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CONTROVERSIES IN PATIENTS WITH HEAD AND NECK TUMOURS UNDERGOING RADIOTHERAPY: THE NEED FOR ADAPTIVE RADIOTHERAPY

Egilea /Autor:
ANGÉLICA MOLINILLO MARÍN
Zuzendaria / Director/a:
JON CACICEDO FERNÁNDEZ DE BOBADILLA

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ABSTRACT

El tratamiento de los tumores de cabeza y cuello se basa en la cirugía, la radioterapia y la quimioterapia. La elección de cada uno de ellos o de su combinación depende de la etapa en la que se encuentre el tumor: en tumores en estadios precoces, la radioterapia y la cirugía obtienen resultados similares y ambos son de elección mientras que en estadios avanzados se suelen combinar los tres tratamientos mencionados.

En lo que al uso de la radioterapia se refiere, su mayor desventaja se basa en la posible radiación de los tejidos sanos, como por ejemplo las glándulas parótidas. Los pacientes con tumores de cabeza y cuello padecen mucositis y disfagia siendo más susceptibles a presentar cambios anatómicos durante el tratamiento de radioterapia (que puede durar entre 6-7 semanas), debido a su pérdida de peso o a los cambios en el tamaño tumoral. Esto hace que la dosis de radiación recibida por los tejidos tanto tumorales como sanos, sea diferente a la inicialmente planificada, lo que aumenta el riesgo de aparición de efectos adversos como la xerostomía (por aumento en la dosis recibida por las parótidas). La única manera de compensar los cambios anatómicos es volver a realizar la planificación del tratamiento de radioterapia, denominado radioterapia adaptativa.

El presente estudio retrospectivo ha incluido 85 pacientes consecutivos con tumores localmente avanzados de cabeza y cuello que han recibido cirugía ± radioterapia postoperatoria o tratamiento con radio-quimioterapia con intención radical. Se ha analizado cuáles son los factores predisponentes que ocasionan cambios anatómicos durante la radioterapia provocando una desviación de la dosis recibida por los tejidos sanos peritumorales. Según los resultados, los pacientes que pierden peso corporal durante la radioterapia (especialmente >5%) o que reciben quimioterapia concomitante son altamente susceptibles de precisar radioterapia adaptativa y precisan por tanto, seguimiento cercano para su detección precoz y disminuir los efectos secundarios de la radioterapia.

Palabras clave: *tumores de cabeza y cuello, radioterapia adaptativa, glándulas parótidas, xerostomía, pérdida de peso, quimioterapia concomitante.*

The treatment of head and neck tumours is based on surgery, radiotherapy and chemotherapy. The choice of each of them or their combination depends on the stage of the tumour: in early stage tumours, radiotherapy and surgery obtain similar results and both are valid, while in advanced stages all the mentioned treatments are usually combined.

As far as the use of radiotherapy is concerned, its major disadvantage is based on the possible radiation of healthy tissues, such as the parotid glands. Patients with head and neck tumours suffer from mucositis and dysphagia and are more susceptible to anatomical changes during radiotherapy treatment (which may last 6-7 weeks), due to weight loss or changes in tumour size. This causes the radiation dose received by both tumour and healthy tissues to be different from that initially planned, which increases the risk of adverse effects such as xerostomia (due to an increase in the dose received by the parotid glands). The only way to compensate for the anatomical changes is to re-plan the radiotherapy treatment, a process which is called adaptive radiotherapy.

The present retrospective study included 85 consecutive patients with locally advanced head and neck tumours, who received surgery ± postoperative radiotherapy or radio-chemotherapy treatment with radical intent. The predisposing factors that cause anatomical changes during radiotherapy leading to a deviation of the dose received by healthy peritumoral tissues were analysed. According to the results, patients who lose weight during radiotherapy (especially >5%) or who receive concomitant chemotherapy are highly susceptible to require adaptive radiotherapy and therefore require close follow-up for early detection and to reduce the side effects of radiotherapy.

Key words: *head and neck tumours, adaptive radiotherapy, parotid glands, xerostomia, weight loss, concomitant chemotherapy.*

Buruko eta lepoko tumoreen tratamendua kirurgian, erradioterapian eta kimioterapian oinarritzen da. Horietako bakoitza edo haien konbinazioa tumorea zein etapatan dagoen araberakoa izango da: estadio goiztiarretako tumoreetan, erradioterapiak eta kirurgiak antzeko emaitzak lortzen dituzte, eta biak dira hautazkoak; estadio aurreratuetan, berriz, aipatutako hiru tratamenduak konbinatzen dira.

Erradioterapiari dagokionez, desabantailarik handiena ehun osasuntsuen erradiazioan oinarritzen da, hala nola guruin parotidoetan. Buruko eta lepoko tumoreak dituzten pazienteek mukositisa eta disfagia izaten dituzte, eta erradioterapia-tratamenduan (6-7 aste iraun dezake) aldaketa anatomikoak izateko joera handiagoa izaten dute, pisua galtzeagatik edo tumore-tamaina aldatzeagatik. Hori dela eta, ehunek, hala tumore-ehunek nola ehun osasuntsuek, jasotzen duten erradiazioa hasieran planifikatutakoa ez bezalakoa da, eta horrek areagotu egiten du kontrako efektuak agertzeko arriskua, hala nola xerostomia (parotidek jasotako dosia handitzeagatik). Aldaketa anatomikoak konpentsatzeko modu bakarra erradioterapia-tratamenduaren planifikazioa berriro egitea da, erradioterapia moldakorra izenekoa.

Azterlan honetan, 85 paziente hartu dira, buruko eta lepoko tumore aurreratuak dituztenak, ebakuntza ondoko kirurgia ± erradioterapia jaso dutenak edo asmo erradikaleko erradioterapia-kimioterapiako tratamendua jaso dutenak. Erradioterapian aldaketa anatomikoak eragiten dituzten faktore iragarleak zein diren aztertu da, tumorearen hurbil dauden ehun osasuntsuek jasotako dosia desbideratzen dutenak. Emaitzen arabera, erradioterapian gorputz-pisua galtzen duten pazienteak (>5% batez ere) edo aldi berean kimioterapia jasotzen duten pazienteak erradioterapia moldakorra jasotzeko behar handiagoa dute. Ondorioz, hurbileko segimendua behar dute faktore iragarleak garaiz antzemateko eta erradioterapiaren albo-ondorioak murrizteko.

Hitz gakoak: *buruko eta lepoko tumoreak, erradioterapia moldakorra, guruin parotidak, xerostomia, gorputz pisuaren galera, aldi bereko kimioterapia.*

1. INTRODUCTION

1.1. RELEVANCE OF HEAD AND NECK TUMOURS

The term head and neck tumour alludes to a series of malignant processes located in the paranasal sinuses, nasopharynx, oropharynx, hypopharynx, larynx, oral cavity, tongue and salivary glands.

Overall, they constitute a non usual group (approximately 5% of the tumours). However, they are responsible of more than 330.00 deaths annually (1). They occur more frequently in men, but during the last decades, there has been an increase in their appearance in women due to an increment in their smoking habit (2). Furthermore, not only smoking can lead to these kind of tumours, but also alcohol consumption, human papillomavirus infection (HPV) and Epstein Barr virus infection (EBV) (3). Regarding to these risking factors, some considerations should be taken into account:

- Heavy smokers present a 5 to 25 fold increased risk of cancer compared with nonsmokers. Nevertheless, the risk of developing cancer does not only depend on the amount of tobacco consumed as exposure can also be a contributing factor (4).
- Alcohol consumption increases the risk of head and neck tumours, but it is difficult to assess this effect since alcohol intake is frequently associated with tobacco use (5). Multiple types of viral infection are associated with these tumours, such as EBV and HPV. More specifically, epidemiologic and genetic evidence has been found relating HPV (6) with the development of head and neck cancer, especially type 16.
- Other risk factors are associated with this kind of neoplasm: genetic factors, diet, mouthwash, immunodeficiency, hepatitis C virus infection, betel nut chewing and occupational exposure (2).

1.2. GENERAL TREATMENT OF HEAD AND NECK CANCERS

Referring to the treatment of head and neck tumours, an important aspect to consider is that it is based on three fundamental (7) pillars (surgery, radiotherapy and chemotherapy) and that a multidisciplinary approach is required for optimal decision

making. Surgery is considered the basic treatment for tumours in early stages. In advanced stages, however, it is used in those which are still resectable. For its part, radiotherapy is utilized both (8) radically and as an adjuvant therapy. In the case of chemotherapy, it can be used before radiotherapy or surgery, so called induction chemotherapy or it can also be used together with radiotherapy (known as concomitant (9)chemotherapy approach), Finally, it can be used after radiotherapy (adjuvant setting) in some tumour locations (nasopharyngeal tumours, for instance).

1.2.1. **Early stage disease**

In general, these patients are treated either with surgery or radiotherapy. Concerning the choice between the use of radiotherapy or surgery, knowing that both have similar (10)effects on the local control and survival, it is based upon the specific site and its requirements, the surgical accessibility of the tumour and the morbidity and mortality associated with each modality. Oral cavity cancers are worth mentioning, as they constitute an exception, since they are best treated with surgery (11) due to better cure rates and toxicity.

1.2.2. **Locoregionally advanced disease**

Locoregionally advanced head and neck tumours are associated with a higher risk of distant metastases and recurrence. As a consequence of the foregoing, it is generally necessary to combine (12)surgery, radiotherapy and chemotherapy.

