–4	1.02–1.07

* 95% confidence limits in parentheses.
\+ Statistically significant different from 1, $p<0.001$.

after laryngectomy. The present analysis only includes patients where the surgical procedure related to laryngectomy is known to be similar. The frequency of laryngectomy and the incidence of failure were largely alike in the continuous and the split-course schedule, and the rate of complications (e.g. fistula) consequently should be expected to be of the same significance in the 2 schedules if not affected by factors such as radiation schedule and dose. There was no dose-response relationship in the continuous treatment schedule, but split-course therapy significantly raised the incidence of fistulae, depending on the total dose (Table 2). A proper iso-effect analysis could therefore not be performed, but an estimate at the 22.5% level showed only a minor, insignificant dose-sparing effect of the split-course regimen. A logit analysis including all 4 data points was not statistically significantly different from that based on split-course radiation data only, which indicates that the dose-response curves after continuous and after split-course radiation came up with the same frequency for fistula. Thus, the introduction of a 3-week interval had no obvious effect neither on the frequency of late oedema nor the frequency of fistula.

Therapeutic ratio. It is obvious that the prominent increase in late complications associated with the lack of a similar improvement in tumour control results in a significant decrease in the therapeutic ratio. This is apparent both from the data in Table 3, and from Fig. 5, which, at 2 dose levels, compares continuous and split-course radiation in schedules yielding almost identical tumour control levels.

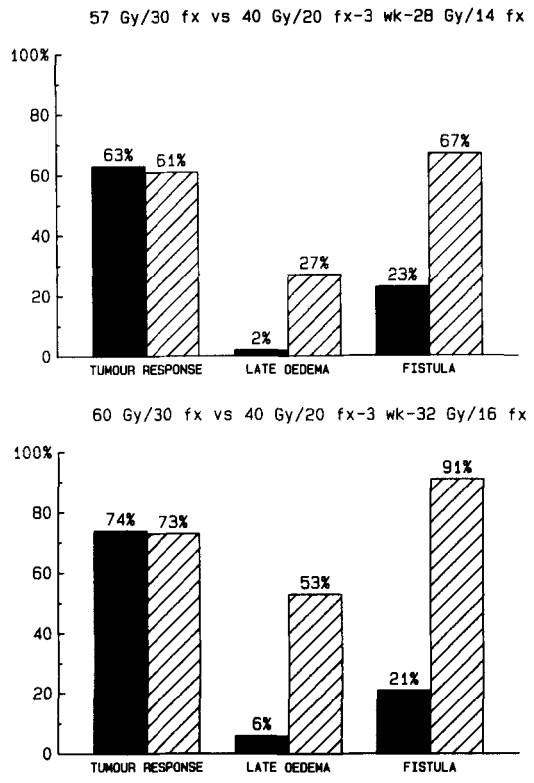

Fig. 5. Comparison of continuous and split-course radiation at 2 dose levels. ■ Continuous irradiation; ■ Split-course irradiation.

Discussion

The purpose of the present paper was not to evaluate Cohen's model; yet it appeared that the actual results obtained did not tally with the predictions offered by the model, in particular for parameters related to regeneration and influence of overall treatment time.

The use of split-course radiotherapy has certain immediate advantages. The patients tend to like the treatment because the interval allows them to recover from the immediate strain of radiotherapy. The acute radiation reaction is reduced and tends to show prominent recovery

