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Review

Deintensification of radiotherapy in oropharyngeal carcinoma of squamous cells.

Deintensificación de la radioterapia en el carcinoma orofaríngeo de células escamosas.

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INTRODUCTION.

The human papilloma virus (HPV) has been associated with oropharyngeal squamous cell carcinoma (OSCC) for 35 years, however there are many characteristics that differentiate both pathologies[1,2] and their prognosis. This opened a line of research to determine the radiosensitivity mechanisms that could be evidenced until recently.[3,4] The American Joint Committee on Cancer (AJCC) has granted a special section for the OSCC VPH$^+$ in its 8th edition of stage classification.

Thus, a tumor earlier predicted as stage IV, for example, is now diagnosed as stage III since stage IV is only reserved for those tumors with metastasis, because it has lost its predictive value for the behavior of the tumor.[5] Nevertheless, the National Comprehensive Cancer Network (NCCN) has basically suggested the same treatment for HPV$^+$ and HPV$^-$ OSCC 6 in its treatment guidelines, as of November 2020.

For its management within clinical trials, radiotherapy (RT) appears as a definitive primary alternative for certain types of HPV$^+$ OSCC due to its radiosensitivity.[7,8] Consequently, deintensified therapy (DI) has been studied as an alternative treatment to reduce the short and long term effects of ionizing radiation.

The objective of this study is to summarize the available evidence regarding protocols that include deintensified radiotherapy as primary therapy for HPV$^+$ OSCC patients, and determine whether a RT/DI regimen improves General survival (GS), Progression-free survival (PFS) and/or Disease-free survival (DFS) of HPV$^+$ OSCC patients in comparison with standard two years of radiotherapy treatment as well as recognizing the type of tumors or HPV$^+$ OSCC patients who would benefit most from RT/DI in their prognosis according to GS, PFS and/or DFS.

MATERIALS AND METHODS.

A systematic search of published and unpublished clinical trials was carried out in the following databases: *CENTRAL*, *clinicaltrials.gov*, *PubMed*, *Web of Science*, *ICTRP*, *Scopus* and *SciELO* between 06/22/2020 and 08/30 /2020 and gray literature was searched on Google Scholar. One hundred and four results were obtained.

Six articles were added by reading other types of articles and their

bibliography. Post elimination of duplicates, inclusion and exclusion criteria were applied.

RESULTS.

Two randomized clinical trials (RCTs) met all inclusion criteria. Trial NRG-HN002 is open-labeled, in phase II and has been completed, and trial Quarterback is single-blinded, in phase III and has not been completed, but shows partial results at 2 years of its start, (Table 1).

Randomized clinical trial NRG-HN002 is a multi-center phase II trial comparing DI/RT *versus* DI/QRT, with weekly cisplatin intake. The 306 patients were recruited with the above criteria and stratified accordingly for unilateral or bilateral radiation.

After this classification, 157 randomly participated in Arm 1, with DI/RT of 60 Gy with 6 weeks of 40 mg/m^2 of weekly cisplatin intake and 149 patients participated in Arm 2, with 60 Gy DI/RT administered for 5 weeks. The PFS for Arm 1 patients was 90.5%, meeting predefined study parameters, while for Arm 2 patients, PFS was 87.6%, not meeting acceptability parameters. GS was similar for patients in both arms and met acceptability parameters.[9]

The Quarterback RCT is a multicenter phase III trial that compares DI/QRT with standard QRT after the use of chemotherapy in patients who had a good or partial response to it. Chemotherapy was applied in 3 cycles with TPF. Patients who fully or partially responded to this protocol received 56 Gy or 70 Gy weekly doses of carboplatin, randomized 2:1 in both arms, respectively. Patients who did not respond were treated with conventional therapy. For Arm 1, 12 patients were selected and for Arm 2, eight patients were selected. The remaining six patients, were treated with conventional therapy.

The primary objective was to obtain the same DFS at three years in both arms.[10] In 2017 partial results were presented; at that moment the DFS at 2 years of the start of the study for the control group (Arm 2) was 87.5% *versus* 83.3% for the DI therapy (Arm 1).[8]

Table 1. Randomized clinical trials included in the review.

Numbers of registers and other names	NCT02254278/ NRG-HN002[9]	NCT01706939/ Quarterback[10]
Trial start year	01/10/2014	15/10/2012
State	Active, not recruiting	Active, not recruiting
Type of intervention	RCT	RCT
Phase	II	III
Model of intervention	Parallel assignment, open tag	Parallel assignment, open tag
Number of patients recruited as of 10/10/2020	306	23
Stage of recruited patients	OSCC HPV+, Stage I y II (AJCC 7th edition)	OSCC HPV+, Stage III y IV, with M0 HPV+ (AJCC 7th edition)
VPH+ status determination method	p16 IHC	p16 IHC and HPV E6/E7-PCR
ECOG or Zubrod score required	Zubrod 0-1	ECOG 0-1
Packs/year of cigarettes allowed	≤10 packs/per year ≤20 packs/per year	
Study design	**a: Arm 1:** IMRT DI of 60 Gy with weekly Cisplatin **b: Arm 2:** IMRT DI of 60 Gy	**Chemotherapy:** 3 cycles of docetaxel, cisplatin, fluorouracil (TPF) for patients with good and bad partial responds to them, randomly in 2:1: **a: Arm 1:** IMRT DI of 56 Gy with weekly carboplatin **b. Arm 2:** standard IMRT of 70 Gy with weekly carboplatin. For patients that show no responds, standard QRT or surgery.
Results	PFS at 2 years for arm 1: 90.5% PFS at 2 years for arm 2: 87.6% GS at 2 years for arm 1: 97.6% GS at 2 years for arm 2: 97.3%	DFS at two years for arm 1: 83.3% DFS at two years for arm 2: 87.5%[8]

RCT: Randomized Clinical Trial. OSSC: Oral Squamous Sell Sarcinoma. PFS: Progression-free survival. DFS: Disease-Free Survival. IMRT: Intensity-Modulated Radiation Therapy. CRT: Chemoradiotherapy. ECOG: Eastern Cooperative Oncology Group.

