



EVALUATION OF DYSPHAGIA WITH LARYNGO-PHARYNGEAL SPARING INTENSITY MODULATED RADIOTHERAPY IN HEAD AND NECK CANCER PATIENTS

Radiotherapy

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ABSTRACT

Prior to receiving laryngo-pharyngeal sparing intensity modulated radiotherapy (IMRT), patients with head and neck cancer must have their dysphagia, also known as difficulty swallowing, evaluated. This evaluation is a crucial step in the treatment planning process as well as in the provision of post-treatment care. The primary objective of the present study is to assess the objective and subjective swallowing function over the long term, as well as the relationship between dysphagia and The radiation dosage delivered to important anatomical areas in patients with head and neck cancer treated with intensity-modulated radiation treatment and a midline protective contour. In this retrospective analysis, 82 individuals with phase III/IV squamous cells carcinoma of such larynx, oropharynx, or hypopharynx who had successful definitive or postoperative sequentially integrated boost (SIB) -IMRT alone or in conjunction with chemotherapy (85%) were assessed. A laryngo-pharyngeal centerline conserving contour was drawn outside the PTV for each patient. The findings indicate that preserving the swallowing structures with IMRT seems to be beneficial and reasonably safe in terms of preventing chronic grade 3/4 late dysphagia and controlling local illness.

KEYWORDS

Intensity Modulated Radiotherapy (IMRT), Dysphagia, Laryngo-pharyngeal Sparing,

INTRODUCTION

Dysphagia is a medical term that refers to difficulty swallowing. It can be caused by a variety of conditions, such as neurological disorders (such as stroke or Parkinson's disease), structural problems in the throat or esophagus, or certain medical treatments (such as radiation therapy for cancer). Symptoms of dysphagia may include difficulty starting a swallow, food getting stuck in the throat, and feeling like food is not going down properly. Treatment for dysphagia may include changes to diet, speech therapy, and/or medication. In some cases, surgery may be necessary to correct the underlying problem [1].

Laryngo-pharyngeal sparing is a method used during radiation treatment that reduces the amount of radiation that is exposed to the larynx (voice box) and the pharynx (throat), yet still successfully treats the cancer [20]. This may be crucial for patients who have tumours of the head and neck since radiation to these tissues may produce substantial adverse effects such as changes to the patient's voice, trouble swallowing, and dry mouth. Radiation oncologists make use of cutting-edge technology, such as intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT), to carefully shape the radiation beams in order to avoid or minimise exposure to the larynx and pharynx [2]. This is how they achieve the goal of laryngo-pharyngeal sparing [19]. Either by rerouting the beams so that they go past the buildings in question or by reducing the amount of radiation that is delivered to these regions, this goal may be accomplished. This method, which is also known as larynx and pharynx sparing radiation therapy, is intended to assist the patient maintain their quality of life following treatment by preserving their ability to speak, swallow, and otherwise function normally. Patients who have tumours in the top region of their neck, larynx, or base of their tongue are often the ones that benefit from this treatment [3].

Intensity Modulated Radiotherapy (IMRT) is a type of external beam radiation therapy that uses advanced technology to deliver precise doses of radiation to a tumor while minimizing exposure to surrounding healthy tissue [27]. IMRT uses a machine called a linear accelerator to produce a beam of high-energy radiation that is then shaped and directed to the tumor using a series of computer-controlled multi-leaf collimators (MLC) [18]. This allows the radiation oncologist to deliver higher doses of radiation to the tumor while minimizing exposure to surrounding healthy tissue. This can help reduce side effects of the treatment and improve the chances of controlling the tumor. IMRT is typically used to treat cancers of the head and neck, prostate, lung, and certain types of brain tumors, as well as other types of cancer [4].

Evaluation of dysphagia, also known as difficulty swallowing, in patients diagnosed with head and neck cancer prior to receiving laryngo-pharyngeal sparing intensity modulated radiotherapy (IMRT)

is an essential component of both the treatment planning process and the follow-up care that is provided [5].

There are several methods that can be used to evaluate dysphagia in head and neck cancer patients undergoing laryngo-pharyngeal sparing intensity modulated radiotherapy (IMRT). Some of the most common methods include [6]:

Video fluoroscopic swallow study (VFSS):

This test uses X-ray imaging to capture video images of the patient swallowing a liquid or soft food bolus. It allows the radiologist to evaluate the patient's swallowing mechanics and assess for any areas of difficulty or dysfunction.