in the split interval. The overall compliance during and immediately after treatment is therefore better in a split-course regimen than in a similar continuous, daily schedule. However, in a rapidly proliferating tumour, like a squamous cell carcinoma of the larynx a very high price in terms of total doses must be paid to obtain a similar tumour control probability as the one achieved with a continuous regimen. The approximate 20% increase required in the present study is in agreement with more recent data of split-course treatment in head and neck tumours which show either a decrease in tumour control, when giving identical total doses, or a need for compensation to yield similar results in a split-course regimen (2, 3, 7, 8, 11, 15, 22). However, to our knowledge we are the first to produce dose-response data that allow estimation of iso-effect and a comparison between a continuous and a split-course schedule. The 12 Gy interval observed at the 65% tumour control level is the result of a 3-week interval. There is a striking similarity between this value and the observations by BUDIHNA et al. (3) and MACIEJEWSKI et al. (12) that a prolongation of the overall treatment time should be compensated for with approximately 0.5 Gy per day (see WITHERS et al. (22) for a detailed overview). Assuming that this increment in dose solely or mainly is due to regeneration during the interval, the increase in clonogenic tumour cells can be calculated. On the basis of steepness of dose-response curves and in vitro data, FOWLER (8) has estimated that the dose needed in a normal fractionation schedule to reduce the clonogenic cell population with a factor of 10 is approximately 6 Gy. On this assumption, a 12 Gy increase in iso-effective dose suggests that the number of clonogenic cells in the 3-week interval has increased with a factor of 10^2. A hundredfold increase in the number of clonogenic cells during 3 weeks demands a minimum of 6–7 tumour cell doublings, corresponding to a cellular doubling time of 3–4 days. This rapid proliferation of squamous cell carcinoma is in agreement with the estimates of potential doubling time recently discussed by several authors (3, 7, 8, 18, 19, 22). The present data therefore confirm the point-of-view that introduction of an interval 4 weeks into a radiation therapy course is associated with a very rapid cellular proliferation rate of squamous cell carcinoma of the larynx. Furthermore, this increase in clonogenic cells occurs despite a clinical decrease in tumour volume (Fig. 2), and the clinical prediction therefore does not necessarily reflect the number of clonogenic tumour cells.

We may reasonably deduce that the need for increments in the total dose springs from the tumour cell repopulation, which is a major and clearly the most important parameter in split-course treatment. Although hypoxia may be a significant factor in head and neck tumours, there are several reasons why it may be of less importance in the present study. Firstly, the influence of hypoxia seems less important in laryngeal than in pharyngeal tumours (14), secondly the cases in question are mainly relatively small tumours even showing tumour regression during the 3-week interval (Fig. 2) and therefore an increase in the hypoxic fraction seems unlikely.

A detailed analysis of acute radiation reactions was not performed in the present study due to the insufficiency of the data. However, it was the general impression that the split-course treatment was better tolerated, especially when large treatment fields were applied. Such sparing was certainly not observed with regard to late complications where the incidence of oedema and fistula formation was dramatically increased as a function of total dose. No significant sparing was observed as a function of the 3-week interval, which confirms clinical and experimental observations that the overall treatment time has no or only little influence with regard to late responding normal tissues (1, 6, 7). The 3-week interval is simply too short for the tissues in question to respond with repopulation, and the damage will consequently correspond to the total dose applied. This lack of influence of the overall treatment time issues a grave warning against the use of fractionation models where this parameter is included. On the other hand, it lends some support to the use of the linear quadratic model for prediction of late normal tissue damage when altering fractionation schedules (7).

The linear quadratic model does not include a parameter for overall treatment time, which apparently is not critical for prediction of late normal tissue damage. The present study indicates that one should not expect an increased treatment time to reduce late normal tissue complications, and it clearly demonstrates that even a small increment in total dose may result in a very significant increase in the complication rate, i.e. the dose response curve for late complications is very steep.

The incidence of fistula was very high in the present study which may be explained by the inclusion of fistulas of very short duration. The use of this end-point is associated with a number of problems recently reviewed (20).

In squamous cell carcinoma of the head and neck, the obvious decrease in the therapeutic ratio with increasing overall treatment time is caused partly by the short cellular doubling time and partly by the lack of regeneration in late responding normal tissues. Therefore, any increase in overall treatment time must be compensated for by an increase in dose which, in turn, will be associated with an increase in normal tissue complications, the magnitude of which will be considerable because of the steepness of the dose-response curve. On the other hand, evidence is gathering in support of an improvement of the therapeutic effect by a shortening of the overall treatment time, and several clinical studies have shown a remarkable result in patients with similar tumours treated with multiple daily fractions for a short treatment period (16, 18, 21). The present investigation has, indeed, underlined the importance of treatment time, and it strongly indicates that a radiation treatment once commenced should be completed as soon as possible without any unnecessary delay.

