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CLINICAL STUDY

# Radiobiological approach to treatment gaps in locally advanced head and neck cancers radical radiotherapy arising from the COVID-19 pandemic

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**ABSTRACT**
Gaps of radiotherapy treatment are one of the factors recognized as unfavorable in terms of tumor control and disease prognosis. All strategies for compensating the negative effect of radiotherapy treatment gaps are based on radiobiological models. Using the modified square linear formalism (Dale`s equation) it is possible to calculate the additional dose in order to compensate the accelerated tumor repopulation effect. SARS-CoV-2 infection is an important factor that can lead to an interruption of irradiation for medium and long- term intervals. We aim to present the radiobiological data underlying the recalculation of radiotherapy treatment and exemplification for different clinical scenarios in the case of head and neck cancers *(Ref. 17)*. Text in PDF *www.elis.sk*
KEY WORDS: radiobiology, treatment gaps, locally advanced head and neck cancers, radical radiotherapy, COVID-19 pandemic.

## Introduction

The entire activity of caring for cancer patients has been severely affected by the COVID-19 pandemic. Cancer patients are both at increased risk of developing severe forms of the disease through cancer-induced immune-compromised status, but are also collateral victims of severe restriction access to health care during this period. In this context, we can easily estimate that the consequence of postponing treatments will lead to an explosion of locally advanced and metastatic cancers. The need to ensure social distancing and limiting visits to radiotherapy departments in order to reduce the risk of contracting the SARS-CoV2 virus has led to the rapid implementation of hypo-fractionated radiotherapy regimens. However, if the patient contracts the new coronavirus, it may be necessary to discontinue treatment. Although most opinions support the continuation of radiotherapy treatment, especially in rapidly proliferating tumors for asymptomatic COVID-19 disease case, there are particular situations when the protection of other patients cannot be ensured, being necessary to discontinue radiotherapy treatment. Severe forms of the disease that require hospitalization in specialized departments or even in the intensive care department are cases for which the interruption of radiotherapy treatment can exceed 2–3 weeks.

Head and neck cancers, due to the risk of contamination associated with diagnostic and therapeutic procedures involving the upper aero-digestive tract, but also through intensive management sometimes including three therapeutic modalities (surgery, chemotherapy and radiotherapy) represent a category of risk. Prolonged duration of treatment by radiotherapy or radio-chemotherapy (6–7 weeks) and the tumor biology, head and neck squamous cell carcinomas (HNSCC) being generally fast-growing tumors, there are factors that confer a special vulnerability to severe detrimental effects associated with radiotherapy treatment gaps (1–5).

Head and neck cancer, although it is only the seventh most common type of cancer with a European incidence of 145,000 new cases per year, is notable for a high rate of therapeutic failures, especially due to loco-regional recurrences despite the multimodal treatment progress. Most patients are diagnosed in advanced stages of the disease, in the vast majority being HNSCC. Definitive chemo-radiotherapy is currently the standard treatment for the locally advanced stage of disease. The addition of concurrent chemotherapy to radiotherapy brought a benefit in overall survival (OS) of about 5 %. Administration of a weekly dose of Cisplatin 40 mg/m$^2$ weekly or 100 mg/m$^2$ and radiotherapy using Intensity Modulated Radiation Therapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT) techniques with a median dose of 70 Gy in

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33–35 daily fraction is recommended by current therapeutic guidelines. The irradiation protocol also includes irradiation with doses between 60–66 Gy and 50–54 Gy for higher risk of lymph node tumor involvement level respectively for prophylactic irradiation of nodal regions with low risk of tumor invasion. Other regimens such as Mitomycin C/5-Fluorouracil according to the ARO 95-06 randomized phase III trial, Carboplatin or Cetuximab have been evaluated in combination with radiotherapy but have not been established as a therapeutic standard. Strategies for intensifying treatment by escalating radiation dose and chemotherapy with Cisplatin were also explored. GORTEC 2004-01 randomized phase III trial evaluates the benefit of IMRT irradiation up to a total dose of 75 Gy/35 fractions associating 3 cycles of concurrent chemotherapy with Cisplatin 100 mg/m$^2$ compared to conformal 3D irradiation in a dose of 70 Gy in 35 fractions. The study confirms the benefit of the IMRT technique in reducing xerostomia but does not confirm an advantage of escalating chemotherapy and radiotherapy in terms of local tumor control (4, 6–8).