Fiberoptic endoscopic evaluation of swallowing (FEES):

This test uses a small flexible endoscope to view the patient's swallowing mechanics from inside the pharynx and larynx. It can be used to assess for any areas of difficulty or dysfunction, as well as to evaluate the effectiveness of any swallowing therapy.

Dysphagia outcome and symptom scale (DOSS):

This is a self-reported questionnaire that is used to assess the patient's symptoms and quality of life related to swallowing. It can be used to track changes in the patient's swallowing function over time.

Modified barium swallow (MBS):

This test uses a liquid or paste with barium to make the swallowing process visible on X-ray. It allows the radiologist to evaluate the patient's swallowing mechanics and assess for any areas of difficulty or dysfunction.

Cineradiography:

This test is similar to MBS but it uses a video camera to record the process of swallowing, allowing for a more detailed analysis of the swallowing process.

All of these methods have their own advantages and disadvantages and can be used in combination depending on the clinical situation. They are performed by a Speech-Language pathologist and radiologist, who will interpret the results and make recommendations for treatment or therapy to improve the patient's swallowing function [7].

It is crucial to note that the dosage to the larynx and pharynx is lowered when using a technique called laryngo-pharyngeal sparing IMRT [26]. This helps to maintain swallowing function and is a vital point to keep in mind. However, it is still vital to monitor the patients for any difficulty swallowing and to give appropriate assistance whenever it is required to do so [8].

There is a lack of information about the long-term function of swallowing in patients who were treated with intensity modulated radiotherapy (IMRT) and were at risk for dysphagia [17]. The purpose of this study was to evaluate the objective and subjective long-term swallowing function of our consecutively IMRT (with or without chemotherapy) treated head and neck cancer patients, as well as to determine the relationship between dysphagia and the radiation dose that was delivered to the critical anatomical structures. The researchers paid particular attention to major subjective symptoms in addition to objective ones (late effects graded as a 3/4) [9].

Recently, the scientists released a research on swallowing-sparing intensity-modulated radiation, or SW-IMRT, for treating head and neck cancer (HNC). In this investigation, we established that the dosage to swallowing organs at risk (SWOARs) may be greatly lowered compared to conventional intensity-modulated radiotherapy (ST-IMRT), with the aim of lowering the radiation solely to the parotid glands [10]. By integrating the results of in-silico preparation comparative studies and multivariable estimation techniques for physician- & patient-rated swallowing problems, it is possible to realise the potential therapeutic benefits of SWOAR dose reductions. During the development phase, we discovered that the normal average tissue complication probability (NTCP) of physician-rated Radiation Therapy Oncology Group (RTOG) grades 2–4 swallowing dysfunction could be lowered from 42.3% with ST-IMRT to 33.4% on average with SW-IMRT. This decrease happened as a result of abandoning ST-IMRT [11].

When considering the initial NTCP readings with ST-IMRT and the decreases that could be attained with SW-IMRT, it was discovered that there was substantial variance across patients [25]. This held true for both SW-IMRT and ST-IMRT [12]. Despite the limited sample size and descriptive study approach, it appears that tumour site and nodal stage influenced both the baseline NTCP-values and the potential NTCP-reductions. It was the case at this point the descriptive nature of the research [16] design. However, it is essential to remember that the findings of that research were acquired under perfect conditions. Specifically, all treatment regimens were rigorously optimised by a seasoned research recommended to obtain (HPvDL) without the strain and pressure of regular practise. The results that were obtained were then reported. In addition, the planning of the therapy was carried out in a precise manner in accordance with the study protocol that had been established beforehand [13].

The methodology for evaluating dysphagia (difficulty swallowing) in patients with head and neck cancer who have undergone laryngo-pharyngeal sparing intensity modulated radiotherapy (IMRT) can vary depending on the study or clinic. However, some commonly used methods include [14]:

Subjective assessments:

Patients may be asked to fill out questionnaires or undergo interviews to assess the severity of their dysphagia symptoms and any impact on their quality of life.

Objective assessments:

Clinical measures such as video fluoroscopic swallowing studies (VFSS), Fiberoptic endoscopic evaluation of swallowing (FEES), or manometry may be used to objectively assess the patient's swallowing function.

Imaging:

Radiographic imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) may be used to evaluate the anatomic changes that have occurred in the larynx and pharynx as a result of the IMRT.