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REFERENCES

1. ARCANGELI G., FRIEDMAN M. and PAOLUZI R.: A quantitative study of late radiation effect on normal skin and subcutaneous tissues in human beings. Br. J. Radiol. 47 (1974), 44.
2. BUDIHNA M., FURLAN L. and SMID L.: Carcinoma of the nasopharynx: Results of radiation treatment and some prognostic factors. Radiother. Oncol. 8 (1987), 25.
3. — SKRK J., SMID L. and FURLAN L.: Tumor cell repopulation in the rest interval of split-course radiation treatment. Strahlentherapie 156 (1980), 402.
4. COHEN L.: A cell population kinetic model for fractionated radiation therapy. I. Normal tissues. Radiology 101 (1971), 419.
5. — Biophysical models in radiation oncology. CRC Press, Inc. 1983.
6. DENEKAMP J.: Cell kinetics and radiation biology. Int. J. Radiat. Biol. 49 (1986), 357.
7. FOWLER J. F.: What next in fractionated radiotherapy? Br. J. Cancer 49 (1984), 285.
8. — Potential for increasing the differential response between tumors and normal tissues: Can proliferation rate be used? Int. J. Radiat. Oncol. Biol. Phys. 12 (1986), 641.
9. HJELM-HANSEN M.: Laryngeal carcinoma. IV. Analysis of treatment results using the Cohen model. Acta Radiol. Oncol. 19 (1980), 3.
10. — JØRGENSEN K., ANDERSEN A. P. and LUND C.: Laryngeal carcinoma. II. Analysis of treatment results using the Ellis model. Acta Radiol. Oncol. Rad. Phys. Biol. 18 (1979), 385.
11. LINDBERG R. D. and FLETCHER G. H.: Clinical experiences with altered fractionation. Rev. Interam. Radiol. 7 (1972), 15.
12. MACIEJEWSKI B., PREUSS-BAYER G. and TROTT K.-R.: The influence of the number of fractions and of overall treatment time on local control and late complication rate in squamous cell carcinoma of the larynx. Int. J. Radiat. Oncol. Biol. Phys. 9 (1983), 321.
13. OVERGAARD J., ANDERSEN A. P., JENSEN R. H. et al.: Misonidazole combined with split-course radiotherapy in the treatment of invasive carcinoma of the larynx and the pharynx. Acta Otolaryngol. Suppl. 386 (1982), 215.
14. — HANSEN H. S., JØRGENSEN K. and HJELM-HANSEN M.: Primary radiotherapy of larynx and pharynx carcinoma—An analysis of some factors influencing local control and survival. Int. J. Radiat. Oncol. Biol. Phys. 12 (1986), 515.
15. PARSONS J. T., BOVA F. J. and MILLION R. R.: A re-evaluation of split-course technique for squamous cell carcinoma of the head and neck. Int. J. Radiat. Oncol. Biol. Phys. 6 (1980), 1645.
16. SAUNDERS M. I., DISCHE S., FOWLER J. F. et al.: Radiotherapy employing three fractions on each of twelve consecutive days. Acta Oncologica 27 (1988), 163.
17. SUIT H. D., SHALEK R. J. and WETTE R.: Radiation response of C3H mouse mammary carcinoma evaluated in terms of cellular radiation sensitivity. *In:* Cellular radiation biology, p. 514. The University of Texas, M. D. Anderson Hospital and Tumor Institute. The Williams and Wilkins Company, Baltimore 1965.
18. THAMES H. D., PETERS L. J., WITHERS H. R. and FLETCHER G. H.: Acceleratd fractionation vs hyperfractionation: Rationales for several treatments per day. Int. J. Radiat. Oncol. Biol. Phys. 9 (1983), 127.
19. TROTT K.-R. and KUMMERMEHR J.: What is known about tumour proliferation rates to choose between accelerated fractionation of hyperfractionation? Radiother. Oncol. 3 (1985), 1.
20. VENDELBO JOHANSEN L., OVERGAARD J. and ELBRØND O.: Pharyngo-cutaneous fistulae following laryngectomy. Cancer 61 (1988), 673.
21. WANG C. C., BLITZER P. H. and SUIT H. D.: Twice-a-day radiation therapy for cancer of the head and neck. Cancer 55 (1985), 2100.
22. WITHERS H. R., TAYLOR J. M. G. and MACIEJEWSKI B.: The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncologica 27 (1988), 131.