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Another RCT was found that met all inclusion criteria, but it is still an ongoing trial. It is the MR-ADAPTOR (NCT03224000), which plans, through individual control with weekly magnetic resonance imaging, to administer individualized CRT doses according to the response obtained. It is in phase II and the results are expected by November 2025.

Twenty-three studies were excluded for not meeting one or more inclusion criteria. Of the included studies, the bias due to randomization is medium for Quarterback, since after chemotherapy, patients with partial or complete response were randomly divided in a 2:1 ratio for the first two arms of the study.

The NRG-HN002 study only used the p16 IHC as an exam when recruiting patients. The reviewers were unable to identify any of the studies that presented deviations from the initial intervention, bias in the outcome measurement, or in the selection of the outcome report.

DISCUSSION.

There is not enough evidence to determine which type of patient responds better to RT/DI. The studies should be randomized controlled trials, multicenter and report standardized data to allow for an adequate comparison. RT/DI should remain part of clinical trials, but targeted at the right patients. Based on the trials described, it would be worthwhile to consider HPV^+ OSCC patients as those p16 and HPV-DNA positive. Also, it would be adequate to include patients with AJCC-7^{th} edition stage I and II tumors and look further into chemotherapy studies with RT/DI for those patients who have complete or partial response.

The most widely used virus detection method today is the p16 IHC. Due to its clear advantages, such as its simplicity, low cost, and viability, it has proven to be a valid diagnostic test in the cervix; however, in OSCC it is associated with several problems, even for experienced histopathologists. Despite these limitations, particularly its low specificity, p16 expression is the adequate criterion used for patient recruitment in the original prospective DI treatment trials and is recognized as valid for evaluating HPV-related carcinogenesis in OSCC patients by the AJCC.[5]

Qureishi *et al.*,[12] use a step-by-step algorithm by combining different detection methods: p16 *Immunohistochemistry* (IHC) staining and HPV DNA *in situ* hybridization (ISH). This algorithm provides the most accurate approach to deciphering the presence of integrated and transcriptionally active viruses in formalin-fixed paraffin-embedded samples.

The combination of tests is key for a correct diagnosis. Of the included trials that were analyzed, 1 of 2 used p16 IHC only as a sufficient inclusion criterion. It was not possible to find the number of patients who were recruited only with that criterion.[9]

The results cannot be compared because the studies had a different design. Despite the excellent prognosis presented in the Quarterback trial, HPV^+ OSCC patients experienced toxicities similar to those with HPV- OSCC, thus DI of RT is encouraged in order to reduce toxicity without compromising tumor control.

In contrast, the experimental arm of the NRG-HN002 trial failed to meet the minimum acceptability criteria for DFS, leading to the conclusion that chemoradiotherapy has greater benefits than RT alone. The TNM scoring provides a framework for treatment design and decision, however treatment guidelines are still based on the 7^{th} edition classification until alternative treatments are validated. As for OSCC, the classification has different criteria for clinical and pathological stages.

Due to this, different survival curves have appeared, making it difficult to select the patient for DI therapies. Other factors to consider include resection margins, prior RT dose in case of recurrence, systemic treatment mode, age, cigarette packs smoked per year, and socioeconomic status. It has not been possible to establish the existence of a premalignant lesion.[13]

Considering the variables of patients and their environment, HPV^+ patients turn out to be younger and have a higher socioeconomic status than HPV^- patients, added to this, these patients often do not use tobacco or alcohol or have a reduced intake. These factors are favorable for many head and neck cancers. The risky sexual practices of younger patients could be the cause of the upward trend in the incidence rate of cancers in this area. Since Zur Hausen in 1983 confirmed the association between HPV and cervical carcinoma, the race to fight this disease began.

This is why public health as primary prevention of-

fers health promotion, responsible sexual practices and the vaccine as specific protection. As secondary prevention, the Pap smear and the tests to detect HPV in OSCC are available. No studies on the prevalence of HPV infection in Chile were found.

CONCLUSION.

The Chilean national vaccine plan included the HPV vaccine in 4th grade girls (9-10 years old) in 2014, and the second dose for 5th grade girls. The Advisory Committee on Vaccines and Immunization Strategies (CAVEI, for its acronym in Spanish) added boys in the second half of 2019, where it was expected to vaccinate a total of 130,000 boys and girls in 4th grade (9-10 years).[14]

From the 2019 National Youth Survey, carried out throughout Chile, it can be deduced that young people in our country have risk factors for HPV infection, such as early start of sexual activity, number of sexual partners and low adherence to the use of contraceptive methods that prevent sexual transmitted infections. The adolescents do not have information about HPV and that it is a sexually transmitted virus.[15]

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