Treatment response:

The patient's response to treatment for dysphagia, such as speech therapy or dietary modifications, may also be considered as part of the evaluation process.

Ultimately, a comprehensive evaluation that combines multiple methods is likely to provide the most accurate assessment of the patient's dysphagia symptoms and the effectiveness of the IMRT treatment [15].

METHODOLOGY

Patient, illness, and stage features:

Eighty-two of ninety-six patients "at risk" for dysphagia because of stage III/IV laryngeal, oropharyngeal, or hypopharyngeal squamous cell carcinoma participated in our retrospective evaluation. Simultaneous integrated boost (SIB)-IMRT, alone or in conjunction with chemotherapy or surgery, was curative for all patients included. Institutional review board permission was obtained prior to analysis. Patients were first contacted by phone to notify them that they would be receiving an EORTC quality of life (QOL) questionnaire and a SOMA LENT scale for late toxicity in the mail. First evaluations (mean 20 months; range 4-40 months) using questionnaires yielded subjective replies [21]. This study included 19 consecutive eligible patients treated during the indicated time period who underwent surgery (without tracheostomy or laryngectomy) followed by postoperative IMRT because this postoperative set up was considered similarly 'risky' for the development of late term dysphagia (fibrosis, edema), and therefore provided additional informative value. Patients were classified according to the American Joint Committee on Cancer (AJCC) staging system version 2002 [22].

Evaluation and rating of chronic toxicity:

Radiation morbidity was scored based on the standards established by the Radiation Therapy Oncology Group (RTOG) and the European Organisation for Research and Treatment of Cancer (EORTC) [24]. Both patient- and observer-reported scales and grading systems were used to measure the severity of swallowing problems and dysphagia. The "European Organization for Research and Treatment of Cancer (EORTC) head-and-neck 35-item swallowing and aspiration (QLQ-H&N35)" quality-of-life (QOL) questionnaire was used to assess patients' self-reported clinical swallowing performance [23]. All patients were also examined routinely in our combined clinic at the Department of Head and Neck Surgery four to six weeks after IMRT was finished. The Department of Head & Neck Surgery recommended a physical examination with extra flexible fiberoptic endoscopy generally every 2 months in the first year of follow-up, every 3 months in the second and third year, and every 6 months in the fourth and fifth year [21].

Characteristics of the therapy:

Patients were positioned supine and immobilised using thermoplastic masks available for purchase. Non-operated individuals had a contrast agent infused while CT scans were taken from the base of the vertex towards the level of the carina. The main tumour and surrounding lymph nodes were treated simultaneously using an extended-field IMRT (EF-IMRT) approach. A 6-MV dynamic MLC system was used to produce irradiation at either five or seven coplanar beam angles (Varian Medical Systems, CA). A laryngo-pharyngeal midline 'shielding' contour was drawn outside the PTVs in all instances to preserve the anatomical tissues involved in swallowing. Most individuals with oropharyngeal cancer had this structure shaped starting at the hyoid. Midline shielding is typically insufficient to shield the larynx from the whole tumour dosage in individuals with hypopharyngeal cancer [21].

Clinical variables:

Among the clinical parameters studied in relation to grade 3-4 late toxicity were age, gender, initial site, cancer phase, carcinoma volume, treatment sequence, inclusion of systemic medication, and IMRT treatment regimens [21].

Dosimetric variables:

On the initial IMRT treatment plans, the dose distribution to the swallowing structures was determined. Based on previous research on the swallowing apparatus, the specific boss to report, medium, and inadequate pharyngeal constrictor musculature (PCs), the palatal as well as supraglottic larynx (GSL), and also the musculature of the esophageal opening were all identified and highlighted chronologically on the axial CT-slices of each design (eim). The superior constrictor muscle (scm) went from the peak of the pedicles plates to the top of the hyoid bone. The medium constrictor muscle (mcm) flowed from the top of the hyoid to the bottom. The constrictors were mapped out into a unified structure called PCs. Using the dose-volume histograms, we determined the mean dosage, maximum point dose (Dmax), minimum point dose (Dmin), V30, V50, V60, V65, V70, D50, and D80 to the swallowing structures [21].

Statistical examination:

The StatView® tool (Abacus Concepts Inc., Berkeley, CA) was used to

generate the Kaplan-Meier curves for this study. A p-value less than 0.05 was determined to be statistically significant [21].