Nor should it be forgotten the fact that it is frequently necessary to treat the cervical lymph nodes since these carcinomas tend to metastasize them. Patients whose cervical lymph nodes are affected at diagnosis, are treated with lymph node dissection, radical radiotherapy or chemotherapy or a combination of surgery plus postoperative radiotherapy (12).

1.3. **IMPORTANCE OF RADIOTHERAPY**

In the previous section, in which the different treatment options have been discussed, the importance of the radiotherapy is reflected. Generally, radiotherapy is an important and potentially curative modality for head and neck cancers (13).

1.4. **RADIATION THERAPY TREATMENT PROCESS**

The steps set forth herein are those which are normally followed when a patient is undergoing a radiotherapy treatment.

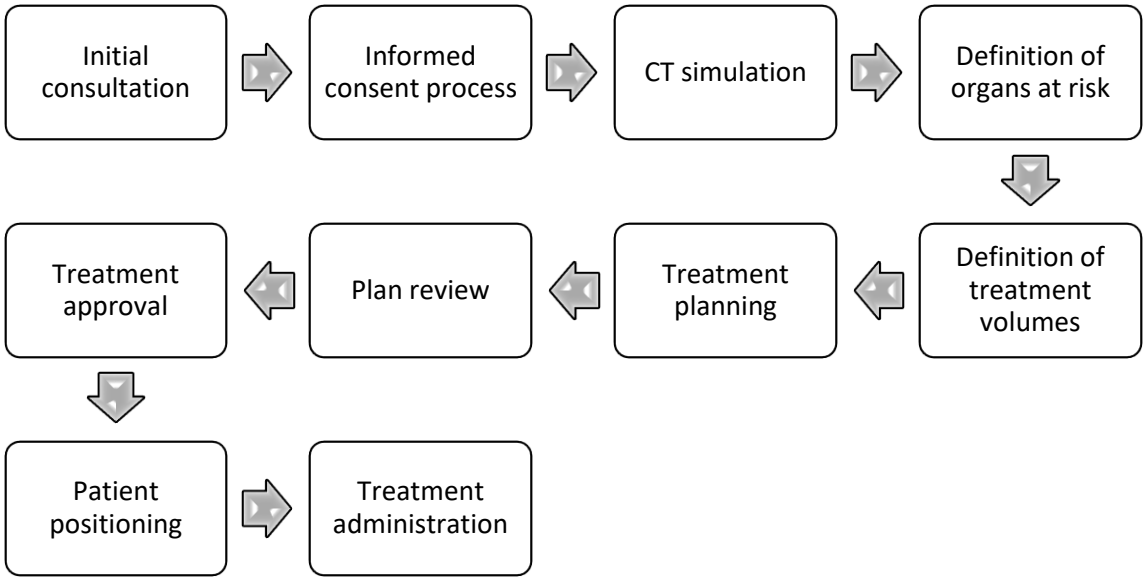

Figure 1. Steps carried out in the radiotherapy treatment process

Next, all the steps will be described:

1. **Initial consultation.** The main objective of this initial consultation is to get in touch with the patients, in order to resolve their doubts about the type of radiotherapy they are going to receive or about the treatment plan. During the visit, a complete physical examination is performed by the corresponding radiation-oncologist. In addition, the patient's medical history is reviewed (14).

2. **Informed Consent Process** Once it is decided that radiotherapy will be part of the patient's treatment, the patient is informed about any possible complication or side effect of such therapy. All the questions and concerns regarding the treatment and prognosis of the disease are widely answered. When the patients completely understand the proposed treatment, the possible risks and side effects, they are asked to sign a consent form (15)**.**

3. **CT simulation.** Before starting the radiotherapy, there is a planning process known as simulation. With the simulation it is possible to determine the part of the body that should receive the radiation. In order to do this, the patient is placed in a specific position, which is the same position in which he will receive all the radiotherapy sessions (15).

A computed tomography (CT) scan of the region to be treated is done. In the case of head and neck tumours a CT from the base of the skull to the clavicles is performed with the patient immobilized with a thermoplastic mask in supine position (***see* Figure *2***) With the information obtained from the CT, it is possible to manually design by the radiation oncologist, the organs at risk and target volumes (primary tumour + pathologic lymph nodes), generating "a kind of map", in which, by colours, the areas are marked according to the amount of radiation that must reach them (***see* Figure *3***).

Figure 2. The patient is immobilized with a thermoplastic mask in supine position.

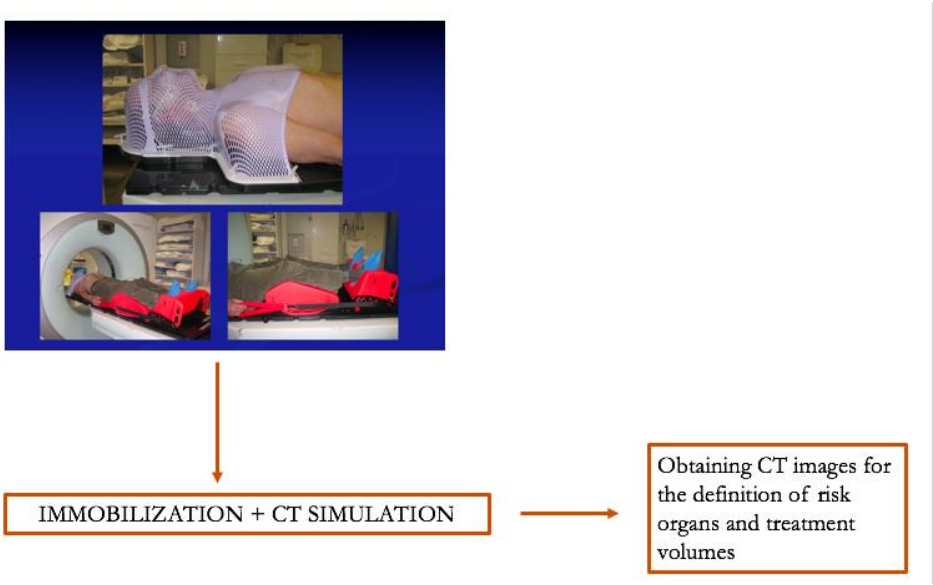

Figure 3. After the immobilization of the patient CT images are obtained. These images help to define the treatment volumes and the organs at risk.

4. Definition of organs at risk. All healthy organs near the tumour, in which it is necessary to limit the radiation dose in order to reduce secondary effects, are outlined on the planning CT images (***see Figure 4)***

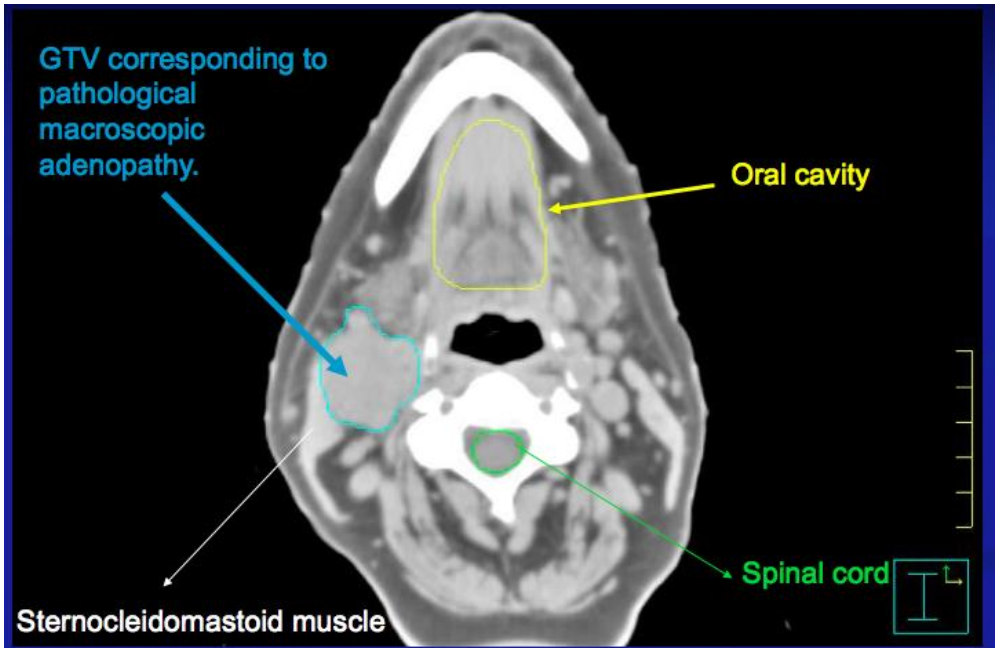

Figure 4. The treatment volumes must be defined (GTV in this case) as well as the surrounding healthy structures (namely parotids, spinal cord, oral cavity, pharyngeal constrictor muscle and submandibular gland).

5. Definition of treatment volumes (16)**.** The treatment volumes are defined on the planning CT images. These volumes can include the primary tumour, macroscopic lymph nodes, tumour bed (in operated patients) or areas at risk of microscopic extension of regional nodal drainage. For this purpose, in addition to the planning CT images, image fusion protocols can be used (associating the CT images with the ones obtained from other image techniques such as PET-CT or magnetic resonance imaging (MRI)). Furthermore, both the dose that the tumour should receive and the one that the nearby organs at risk should not exceed, are strictly defined.

