International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

Updates on radiotherapy in head and neck squamous cell carcinoma

Refka Y. Adeeb*, Wafaa M. Abdel Latif, Amani S. Guirguis, Sherweif M. Abdel Fatah

Department of Clinical Oncology, Faculty of medicine, Minia University, Egypt.

Radiotherapy Department, Minia Oncology Center, Egypt.

Abstract

Treatment of locally advanced head and neck squamous cell carcinomas remains challenging despite technological advancements in radiation therapy techniques. Tumor hypoxia, accelerated repopulation during treatment and inherent radio resistance are the main culprits for the suboptimal tumor control. Head and neck cancers represent 3% of all malignant tumor, and about 40% of patients are diagnosed with locally advanced disease [LAHNC]. Local treatments, including surgery and radiotherapy, evolved in the recent years with improvement in outcome and pattern of toxicity; however, long-term survival in this setting still remains poor, with 30% to 35% of patients alive at 5 years, and varies by anatomic site and stage. Radiation treatment evolved in technique with improvement in target visualization (image-guided radiation therapy) and dose conformity with the use of intensity-modulated radiation therapy (IMRT), with fixed beams or with rotational delivery (volumetric modulated arc therapy [VMAT]). Fractionation of dose has been investigated in the last decades in order to identify the best RT schedule in the management of LAHNC. Radiotherapy schedules are designed to maximize tumor kill and minimize normal tissue damage (therapeutic ratio). Instead, altered hypofractionation schedules seek to overcome the radiobiological challenges, improve therapeutic ratio and enhance patient survival compared with the standard (conventional) fractionation approach of (1,8-2) Gray per fraction, 5 days a week for 6-7weeks. The rationale for this hypo-fractionated technique is that a shortening of overall treatment time with higher biologically equivalent doses per fraction might result in improved local tumor control rates as it counteracts tumor repopulation.

Keywords: HNC, VMAT, IMRT.

Full length article **Corresponding Author*, e-mail: *refka.adeeb@mu.edu.eg*

1. Introduction

Head and neck cancer (HNC) represents one of the top common types with incidence of greater than half a million cases diagnosed annually. Oral, pharyngeal, and laryngeal squamous cell carcinoma (SCC) represent almost 90% of the cases. Surgical resection, radiotherapy or both have been used over the past few decades [1]. The surveillance, epidemiology and end results data in the United States stated that radiotherapy is generally included in primary oncologic treatments [2]. Radiotherapy improves clinical, form, and functional outcomes for cancer patients. Currently, almost 75% of patients with head and neck (SCC) will benefit from radiotherapy, whether primary or adjunct therapy after surgical resection. In the early stages of cancer, radiotherapy can replace the need for surgical resection [3]. Cancer patient can be treated concomitantly with chemoradiotherapy for local advanced cancer or by surgical resection followed by adjuvant radiotherapy. Radiotherapy also used in procedure aims at organ preservation, including avoiding laryngectomy through the use of chemoradiotherapy [4]. The aim of this review was to summarize development of the radiation therapy for head and neck squamous cell carcinoma.

2. Modern radiation technology

Currently, physical examination and multimodality imaging relay on 3-dimensional anatomic details such as computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET CT) are important to evaluate the treatment volume and outline of tumor and normal tissues. Multimodality imaging can be combined for more details. For example, CT can combine MRI for better soft tissue details and PET-CT to add functional and metabolic details. The high dose volume will include the primary site of the cancer with the lymph node regions, which are considered the areas of gross disease or gross tumor volume (GTV). Gross tumor volume extends to involve the spread of the cancer to involve the microscopic cancer involvement, which is the clinical tumor volume (CTV1), which is enlarged by 2.5 to 10 mm to the planning target volume (PTV1) depending on the microscopic evaluation of the surgical specimens.