RESULTS

Out of a total of 96 patients who were qualified to participate and had their cancer effectively treated with SIBIMRT, 82 of them volunteered to take part in our research. Eighty patients filled out all of the questionnaires that were sent to them, while two patients out of 82 chose not to return the surveys but gave their permission to use the objective data that was gleaned during their frequent follow-up appointments. The dysphagia study did not include one of the patients who had previously been exposed to radiation.

Violent toxicity:

14/80 patients (18%) reported perceived grade 3/4 toxicity (G3/4) at the initial post-treatment join, whereas 66/80 patients (82%) had grade 0-2 toxicity. 10% (8/78) of patients exhibited grade 3/4 toxicity at the second follow-up; Table 2 presents subjective and objective late toxicity. Table 1 depicts the mean dose and dose range for people who were definitively irradiated vs those who were irradiated afterwards.

Table 1: Characteristics of Patients and Disease

Features	Number of Patient	Percentage
Identity	68	83
Male	14	17
Female		
Primary Site	25	31
Oropharynx central	27	34
Oropharynx lateral	17	21
Hypopharynx	8	10
Larynx		
Phase III/IV	80	99
RT Intention	69	75
Primary Postoperative	21	22
Concomitant CT	61	71
≥4 cycles		
Previous RT	1	1

Table 2: Probability of grade 3/4 (G3/4) Early toxicity based on subjective and objective assessments.

	Grade3/4chronictotoxicity	
Parameters	Subjective	Objective
SwallowPain	1	NA
Dysphagia	2(1 definitive/1postoperative)	2(samepts.assubjective)
TasteAlteration	9	NA
Xerostomia	3	6 (same3ptsassubjective +3others)
Weightloss ≥10%	NA	0
Hoarseness	0	0
TotalNo.of Points	13/80(19%)	8/77(12%)

Long-term dysphagia prevalence:

At the patient-reported initial assessment (mean 20 months, range 4-40), 77/79 patients had dysphagia degree 0-2; five patients (8%) had dysphagia grade 2, a symptom that persisted in just one patient at reevaluation (objective assessment, mean 32 months, range 16-60). One patient (1%) had persistent dysphagia of grade 3/4. No incidences of clinically symptomatic pneumonia as a probable result of aspiration were reported by patients or documented in their medical records (no radiological swallowing tests were conducted).

At the second assessment (mean 32 months' post-treatment; n loco regionally managed patients with no prior radiation = 77) and the most recent follow-up (mean 50 months, range 16-85), 1 patient subjectively and objectively rated grade (2-) 3 persistent swallowing difficulty.

Loss of weight/PEGs:

Twenty-one of 82 (or 26%) patients had peripheral endoscopic gastrostomy (PEG) feeding tubes placed prior to or during treatment. On average, withdrawal of the PEG tube required eight months (range 5-25). Somewhere at time of the initial study, 6/21 people continued to rely on PEG for all or part of their nourishment. There was no patient who lost more than 10% of their body weight in the year after therapy,

and the median weight loss for all patients was 5.1 kg (range, 0-20 kg). 10 percent of PEG patients and 2 percent of the overall cohort are still reliant on the device, however the other four patients achieved PEG independence 14, 16, 33, and 36 months after IMRT was finished. No loco regionally disease-free patients required PEG placement throughout the observed follow-up period or PEG replacement after removal.

Taking in regimented dosages:

The median doses to the structures involved in swallowing, as well as VD is the fractional volume getting recommended dosages for all patients.

Local dominance and global survival over the long run:

The examined cohort had local control rates of 78% after 3 years and 75% after 5 years, while their overall life expectancies were 80% and 77%, respectively, after 3 years and 5 years, respectively. None of the localised failures were found to be associated with the median protective structure.

CONCLUSION

In conclusion, intensity-modulated radiation therapy (IMRT) that uses a midline contour to spare swallowing structures outside of PTVs is reasonably risk-free and successful in terms of preventing chronic late dysphagia and controlling local illness. The subjective estimation of late dysphagia provided by the patients was shown to be comparable with the objective evaluation of swallowing impairment.