The radiation dose that is prescribed to treat the tumour is defined according to the following international volume defining criteria (known as ICRU (17) nomenclature):

- GTV (Gross Target Volume): this acronym makes reference to the macroscopic extension of the tumour and the lymph nodes. This volume can be delimited in various ways, depending on the physical examination of the patient and the available neuroimaging techniques (CT, MRI or PET-CT) (**Figure 5.**).

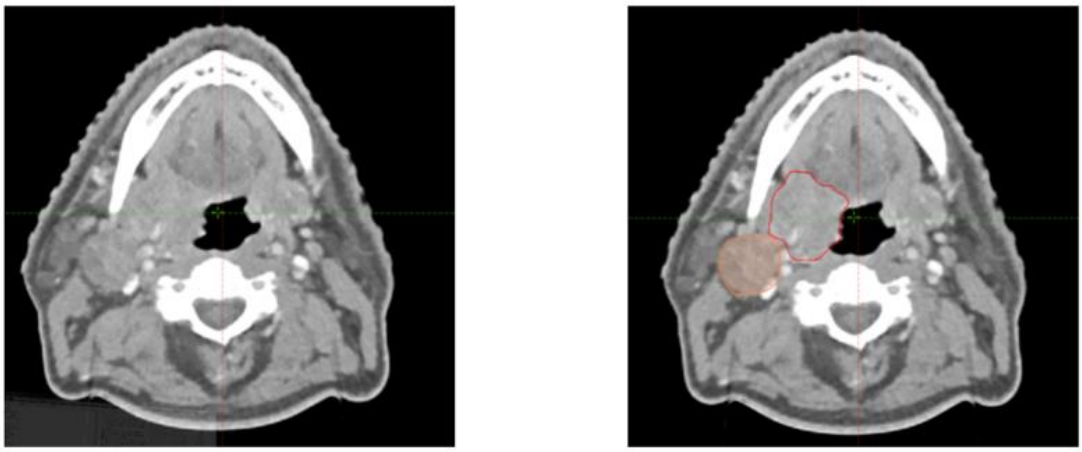

Figure 5. Axial CT simulation slide (left) and GTV of the tumour (red colour) and lymph nodes (orange colour) manually delineated by the radiation oncologist (right).

- CTV (Clinical Target Volume): the CTV includes an additional margin (18)(usually between 5 to 10mm) around to the GTV volume in order to include

the microscopic extension of the tumour and the lymph nodes. The delimitation of this volume depends on the behaviour of each cancer (**see Figure 6**).

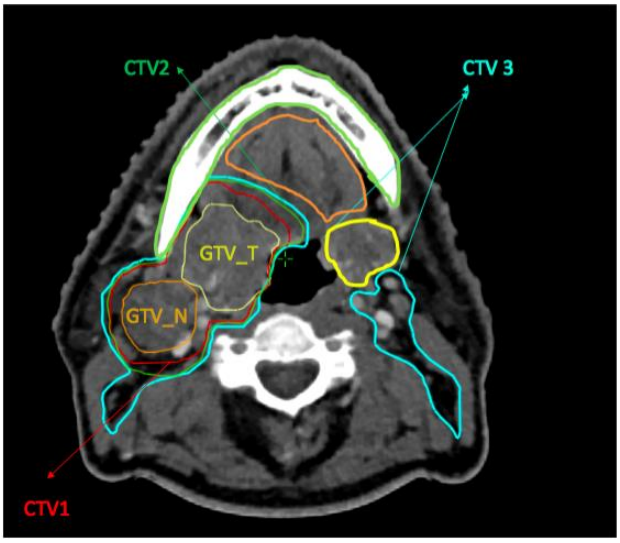

Figure 6. The CTV includes the GTV and a geometrical area around it so the microscopic extension of the tumour is encompassed.

- It needs to be taken into consideration that in the case of patients who are undergoing adjuvant radiotherapy treatment after surgery, there is no GTV because it has been previously removed during the surgery. Therefore, a CTV is directly delineated corresponding to the tumour bed (**see Figure 7**).

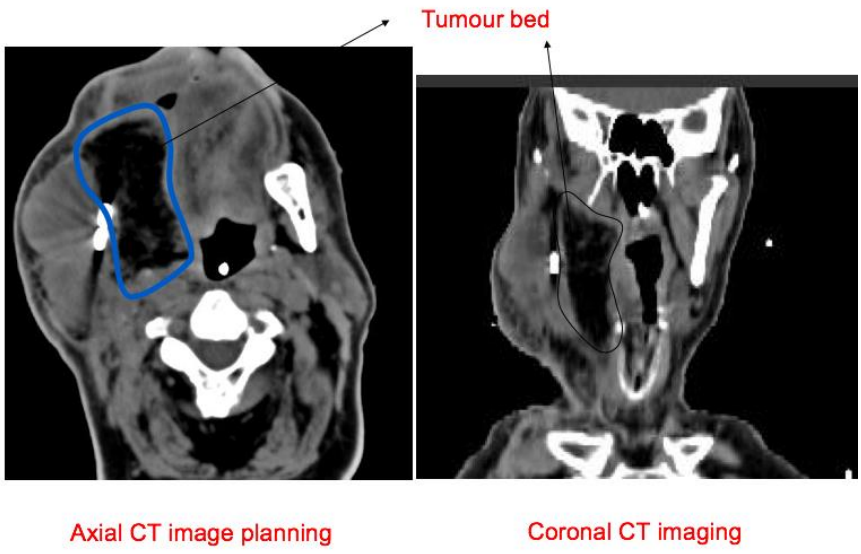

Figure 7. The CTV is delineated corresponding to the tumour bed in an operated patient.

- ITV (Internal Target Volume): the ITV includes the volume which is occupied by the tumour movements. Nevertheless, this volume is not always relevant, as in head and neck tumours, since the cranial cavity is a rigid structure that it is not influenced by the respiratory movements.
- PTV (Planning Treatment Volume): it is similar to the CTV, although PTV may be bigger as it includes areas that can not be prevented from being radiated to ensure that the entire CTV receives the optimal dose. (18) Furthermore, PTV is a geometrical automated margin (between 3-4mm) around each CTV to ensure that the CTV is not undertreated due to variability in positioning and taking into account that adjacent structures do not receive toxic doses.

6. Treatment planning. The treatment is designed and planned using different calculous. After the definition of the target volume and the organs at risk, the planning of the isodose curves is carried out by the physicists (**see Figure *8***). The isodose curves are a visual representation of the dose that will be administered in that region of the body. Therefore, through this process the dose administered to the tumour and to the surrounding healthy tissues is also calculated.

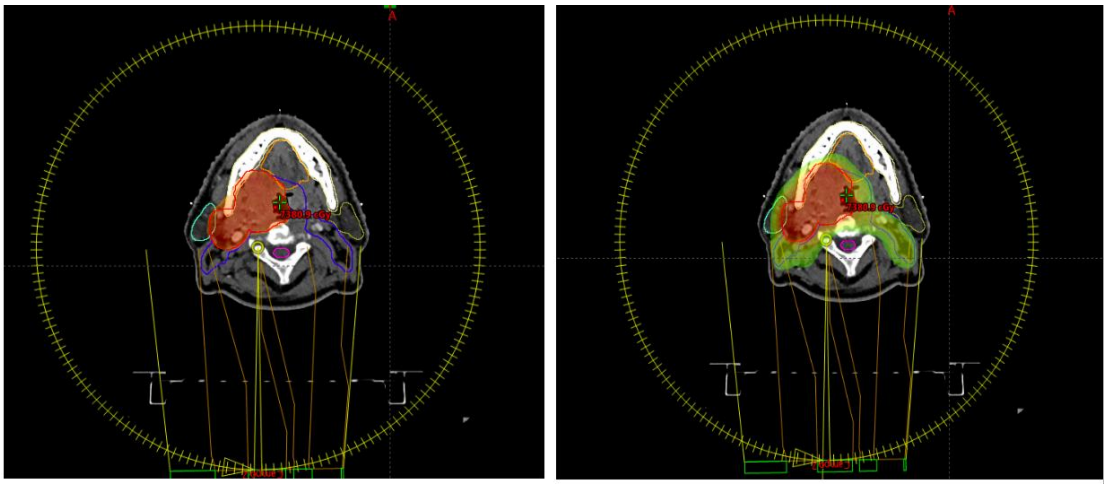

Figure 8. Dose distribution on GTV (red) and on the rest of the neck structures (yellow). Each colour represents an isodose curve that corresponds to a specific dose and therefore to the number of radiotherapy sessions that will be administered. In this case, red means 70Gy and yellow means 50Gy.

7. Plan review. The treatment plan is jointly reviewed together with the radiation oncologist and physicist to confirm that the parameters required have been met. This stage also includes the objective of finding, if possible, improvements in the plan by providing clinical and physical points of view. Once reviewed, quality controls are carried out to verify that the treatment is reproducible in the linear accelerator.

8. Treatment approval. The treatment plan is verified and the patient is informed.

9. Patient positioning (for each radiotherapy session). The patient is positioned as it was done in the planning CT scan. A daily image control is performed (known as cone beam computed tomography (CBCT) before radiotherapy treatment is administered) to verify that the patient is correctly positioned, that the tumour volume is included in the treatment planning and that the organs at risk are not close to the high-dose areas. If everything is correct, the first session is administered.

10. Treatment administration. Radiotherapy technicians perform daily or weekly images, prior to the treatment sessions, to check that the patient positioning is correct. Once the potion is verified, the treatment is administered.