**The effect of radiotherapy gaps in the treatment of head and neck cancers**

A historical study published more than 25 years ago evaluated the effect of treatment gap on tumor control in a group of 971 SCHNC patients with supra-glottic larynx. The follow-up time was at least 3 years, and as causes of radiotherapy treatment gaps the authors mention treatment machine malfunction, national holidays, other intercalated treatments, inter-current diseases or severe toxicities. If the delay in treatment occurs before the 19th day of treatment, a considerable decrease in local control is observed and the benefit was 4.3 % for a 1 % escalation of the compensatory dose of radiation. The gap effect is considered minimal between days 20 and 29 of treatment, local control being slightly affected in this case. The authors also mention a severe reduction in local control for gaps at the end of treatment. The estimated cancer related death rate was 2 times higher in the group where the treatment was extended by at least 3 days and the cancer mortality was 4 times higher if the treatment exceeded 30 days. The authors conclude that accelerated repopulation occurs from the beginning of treatment and an additional dose of irradiation is required in case of unplanned breaks. A retrospective study by Duncan et al. including 383 laryngeal cancer patients treated between 1976–1988 at Western General Hospital, Edinburgh demonstrates the severe effect of prolonging radiotherapy treatment proposed for 28 days and 20 fractions even by 3 days compared to the normal overall treatment time (9–10).

In a review of the literature, Ferreira et al. evaluated the effect of delays in radiotherapy treatment regarding loco-regional control of HNSCC tumors. Subsequently, the authors proposed a compensation protocol, taking into account the existing scientific evidence, establishing such criteria for prioritizing clinical cases in the context of workflow limitations in radiotherapy departments. The study identified 58 original articles and the anatomical location of the larynx was the most common anatomical site evaluated in studies. The values of the loss of therapeutic benefit vary from 1 % to 1.2 % per day and from 12 % to 14 % per week, the proposed dose to compensate for the effect of loss of therapeutic benefit being 0.6–0.8 Gy for each day of radiotherapy postponement. The study by Tarnawski and collaborators proposes a dose-time factor of 0.75 – 0.77 Gy/day. The presumed mechanism involved is the mitotic delay activated if not all clonogens are killed by fractional irradiation. Considering an interval <24 hours as insufficient to overcome mitotic delay, the authors consider that the use of a double daily fraction is not equal in biological effect to the delivery of the lost daily fraction in a day of the weekend. Even if the addition of concurrent chemotherapy brings a benefit in local tumor control equal to that of an additional dose of approximately 7.2 Gy, chemotherapy cannot block accelerated repopulation and fully compensate for the loss of therapeutic benefit. As the study of Budach and collaborators highlights, the therapeutic benefit of concurrent chemotherapy added to the definitive curative irradiation of SCHNC (approximately 12 months and 13 – 15 % in OS at 2 years) is significantly reduced (7.9 months if prolonged total treatment exceeds one week). Ferreira's analysis contradicts data from historical studies according to which the timing of the treatment gap and the sequence of treatment gaps influences OS, but still notes the low probability of accelerated repopulation in the first 2 weeks of treatment (11 – 13).

**GAP compensation – from concept to methods and algorithms**

The calculation of the necessary compensation in case of loss of therapeutic benefit caused by unplanned interruptions in radiotherapy treatment is based on the linear quadratic model (LQ) and Dale`s formalism which incorporates a factor to compensate for the biological effect of accelerated tumor repopulation. The term repopulation is a measure of this effect and is dependent on the K factor, the total duration of treatment and the term TR, which represents the number of days counted from the beginning of treatment to the beginning of accelerated repopulation. In the case of HNSCC, the terms K and TR are estimated at 0.9 Gy/day and 28, respectively (1, 14–15) (formula 1):

$$BED = nD\left(1 + \frac{d}{\left(\frac{\alpha}{\beta}\right)}\right) - K\,(T - T_R) \qquad \text{(formula 1)}$$

BED = biologically effective dose, d = dose per fraction, $\alpha/\beta = 10$ for tumor and 3 for normal tissue, K = repopulation factor (Gy/day), T = total treatment time (days), $T_R$ = repopulation time