REFERENCES

- [1] Studer, G., Huguenin, P. U., Davis, J. B., Kunz, G., Lütolf, U. M., & Glanzmann, C. (2006). IMRT using simultaneously integrated boost (SIB) in head and neck cancer patients. *Radiation oncology*, 1(1), 1-15.
- [2] Feng, F. Y., Kim, H. M., Lyden, T. H., Haxer, M. J., Worden, F. P., Feng, M., ... & Eisbruch, A. (2010). Intensity-modulated chemoradiotherapy aiming to reduce dysphagia in patients with oropharyngeal cancer: clinical and functional results. *Journal of Clinical Oncology*, 28(16), 2732.
- [3] Caudell, J. J., Schaner, P. E., Meredith, R. F., Locher, J. L., Nabell, L. M., Carroll, W. R., ... & Bonner, J. A. (2009). Factors associated with long-term dysphagia after definitive radiotherapy for locally advanced head-and-neck cancer. *International Journal of Radiation Oncology* Biology* Physics*, 73(2), 410-415.
- [4] Greene, F. L., Balch, C. M., Fleming, I. D., Fritz, A., Haller, D. G., Morrow, M., & Page, D. L. (Eds.). (2002). *AJCC cancer staging handbook: TNM classification of malignant tumors*. Springer Science & Business Media.
- [5] Cox, J. D. (1995). Toxicity criteria of the radiation therapy oncology group (RTOG) and the European organization for research and treatment of cancer (EORTC). *Int. J. Radiat. Oncol. Biol. Phys.*, 31, 1341-1346.
- [6] Eisbruch, A., Schwartz, M., Rasch, C., Vineberg, K., Damen, E., Van As, C. J., ... & Balm, A. J. (2004). Dysphagia and aspiration after chemoradiotherapy for head-and-neck cancer: which anatomic structures are affected and can they be spared by IMRT?. *International Journal of Radiation Oncology* Biology* Physics*, 60(5), 1425-1439.
- [7] Levendag, P. C., Teguh, D. N., Voet, P., van der Est, H., Noever, I., de Kruif, W. J., ... & Heijmen, B. J. (2007). Dysphagia disorders in patients with cancer of the oropharynx are significantly affected by the radiation therapy dose to the superior and middle constrictor muscle: a dose-effect relationship. *Radiotherapy and Oncology*, 85(1), 64-73.
- [8] Sanguineti, G., Adapala, P., Endres, E. J., Brack, C., Fiorino, C., Sormani, M. P., & Parker, B. (2007). Dosimetric predictors of laryngeal edema. *International Journal of Radiation Oncology* Biology* Physics*, 68(3), 741-749.
- [9] Caglar, H. B., Tishler, R. B., Othus, M., Burke, E., Li, Y., Goguen, L., ... & Allen, A. M. (2008). Dose to larynx predicts for swallowing complications after intensity-modulated radiotherapy. *International Journal of Radiation Oncology* Biology* Physics*, 72(4), 1110-1118.
- [10] Fang, F. M., Chien, C. Y., Tsai, W. L., Chen, H. C., Hsu, H. C., Lui, C. C., ... & Huang, H. Y. (2008). Quality of life and survival outcome for patients with nasopharyngeal carcinoma receiving three-dimensional conformal radiotherapy vs. intensity-modulated radiotherapy—a longitudinal study. *International Journal of Radiation Oncology* Biology* Physics*, 72(2), 356-364.
- [11] Fu, K. K., Pajak, T. F., Trotti, A., Jones, C. U., Spencer, S. A., Phillips, T. L., ... & Ang, K. K. (2000). A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. *International Journal of Radiation Oncology* Biology* Physics*, 48(1), 716.
- [12] Forastiere, A. A., Goepfert, H., Maor, M., Pajak, T. F., Weber, R., Morrison, W., ... & Cooper, J. (2003). Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *New England Journal of Medicine*, 349(22), 2091-2098.
- [13] Eisbruch, A., Lyden, T., Bradford, C. R., Dawson, L. A., Haxer, M. J., Miller, A. E., ... & Wolf, G. T. (2002). Objective assessment of swallowing dysfunction and aspiration after radiation concurrent with chemotherapy for head-and-neck cancer. *International Journal of Radiation Oncology* Biology* Physics*, 53(1), 23-28.
- [14] de Arruda, F. F., Puri, D. R., Zhong, J., Narayana, A., Wolden, S., Hunt, M., ... & Lee, N. Y. (2006). Intensity-modulated radiation therapy for the treatment of oropharyngeal carcinoma: the Memorial Sloan-Kettering Cancer Center experience. *International Journal of Radiation Oncology* Biology* Physics*, 64(2), 363-373.
- [15] Teguh, D. N., Levendag, P. C., Noever, I., van Rooij, P., Voet, P., van der Est, H., ... & Schmitz, P. I. (2008). Treatment techniques and site considerations regarding dysphagia-related quality of life in cancer of the oropharynx and nasopharynx. *International Journal of Radiation Oncology* Biology* Physics*, 72(4), 1119-1127.
- [16] Dirix, P., & Nuyts, S. (2010). Value of intensity-modulated radiotherapy in Stage IV head-and-neck squamous cell carcinoma. *International Journal of Radiation Oncology* Biology* Physics*, 78(5), 1373-1380.
- [17] Lee, N. Y., de Arruda, F. F., Puri, D. R., Wolden, S. L., Narayana, A., Mechalakos, J., ... & Zelefsky, M. J. (2006). A comparison of intensity-modulated radiation therapy and concomitant boost radiotherapy in the setting of concurrent chemotherapy for locally advanced oropharyngeal carcinoma. *International Journal of Radiation Oncology**