During treatment, patients are assessed at least once a week by the nursing staff and periodically by doctors in order to control treatment's tolerance and possible secondary effects.

Therefore, and as it has been seen, radiotherapy is a frequently used treatment technique for head and neck tumours including very standardized specific steps that should always be followed.

1.5. ADAPTIVE RADIOTHERAPY

However, as with other pathologies, using radiotherapy may involve irradiation of healthy tissues, such as parotid glands (19). It ought to be taken into consideration that patients with head and neck cancers are more liable to morphological changes throughout treatment, due to weight loss or a decrease in tumour size, which causes the dose received by the various structures possibly differ from the one originally planned (20). These dose deviations are generally more important in the organs at risk. This means that the original dose calculated might not be the real dose administered to some structures due to anatomical changes that occur during the several weeks that

the patient is receiving radiotherapy. Below (***see* Figure 9***)*, the image on the left corresponds to the parotid glands of a patient before starting radiotherapy treatment. The image on the right corresponds to the same patient after significant weight loss and after treatment. The structural change undergone by the parotids can be seen, which leads to an alteration in the radiation dose received by the glands.

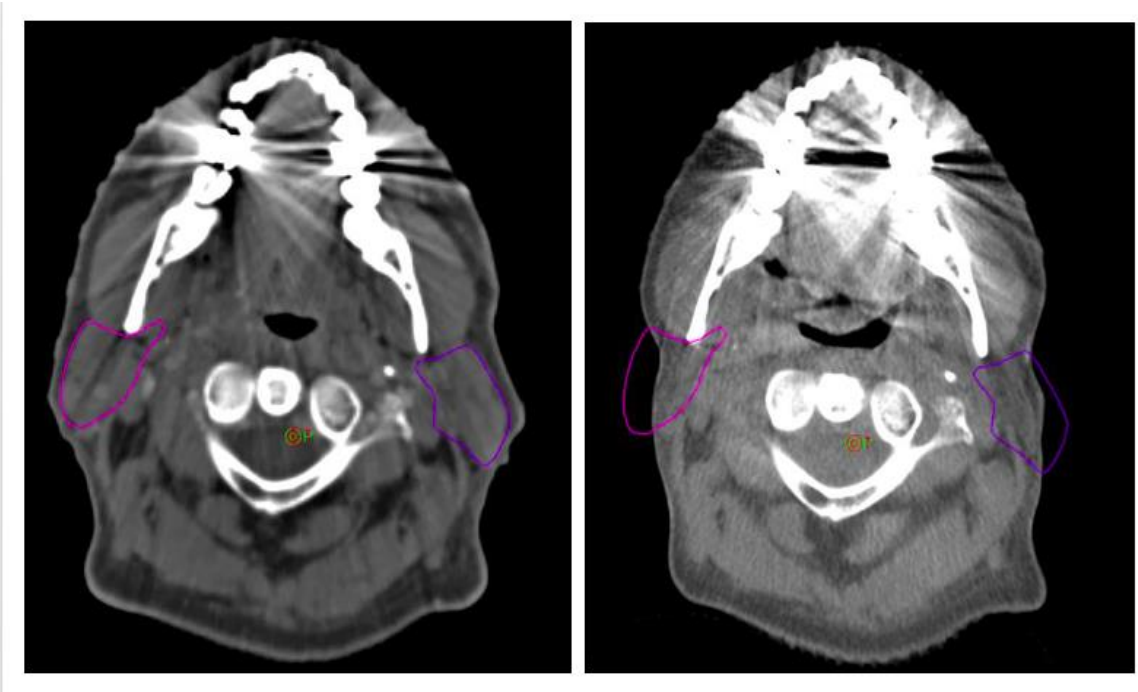

Figure 9. Parotid glands before starting radiotherapy treatment, in the planning CT (left). Parotid glands after significant patient weight loss and after receiving radiation (right).

If what aforementioned comes about, it might be necessary to re-plan the patient and to correct the deviation (21), which leads to the mobilization of both human and time resources. What is more, the decision of re-planning is generally made late, when anatomical changes already occurred, what occasionally brings the administration of several fractions of the treatment with a suboptimal planning until the preparation of a new one. In consequence, the quality of the treatment and its effectiveness depends on being able to anticipate whether a patient might need to be re- planned or not.

For all of the above-mentioned, numerous studies, such as the one conducted by the University of California in 2006 (22), suggest the need for repeated CT imaging and replanning during the treatment of selected patients with head and neck tumors. This

is essential to identify dosimetric changes and to ensure adequate doses to target volumes and safe doses to normal tissues.

In summary, the steps to be carried out are the following (**see Figure *10)***:

- After the initial consultation, a planning CT is carried through so the treatment volumes are obtained and the risk organs are defined. After verifying them, the treatment is started.
- Every day that the patient receives treatment, a pre-treatment imaging test is performed (so called CBCT: Cone Been Computed Tomography). The main objective is to detect through these imaging tests anatomical changes that may have dosimetric repercussions.
- Next, a fusion is made between the CBCT and the planning CT to detect possible anatomical changes.
- In the case that the anatomical alteration has an impact on the dose, the solution is to implement adaptive radiotherapy.

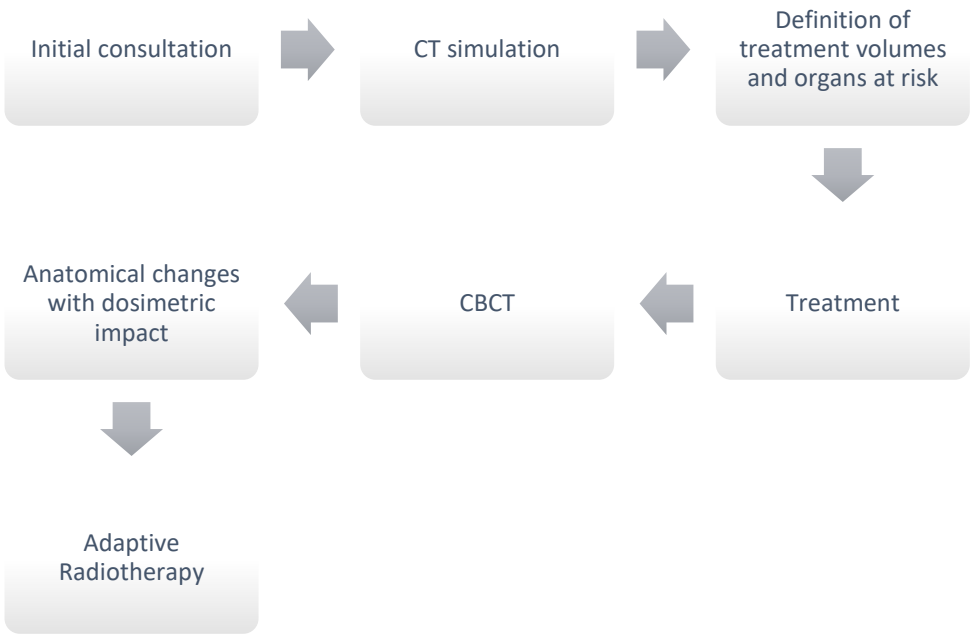

Figure 10. Steps that should be followed to implement adaptive radiotherapy.

Thus, adaptive replanning can be used to improve the accuracy of treatment when there have been significant anatomic changes due to patient weight loss, tumor shrinkage or normal tissue change. In the case of the salivary glands, adaptive radiotherapy may improve salivary sparing (in order to reduce xerostomia), as they often shift medially and reduce their volume during the course of treatment.

2. OBJECTIVES

The proposed objectives of the present study are the following:

- To study the volume variation in the parotid glands throughout the treatment and to try to relate this variation to some dosimetric indicator.
- To study if it is possible to define simple predictors that could indicate the probability of a patient being re-planned.

3. MATERIALS AND METHODS

3.1. PATIENTS ASSESSMENT

As previously stated, when a patient is undergoing radiotherapy treatment, a series of steps are carried out. After an initial consultation in which a clinical interview and physical examination are performed, the planning process commences. In this planning process, patients are immobilized with a thermoplastic mask while a CT scan, from the base of the skull to the clavicles, is performed. With the image obtained, the organs at risk and the treatment volumes can begin to be defined. Once designed, treatment begins (usually lasting 30-35 days in total during 6-7 weeks). As long as treatment takes place, patients are assessed by both medical staff and nursing staff (at least once a week) to check the treatment tolerance and possible secondary effects. Thus, it is possible to know if the patients are tolerating the treatment, the adverse effects that may be appearing, as well as to monitor aspects such as their weight loss.

Nevertheless, anatomical changes in the patient may emerge during treatment. These changes might cause the dose that the tissues are receiving to be different from the one that was originally planned. Consequently, the risk of treatment-related adverse

effects, such as xerostomia, increases. This is the main reason why the need for early detection of structural changes arises.

For this purpose, CBCT is performed before each session. Hence, if significant changes are detected, the dose reaching the tissues can be calculated and replanned, if necessary, reducing the risk of the appearance of secondary effects such as xerostomia.