The reference course is the prescription of the dose made by the radiation oncologist and approved at the beginning of the treatment (for example 70 Gy in 35 daily fractions, 5 fractions per week, 49 days). Reference biological effective dose is calculated using the LQ model using either the approximate value 10 for $\alpha/\beta$ ratio in the case of tumors and 3 for normal tissues. Another option, much closer to biological tumor reality is the use of estimated value of $\alpha/\beta$ ratio for each tumor type and organs at risks (OARs), values selected from translational or preclinical radiobiology trials. In the case of HNSCC $\alpha/\beta$ ratio is estimated to about 10, but for other

tumor types the ratio values can be 4 or even 2 as in the case of breast cancer and prostate adenocarcinoma. The original phase is considered radiotherapy delivered before the interruption, the interruption phase is the total number of days without treatment and the compensation rate is calculated and proposed by the radiation oncologist and the medical physicist to counteract the effects of accelerated clonogens repopulations.

In clinical practice, 4 compensation methods are agreed:

*1) Simple acceleration* involves the delivery of the compensation phase either by delivering 6 fractions per week or using two fractions per day without changing the initial prescription (total dose and dose per fraction). It should be mentioned that in the case of hypo-fractionated regimens even in moderate variants with higher doses of 2.2 Gy per fraction, this method is not recommended.

*2). Iso-fractionated acceleration* – in which the total dose is escalated keeping the same fractionation regime and the same dose per fraction.

*3) Hypo-fractionated dose escalation* – the variant in which both the fractional dose and the total dose are escalated and the effect is double both by arithmetic summation and by increasing the biological dose by hypo-fractionation. In this situation it is necessary to calculate the tumor dose and the tolerance of organs at risk (OARs) by normalizing the dose to 2Gy (calculation simplified biologically equivalent doses – EQD2) and then summing the values obtained.

*4) Other methods of compensation* – in some situations especially if the tolerance of OARs can be exceeded by escalating doses the compensation can be done by adding to the reference plan an external beam or a brachytherapy boost.

Gay et al evaluates the impact of different scenarios included in the "Lessons Learned from Hurricane Maria in Puerto Rico: Practical Measures to Mitigate the Impact of a Catastrophic Natural Disaster on Radiation Oncology Patients" article published in Practical Radiation Oncology journal 2 years ago. By analogy the COVID-19 pandemic situation could have an impact on radiation oncology services like Hurricane Maria in Puerto Rico through disruption of electrical, medical, communication and transportation services. Beyond the "Prepare, Communicate, Operate, Compensate algorithm", the authors propose recommendations for the management of a gap in radiotherapy treatment of 2 – 3 weeks for different cancer types and clinical settings. In the first scenario a discontinuation of treatment for 2 – 3 weeks after a week of treatment leads to loss of biological effect and the full resumption of a treatment of 60 – 70 Gy from the beginning may be recommended, checking if we are within the dosimetric tolerance limits of OAR's. In the second case where more than one week of treatment have already been administered, the authors recommend the use of accelerated or hypo-fractionated regimens to keep the total treatment time proposed in reference plan. The third imagined scenario is one in which a large majority of treatment has already been administered followed by a few weeks or even months gap in radiotherapy treatment. In this case the authors' recommendation is to re-irradiate with full dose but only on gross tumor disease so as not to compromise the radiosensitive OARs, the alternative being a salvage surgery. In the pandemic context, some authors recommend a moderate hypo-fractionated regimen of 60 Gy in 25 fractions, 5 fractions per week over 5 weeks, using a 2.4 Gy per fraction. The association of a gap due to Sars-Cov-2 infection to a proposed and partially administered hypo-fractionated regimen as a reference plan creates difficulties in the management of compensatory radiation dose supplementation, most of the scenarios being proposed for the standard fractionation reference regimen (70Gy in 35 daily fractions) (14, 16–17).

## Conclusions

An iso-fractionated compensation regimen, considering dose escalation only on gross tumor volume if OARs tolerance is exceeded may be a rational strategy in order to counteract the effect of gaps in radiotherapy treatment for locally advanced HNSCC, if the moderate hypo-fractionated regimen is used as a reference course in a high-risk pandemic COVID-19 context. It is necessary to formulate recommendations that include this scenario of reference hypo-fractionated treatment and treatment gaps due COVID-19 infection. All HNSCC patients experiencing radiotherapy treatment gaps caused by SARS-CoV-2 infection should be treated by IMRT/VMAT techniques to maintain OAR's dose below the tolerance limit in case of compensatory dose escalation.

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