Microscopic evaluation of the surgical specimens is the typical treatment dose that is usually 66 to 74 Gy (Gray) in 2 Gy fractions or 81.6 Gy in 1.2 Gy fractions. Therefore, multiple radiation beams will be directed towards the tumor from different angles and planes. Each beam is designed to follow the outline of the target with the aim to converge in order to deliver the planned dose with only fractions of radiation to the normal surrounding tissues. Therefore, the process of tumor wrapping with high radiation dose with minimum dose delivered to the normal adjacent tissues is called conformal radiation therapy [5]. Numerous advanced radiotherapy techniques had been used to reduce the radiation induced toxicities such as intensity modulated radiation therapy (IMRT), which is an advent form of 3-dimensional conformal radiation therapy (3D CRT) with the ability to change the intensity of radiation across each beam, whereas 3D CRT delivers radiation to the target with a minimum dose to the adjacent tissues. Over the past 20 years, IMRT became a common technique for HNC patients due to its ability to selectively target the primary site and lymph node regions at risk by decreasing the dose to the healthy adjacent tissues, thus improving therapeutic index by decreasing the acute and chronic morbidity, improving target volume coverage with locoregional control [6]. Intensity modulated radiation therapy permits improved dose confirmation over irregular-shaped cancer with better sparing of adjacent normal structures. It is employed usually for the nasopharynx and oropharynx, avoiding important structures such as brain, brain stem, optic, optic stem and parotid salivary gland. Lamberchet et al reported significantly less xerostomia related to IMRT when compared to 3D CRT after 6 months of treatment (82% versus 91%). Additionally, Rathod et al compared the quality-of-life outcomes for head and neck SCC treated with 2 different radiation therapies, IMRT and 3D CRT, and they found significantly better dry mouth, mouth opening, sticky saliva, pain, senses, swallowing, feeling ill and insomnia on the symptoms scale. Volumetric modulated arc radiotherapy is the advanced form of IMRT, which delivers an exactly shaped 3D dose distribution with a 360-degree rotation of the gantry in a single or multi-arc treatment. Therefore, the radiotherapy machine can spin over the patient body during the course of treatment. The machine constantly reshapes and changes the intensity of the radiation beam as it rotates around the patient [7].

3. Fractionation of radiotherapy

Fractionation of radiotherapy is defined as radiation dose over time that is considered one of the essential factors that controls the outcome of radiotherapy. For standard radiotherapy, it is generally given in 2 Gray (Gy) fractions per day, 5 days per week for a total of 60 to 70 Gy. In order to improve local control and reduce the toxicity effect, it can be divided in 2 approaches of fractionation: hyperfractionation and accelerated fractionation. Hyperfractionation represents small doses of radiation given to the patient 2 or 3 times per day, usually 1.10-1.25 Gy, aiming to reduce the toxicity effect on the normal cells, whereas accelerated fractionation aims to reduce cancer repopulation between the sessions by reducing the total treatment time and adding more fractions per week (10 Gy per week), resulting in improved locoregional control [8].

Bourhis et al reviewed 15 trials in their meta-analysis study that compared conventional radiotherapy with hyperfractioned and accelerated radiotherapy for SCC patients and concluded that the patients who received altered fractionated radiotherapy had better tumor control and survival compared to conventional therapy. Additionally, Fu et al found that the hyper fractionation and accelerated fractionation were more efficient than conventional fractionation for locally advanced cancer Hypofractionation of radiotherapy also has been used as palliative treatment for advanced HNC, where a small amount of fractionation is given with higher radiation doses over a shorter period of time compared with the other regimens [9].

4. Proton radiotherapy

Proton beam therapy was introduced in radiotherapy to be used when the cancer is close to critical anatomical structures because the beam energy can be aimed at an exact depth, with consequent dose decrease. Therefore, it is different than external photon (x-ray) radiotherapy in which it can keep the same radiation dose for the normal adjacent tissues when the radiation dose is escalating to the tumor area. Additionally, it can deliver a reduced dose to the surrounding structure with the same radiation dose delivered to the tumor [10].

5. Cellular and cancer response to radiation

When high-voltage x-ray penetrates the tissues, it ionizes the oxygen and produces free oxygen radicals and cancer death. Therefore, this high-voltage x-ray can damage the genetic material of the cells (DNA), which blocks division and proliferation [11].