3.1.1. **Study variables**

In this study, several variables have been evaluated to try to determine which ones influence the anatomical changes presented by the patients, and therefore in the need of replanning. The variables studied were as follows:

- Number of sessions received by the patient (total dose administered)
- Tumour location (options: paranasal sinuses, salivary glands, larynx, hypopharynx, oropharynx, nasopharynx, oral cavity or unknown).
- Type of treatment (it can be postoperative or radical)
- If the treatment has been bilateral neck radiotherapy or not
- Concomitant chemotherapy administered or not
- Weight at first visit
- Weight in the first week
- Weight in the second week
- Weight in the third week
- Weight in the fourth week
- Weight the fifth week
- Parotid anatomic volume modifications according to the daily CBCT

3.2. **ANATOMICAL CHANGE IMPACT MEASUREMENT**

In order to know whether or not there are variations in the size of the parotid glands, the CBCT can be used. Through it, the temporal evolution of the structures of interest and their structural changes can be observed.

The use of CBCT is based on carrying out a deformable registration together with the planning CT, during each treatment session. In this way, the CBCT is fused with the planning CT, after which a deformable registration is performed and the deformed structures are transferred from the CT to the CBCT.

3.3. **STATISTIC ANALYSIS**

Continuous variables have been expressed as median and range, while categorical variables are presented as frequencies and percentages. The correlation between the following variables and the need for replanning was studied: administration of concomitant chemotherapy (yes/no) with radiotherapy, anatomical location of the primary tumour, weight loss during radiotherapy, elapsed time (in days) between the planning CT scan and the start of treatment and the administered radiation dose to the left and right parotid glands, including their volumes.

The statistical tests used were as follows:

- To determine whether two distributions are significantly different, the **Student's T test** was used with unpaired samples.
- **Spearman's correlation test** was used to study the possible bivariate correlations between the different variables. Spearman's correlation coefficient (rS) is a non-parametric measure of rank correlation. Furthermore, and unlike Pearson's correlation test which imposes a linear relation between the two variables, Spearman's correlation test only requires the relationship between the two variables to be monotonous.

The result was considered significant with a **p value <0.05.** The data were analysed using *Statistical Package for the Social Sciences (SPSS, version 23.0).*

4. RESULTS

4.1. **DESCRIPTION OF THE RESULTS**

In order to carry out the corresponding study, a sample of 85 consecutive patients was selected and the records were included in a prospective base data at the department of radiation oncology. Next, we retrospectively analysed the data regarding the need of

replanning. In relation to the number of variables studied, these were a total of 5 (the use of concomitant chemotherapy with radiotherapy, weight loss during treatment, anatomical location of the primary tumour, elapsed time between the planning CT and the start of treatment and the administered radiation dose to the left and right parotid glands, including their volumes). In the following paragraphs the characteristics of the sample and the variables mentioned are going to be explained.

4.1.1. **Sample characteristics**

A sample was selected with a total of 85 patients with locally advanced head and neck tumours **(from September 2019 to January 2021)** of whom a total of 50 (i.e., 58.8%) received radiotherapy with radical intent and 35 (i.e., 41.2%) postoperative radiotherapy.

It should be taken into consideration that the objective was to know how many of these patients had required replanning during treatment, due to anatomical changes produced during the course of treatment. Of the 85 patients studied, 45 (i.e., 52.9%) had to be replanned, compared to 40 in whom no changes were made (i.e., 47.1% of the patients were not replanned). Therefore, it corresponds to a Boolean variable in which the value 0 refers to patients who did not need to be replanned and the value 1 to those who were replanned.

4.1.2. **Description of the variables to be analysed**

During the study several variables have been taken into account, in order to try to determine the behaviour of the parotid glands during radiotherapy, as well as which of them are related to the anatomical changes produced in the patients (and therefore, with the need to replan the treatment). The variables studied were the following: administration of concomitant chemotherapy (yes/no), anatomical location of the primary tumour, weight loss during radiotherapy, elapsed time (in days) between the planning CT scan and the start of treatment, doses and the administered radiation dose to the left and right parotid glands, including their volumes.

The results of each of these variables are described below:

- The treatment of head and neck tumours may require the use of chemotherapy. Of the 85 patients studied, 44 received **concomitant chemotherapy treatment** in addition to radiotherapy (51.8%). The remaining 41 patients received only radiotherapy treatment (42.8%). Thus, whether or not chemotherapy was received is considered a Boolean variable, with a value of 0 corresponding to not having received chemotherapy and 1 to the opposite. As it will be shown in the following section, patients who have received radical treatment with concomitant chemotherapy are more likely to be replanned.
- **The location of the primary tumour** (***see* Figure *11)*** must also be taken into account as it directly influences the choice of treatment and the region of healthy mucosa to be irradiated. Regarding to the location:
    - Pharynx: 37 patients
    - Larynx: 25 patients
    - Oral cavity: 13 patients
    - Paranasal sinuses: 10 patients

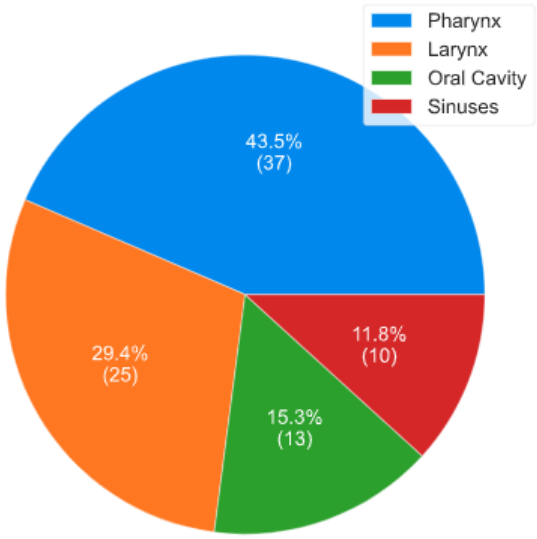

Figure 11. Distribution of patients according to the location of the primary tumour.

The following figure (***see* Figure *12***) shows the distribution of patients according to the location of the primary tumour and whether the corresponding treatment included

chemotherapy. As it can be seen, for all locations **except for paranasal sinuses**, the number of patients with or without chemotherapy is approximately the same.

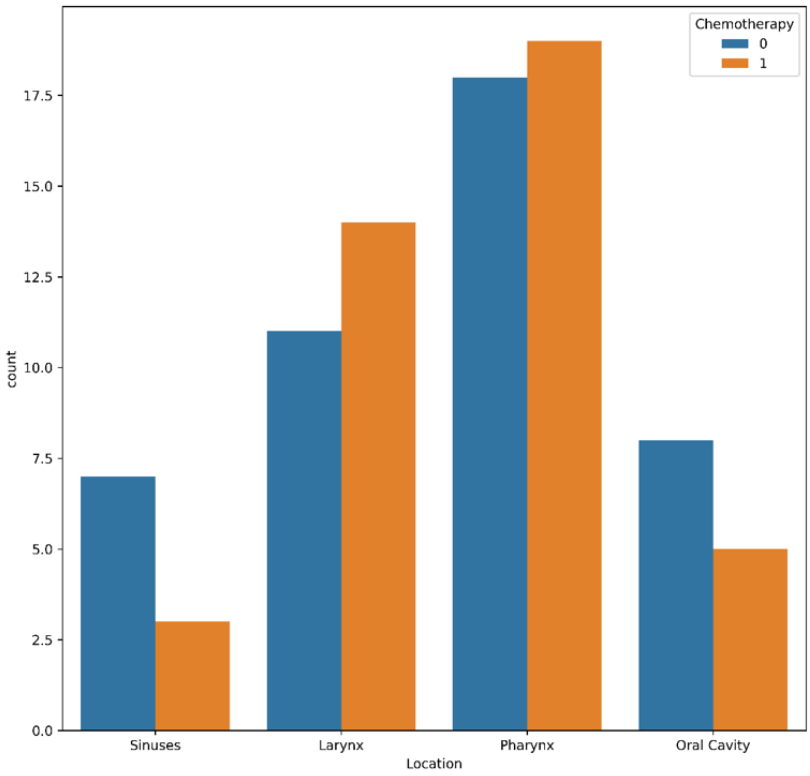

Figure 12. Number of patients for the different tumour locations that either did not received chemotherapy treatment (chemotherapy=0) or received chemotherapy treatment (chemotherapy=1).

- **Patients' weight (see Table *1*).** Two variables were studied in relation to patients' weight:
    - The variable W0. This variable corresponds to the initial weight of the patients measured at the first consultation (in kg).
    - The variable Wloss, which refers to the difference between the weight at the first session and the weight at the end of treatment. As it can be seen in the following table, there is a wade range in which the maximum weight gained is 5 kg and the lost is of 12kg.
    - The variable RTT ΔW (%) refers to the weight change during radiotherapy treatment (W5) in relation to the weight the first day of radiotherapy treatment (W1), expressed as an absolute value:

$$RTT\ \Delta W\ (\%) = 100 \left| \frac{W1 - W5}{W1} \right|$$

Table 1. Median and range of the variables: weight of the patients measured at the first consultation (W0), difference between the weight at first session and at the end of treatment (Wloss) and weight change during radiotherapy treatment in relation to the weight the first day of treatment expressed as an absolute value (*RTT ΔW).*

	Median	Range
W0	69.3	43-122
Wloss	3.2	(-5.9)-12.3
RTT ΔW	4.59%	0.16%-16.14%

- **Elapsed time.** The variable time_CTRT refers to the elapsed time (in days) between the planning CT and the beginning of radiotherapy treatment. It has a median of 18 days (4-39). In the following illustration it can be seen how patients receiving concomitant treatment with chemotherapy take slightly less time to star treatment than those who do not receive chemotherapy (no: 19.5 days, yes: 17.9 days).