- Biology*Physics*, 66(4), 966-974.
- [18] Fua, T. F., Corry, J., Milner, A. D., Cramb, J., Walsham, S. F., & Peters, L. J. (2007). Intensity-modulated radiotherapy for nasopharyngeal carcinoma: clinical correlation of dose to the pharyngo-esophageal axis and dysphagia. *International Journal of Radiation Oncology* Biology* Physics*, 67(4), 976-981.
- [19] Huguenin, P., Beer, K. T., Allal, A., Rufibach, K., Friedli, C., Davis, J. B., ... & Glanzmann, C. (2004). Concomitant cisplatin significantly improves locoregional control in advanced head and neck cancers treated with hyperfractionated radiotherapy. *Journal of clinical oncology*, 22(23), 4665-4673.
- [20] Caudell, J. J., Schaner, P. E., Desmond, R. A., Meredith, R. F., Spencer, S. A., & Bonner, J. A. (2010). Dosimetric factors associated with long-term dysphagia after definitive radiotherapy for squamous cell carcinoma of the head and neck. *International Journal of Radiation Oncology* Biology* Physics*, 76(2), 403-409.
- [21] Peponi, E., Glanzmann, C., Willi, B., Huber, G., & Studer, G. (2011). Dysphagia in head and neck cancer patients following intensity modulated radiotherapy (IMRT). *Radiation Oncology*, 6(1), 1-8.
- [22] Feng, F. Y., Kim, H. M., Lyden, T. H., Haxer, M. J., Feng, M., Worden, F. P., ... & Eisbruch, A. (2007). Intensity-modulated radiotherapy of head and neck cancer aiming to reduce dysphagia: early dose-effect relationships for the swallowing structures. *International Journal of Radiation Oncology* Biology* Physics*, 68(5), 1289-1298.
- [23] Studer, G., Peponi, E., Kloeck, S., Dossenbach, T., Huber, G., & Glanzmann, C. (2010). Surviving hypopharynx-larynx carcinoma in the era of IMRT. *International Journal of Radiation Oncology* Biology* Physics*, 77(5), 1391-1396.
- [24] Langendijk, J. A., Doornaert, P., Rietveld, D. H., Verdonck-de Leeuw, I. M., Leemans, C. R., & Slotman, B. J. (2009). A predictive model for swallowing dysfunction after curative radiotherapy in head and neck cancer. *Radiotherapy and Oncology*, 90(2), 189-195.
- [25] Werbrout, J., De Ruyc, K., Duprez, F., Veldeman, L., Claes, K., Van Eijkeren, M., ... & Thierens, H. (2009). Acute normal tissue reactions in head-and-neck cancer patients treated with IMRT: influence of dose and association with genetic polymorphisms in DNA DSB repair genes. *International Journal of Radiation Oncology* Biology* Physics*, 73(4), 1187-1195.
- [26] Chao, K. C., Ozyigit, G., & Thorsdad, W. L. (2003, December). Toxicity profile of intensity-modulated radiation therapy for head and neck carcinoma and potential role of amifostine. In *Seminars in oncology* (Vol. 30, pp. 101-108). WB Saunders.
- [27] Denis, F., Garaud, P., Bardet, E., Alfonsi, M., Sire, C., Germain, T., ... & Calais, G. (2003). Late toxicity results of the GORTEC 94-01 randomized trial comparing radiotherapy with concomitant radiochemotherapy for advanced-stage oropharynx carcinoma: comparison of LENT/SOMA, RTOG/EORTC, and NCI-CTC scoring systems. *International Journal of Radiation Oncology* Biology* Physics*, 55(1), 93-98.