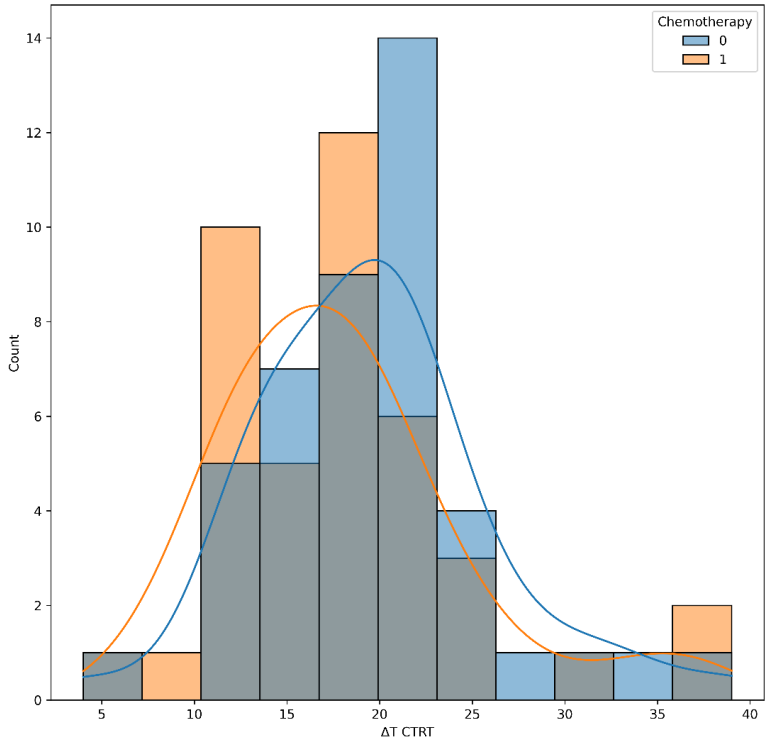

Figure 13. Difference in elapsed time between planning CT and beginning of treatment in patients receiving chemotherapy (chemotherapy yes: 1) vs. those not receiving chemotherapy (chemotherapy no: 0).

- **Dose and volumes of the left and right parotids** (**seeTable 2***).*
    - Accumulated dose: the variable D_ac refers to the mean dose (in Gy) accumulated in the right and left parotids.
    - Initial volume: the variable V0 refers to the initial volume (painted on the CT) of the left/right parotids measured in cm^3.
    - The variable deltaV corresponds to the fraction between final volume and initial volume. Hence, it is the relative volume of the parotids at the end of the treatment compared to the initial volume.
    - DeltaW: the variable DeltaW refers to the difference between the initial weight and the weight at the end of treatment of the parotid glands.

Table 2. Mean and range of doses and volumes of right and left parotids

	Median	Range
D_ac right parotid	27.93	1.07-56.8
D_ac left parotid	28.46	1.33-52.04
V0 right parotid	24.8	6.6-64
V0 left parotid	24.9	10.1-56.1
DeltaV right parotid	0.811946903	0.5829-0.9957
DeltaV left parotid	0.793387314	0.4335-0.9892
DeltaW	0.8	(-4.1)-6.8

4.2. ASSOCIATIONS BETWEEN ANALYSED VARIABLES AND THE NEED OF REPLANNING

4.2.1. Replanning versus Chemotherapy

Patients who have received chemotherapy during treatment have a higher probability of being replanned. In fact, the correlation coefficient between the two variables (receiving chemotherapy treatment and the need to be replanned) is 0.61 **(rS = 0.61 ($p<10^{-5}$)),** which means that the result is statistically significant. Hence, chemotherapy

strongly correlates with the likelihood of replanning. The figure ***(see* Figure *14)*** below shows the distribution of patients who had to be replanned (replanning = 1) or not (replanning = 0) depending on whether they also received chemotherapy treatment.

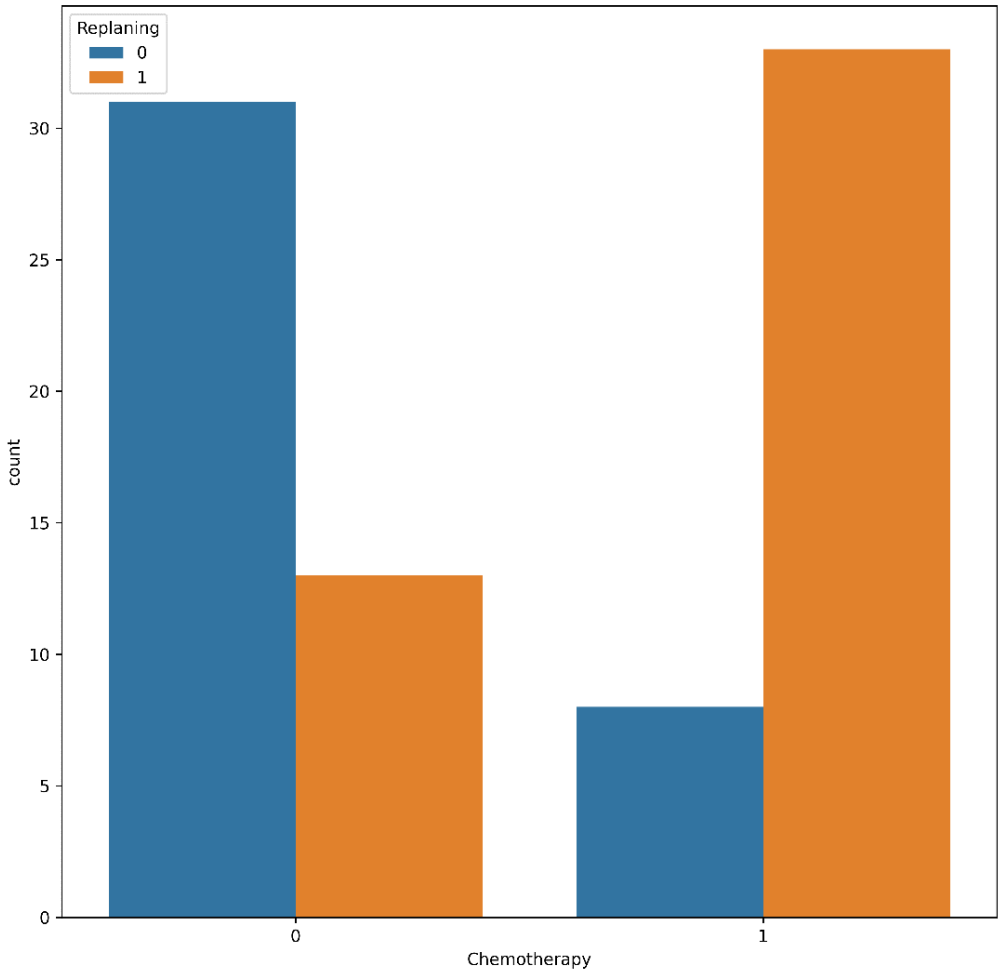

Figure 14. Patient who were replanned (replanning yes= 1. Replanning no= 0) according to whether the treatment involved chemotherapy or not.

The following figure (***see* Figure *15***) shows the distribution of patients according to whether the treatment was radical (type=1) or postoperative (type=0) and whether they underwent chemotherapy. It can be seen that patients receiving a radical treatment more frequently present concomitant treatment with chemotherapy. Therefore, patients who undergo radical treatment, of which chemotherapy is often a part, are at higher risk of being replanned.

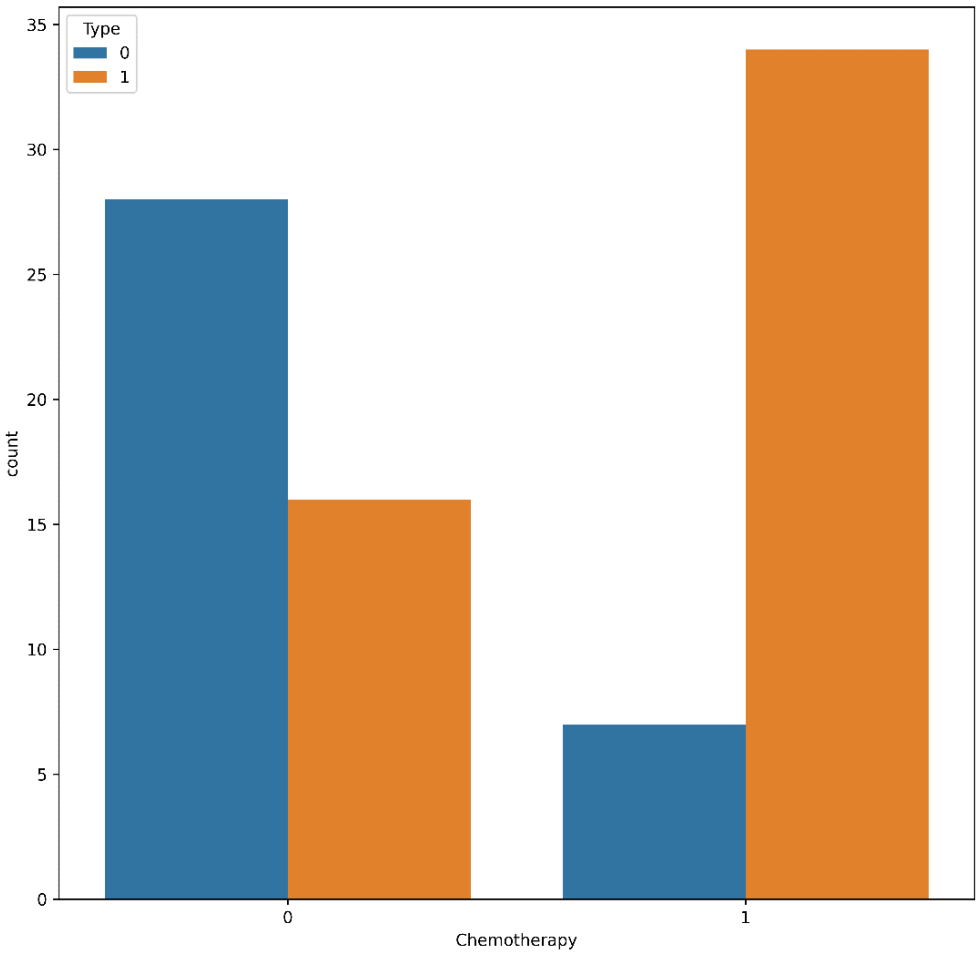

Figure 15. Patient's distribution depending on the type of treatment (postoperative Type= 0. Radical treatment Type= 1) and the use of chemotherapy (0= no, 1= yes).

4.2.2. **Replanning versus weight variation**

It should be taken into consideration that there is an association between the use of concomitant chemotherapy and the weight variation during radiotherapy treatment (from first session to the last one). There is statistical significance between both distributions **($p < 10^{-5}$).**

As a result, the weight variation throughout treatment in patients who received chemotherapy is of about 6.9%, while patients who did not receive chemotherapy varied their weight by 3.5%.

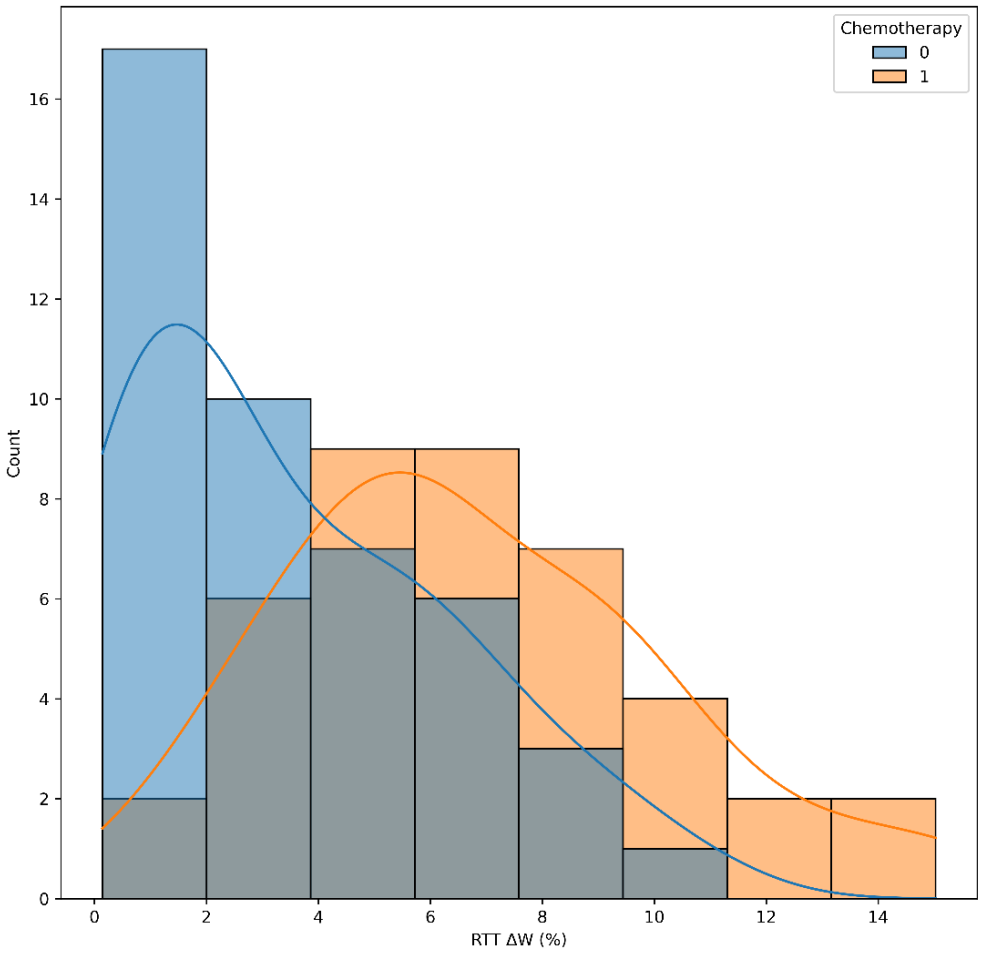

Figure 16. RTT ΔW refers to the weight change during radiotherapy treatment in relation to the weight the first day of radiotherapy treatment, expressed as an absolute value. In this figure, it can be seen the variation of that value as a function of whether the patients received chemotherapy or not.

As a consequence of there being a relation between patients receiving chemotherapy and weigh loss during treatment, the possibility of the existence of a correlation between weight variation and the probability of the patient having to be replanned is also raised. The mean weight variation for those not replanned was 3.1%, while for those replanned it was 6.8%. Furthermore, there is statistical association between both variables as $\mathbf{r_S = 0.55\ (p<10^{-4})}$.

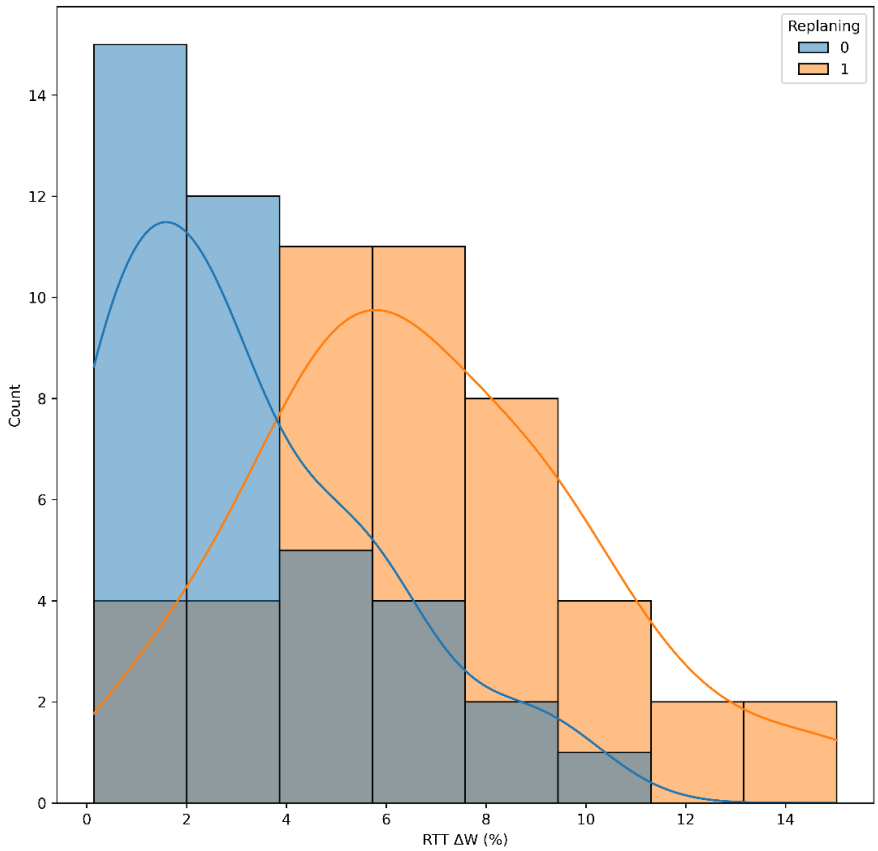

Figure 17. Weight variation during radiotherapy treatment (from first session to the last one) according to whether the patients were replanned (replanning=1) or not (replanning=0).

4.2.3. **Replanning versus elapsed time**

Despite the fact that it has been previously mentioned that patients who receive chemotherapy start treatment earlier than those who do not, there is no statistical correlation **(p= 0.25)** between this difference in days and the subsequent need for replanning. This seems to indicate that the replanning criterion does not include changes suffered before starting treatment, and that it only assesses changes occur during treatment.

4.2.4. **Dose and volumes of the left and right parotid glands**

Hitherto, the variables related to the need of the patient being replanned have been seen. As aforementioned, when anatomical changes occur in the patient, the doses foreseen in the initial treatment may vary significantly causing the treatment to be modified (replanning). This is especially important in the case of parotid glands,

organs at risk that are generally very close to the PTV, and therefore, at risk of receiving high doses of radiation. As a consequence of the increased radiation dose to the parotid glands, the risk of side effects, as xerostomia, increases, leading to significant alteration in the quality of life of patients.

The following figure (***see Figure 18***) shows the mean dose received in the parotid glands over the course of treatment relative to the mean dose predicted in the initial treatment for a patient that should have been replanned (but it was not). The mean dose in each parotid gland increased by more than 20% of the mean dose initially foreseen in the original planning.

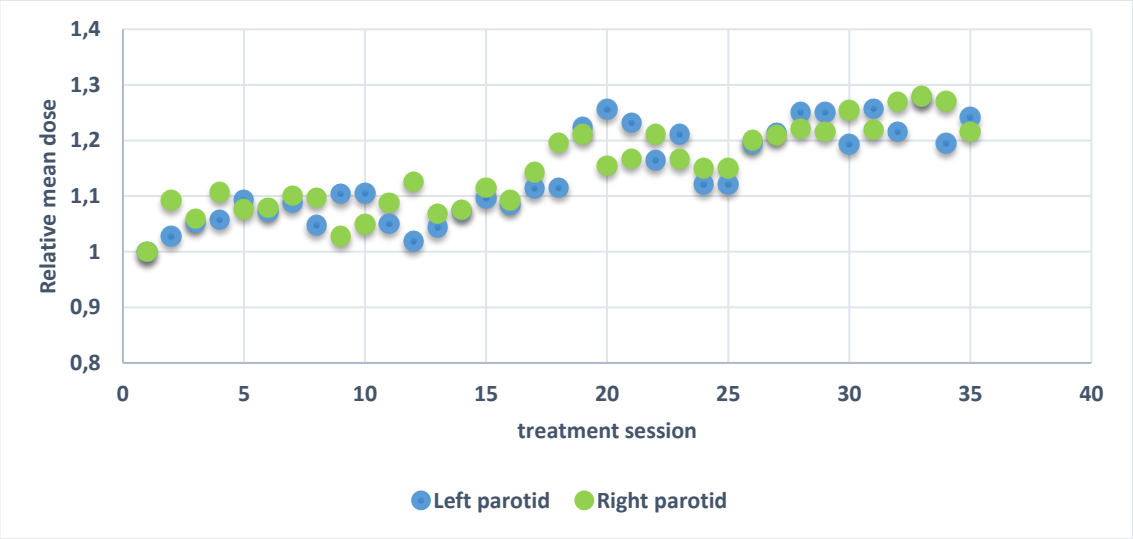

Figure 18. Mean dose received by parotid glands vs. mean dose initially planned. There is a 20% increase in the total dose received with respect to the one originally planned.

For this reason, the variation of the volume in the parotid gland with respect to the accumulated dose throughout radiation treatment has been studied, finding **a strong correlation (r_S = 0.61 ($p<10^{-5}$))**. As it is shown in the figure below (***see Figure 19***), as the parotid glands receive a higher radiation dose, the decrease in their volume is greater. Nevertheless, this takes place up to a certain extent in which the decrease in volume becomes almost constant in spite of increasing dose (during the first 3000cGy there is a large decrease in volume and from that moment on the decrease becomes slower and more constant).

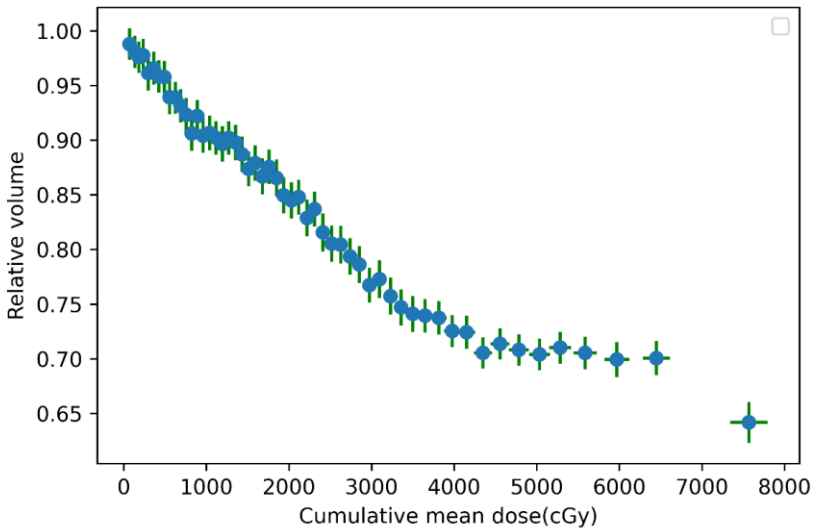

Figure 19. As the parotid glands receive a higher dose, the volume decrease is greater up to a certain point (3000cGy) where the decrease becomes slower and more uniform.

3. DISCUSSION

Patients with head and neck tumours present anatomical and structural changes during radiotherapy (23) treatment. These changes occur in various structures including the parotid glands. Consequently, as the size of the parotid glands decreases or changes, the radiation dose that reaches them increases (24), leading to a greater occurrence of side effects such as xerostomia (25). It is for this reason that it is important to identify early those patients who will benefit from the use of adaptive radiotherapy. In fact, in the present study it has been found that weight loss during radiotherapy as well as the average dose received by the parotids are determining factors that indicate the need for replanning.

One of the objectives of the study was to try to determine which variables are most closely related to the anatomical changes produced and, consequently, to the need for replanning, in order to be able to quickly identify patients with predisposing factors who are going to need adaptive radiotherapy. Through various statistical tests it has been determined that the variables most frequently associated with structural changes in this study are: whether or not concomitant chemotherapy has been administered,

weight loss during radiotherapy treatment and the administered radiation dose to the left and right parotid glands, including their volumes.

The use of concomitant chemotherapy is one of the most associated factors with the anatomical changes suffered by patients. Figen et al (26)suggest in a study performed in 290 patients with head and neck tumours that 10.6% of them required replanning. In their case, they found a statistical correlation between the concomitant use of chemotherapy with radiotherapy of p=0.0034, demonstrating that patients who also receive chemotherapy are more susceptible to replanning, this being more frequent in those with advanced stage tumours (T3-T4, N2-N3). In our study we found a strong correlation between the use of concomitant chemotherapy and the need for replanning. However, it is worth noting the lack of studies focused on studying the relation between these two variables, which could be an interesting area to study in the future.

Patients with head and neck tumours often present weight loss during radiotherapy treatment attributable to mucositis and dysphagia occurring during radiation therapy. Our study shows a significant relation between weight loss and the use of concomitant chemotherapy. Patients receiving chemotherapy have a greater weight loss during treatment. This relation is reasonable since chemotherapy presents adverse effects such as nausea and vomiting, in addition to a radiosensitizing effect on the mucosa, which can produce greater toxicity, and therefore, greater weight loss. Our study also found a correlation between weight loss and the need for replanning, since the greater the weight loss, the greater the anatomical changes and therefore the greater the need for replanning. This coincides with the results obtained in other studies, such as the one published by Brown et al, (27)in which after studying 110 patients with head and neck tumours, it was determined that among the factors associated with a greater need for adaptive radiotherapy there was the change in patient's weight during treatment, especially in those patients with an initial weight greater than 100kg. Wei-Hsien Hou et al (28)demonstrated in a study of 217 patients receiving radiotherapy treatment that patients with a weight loss greater than 5% were at higher risk of treatment planning errors. Mahmoud et al (29) conducted a study of 20 patients with stage III-IV head and neck tumours in which they demonstrated that a weight loss bigger than 9.6% is critical in triggering over-dosage of structures such as the spinal cord or parotid glands.

However, there are studies such as the one conducted by Noble et al (30) that suggest that patients with head and neck tumours may present anatomical changes independently of weight loss, as in the case of neck diameter, which is usually reduced in all patients.

In relation to the doses received and the volumes of the parotid glands, Hui Wu et al (31) point out that the reduction in the volumes of the parotid glands in patients with head and neck tumours treated with radiotherapy has been widely reported in different studies. Hansel et al (22), through a retrospective study of 13 patients with head and neck tumours in which they compared the mean volume of both parotids on planning CT and replanning CT, determined a volume difference of 21.5% for the right parotid and 15.6% for the left parotid. For their part, Vasquez Osorio et al (32) in a study with 10 patients with oropharyngeal tumours determined a change in the mean volume of both parotid glands of 14%. Raghavan et al (33)also demonstrated a decrease in the size of the parotid glands, finding a different decrease in volume depending on whether they are ipsilateral or contralateral. The ipsilateral glands presented a decrease in volume of 31.1% while the contralateral ones of 21.8%, which is to be expected since the initially planned dose is higher in the ipsilateral glands. This same study also relates the contraction in the volume of the parotid glands not only with the originally planned dose, but also with the weight loss presented by patients during treatment. The greater the weight loss and the higher the initial planned dose, the greater the volume loss of the parotid glands.

As it has already been mentioned, one of the effects of reducing the size of the glands is an increase in the radiation dose received by them, increasing the risk of xerostomia. Vives-Soler et al (34)show that together with mucositis, xerostomia is the most frequent side effect of radiotherapy in head and neck tumours.

The main limitations of this study are its retrospective nature and limited sample size. Nevertheless, despite these limitations, the fact that this is a study carried out using a database obtained from patients treated according to routine clinical practice, and under real conditions, allows us to guide clinicians in making the most appropriate therapeutic decisions and whose results are applicable in daily clinical practice, improving the quality of care in the radiation oncology service.

4. CONCLUSIONS

Based on the results obtained, it can be concluded that patients with head and neck tumours undergoing radiotherapy treatment can benefit from the use of adaptive radiotherapy. Factors such as the decrease in weight that they tend to present during treatment or the use of concomitant chemotherapy, lead to anatomical and structural changes of the radiated tissues, both tumour and healthy. Consequently, it increases the risk of adverse effects such as xerostomia. Early identification of the aforementioned factors and the performance of imaging tests, such as CBCT, prior to each treatment session can help to identify early on those patients who are undergoing changes, thus rapidly replanning the radiation doses, reducing the risk of undesirable effects and probably improving the quality of life of the patients.

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