6. Hypofrationaion

Concomitant chemoradiotherapy (cCRT) improves locoregional control (LRC) and overall survival (OS) in locally advanced head and neck cancer (LAHNC) compared with radiotherapy (RT) alone; consequently, chemoradiation is the standard of care for these patients. Three-week 100 mg/m2 cisplatin concomitant with conventional fractionation radiotherapy (CFRT - 35 2-Gy fractions over 7 weeks) are the most studied regimen and is associated with significant toxicity, which compromises patient compliance and may not be suitable for all patients. Altered fractionation is an alternative for patients who are not suitable for cCRT and can improve OS compared with CFRT alone [12]. Accelerated RT, in which the total dose is delivered in a short period of time, has radiobiological advantages and is also associated with improved clinical outcomes. Hypofractionation is an attractive method for accelerating RT and has been used with success with other tumor sites, showing comparable outcomes and a reduced cost compared to those of CFRT [13]. A remarkable moderate hypofractionated RT (HYP-RT) schedule for head and neck cancer, which delivers 55 Gy in 20 fractions (2.75 Gy per fraction) for 5 days per week, has been described in Birmingham/Edinburgh [14]. The biologically effective dose (BED) of the HYP-RT is approximately the same of CFRT.The United Kingdom Head and Neck (UKHAN1) trial was one of the largest trials to demonstrate the superiority of cCRT over RT alone for LAHNC.

In the UKHAN1 trial, almost 50% of patients were submitted to hypofractionated RT, including the HYP-RT schedule, and hypofractionation did not affect event-free survival compared with CFRT. The chemotherapy regimen used in the UKHAN1 trial was non-platin- based and, to the best of our knowledge, no data exists regarding HYP-RT concomitant with CDDP [15]. Patients from low- and middle-income countries (LMIC) have limited resources for RT and face long waiting times to be treated. Consequently, in addition to the radiobiological and clinical benefits of accelerated RT, hypofractionation regimes can also be an important strategy to shorten treatment times and thus improve access to RT. Additionally, a short RT schedule is associated with better patient compliance [16]. Altered fractionation is a well-established alternative of RT in the LAHNC treatment because many studies have demonstrated its superiority in disease control and survival compared with CFRT. By reducing the OTT, the accelerated repopulation effect is minimized, which may explain the improved outcomes when treatment is accelerated. Hypofractionation is a remarkable method for accelerating cancer treatment and is associated with better RT compliance. Additionally, radiobiological and long-term clinical data have suggested that the HYP-RT regimen of 55 Gy in 20 fractions is, at least, equivalent to CFRT for LAHNC. However, despite recent technological RT advances and successes in other tumor sites, the use of hypofractionation regimens with radical intent in LAHNC is modest and restricted to a few countries, particularly the United Kingdom. The main reason for this restriction is the toxicity concern regarding the high dose per fraction, notably with concomitant chemotherapy [17]. Moreover, whether concomitant CDDP improve outcomes in the context of hypofractionation for LAHNC is unknown. The long-term outcomes of the UKHAN1 trial, which included CFRT and HYP-RT, demonstrated good compliance, a low rate of late toxicity, improved disease control, fewer new tumors and reduced mortality when cCRT was compared to RT alone. Nevertheless, the chemotherapy used in the UKHAN1 trial was non-platin based. Although Madhava and colleagues have already demonstrated the feasibility of carboplatin with HYP-RT, to the best of our knowledge, our trial is the first to address the feasibility of concurrent CDDP with hypofractionation in LAHNC. With a 95% of completion rate, our early data demonstrate the good compliance and suggest the feasibility of this protocol for patients from a middle-income country. The standard concomitant chemotherapy with CFRT comprises the full dose of CDDP (3 cycles of 100 mg/m2 every 21 days), and the treatment is associated some toxicity, poor treatment compliance and treatment delays.

7. Conclusions

LAHNC tumor burden and treatment toxicity are associated with significant suffering and disability and are the primary causes of treatment interruptions. Because this was a safety trial, we determined that the OTT was as important as the completion rate, which used the OTT as a parameter to define treatment feasibility. Indeed, we were concerned that by increasing acute toxicity, the OTT would be prolonged due to unplanned treatment breaks. However, our data suggest the good tolerance profile of the protocol, whereby no patient needed a treatment break due to toxicity and no significant delay was experienced. In addition to treatment toxicity, many other factors underlie RT prolongation, including low socioeconomic status, a long treatment course, an unplanned equipment breakdown and the travel distance from the patient's home to the RT site. An integrated multidisciplinary approach plays an essential role in improving tolerance and RT compliance in LAHNC.

References

[1] A. C. Chi, T. A. Day, B. W. Neville. (2015). Oral cavity and oropharyngeal squamous cell carcinoma—an update. CA: a cancer journal for clinicians. 65 (5): e401-e421.

[2] B. A. Virnig, J. L. Warren, G. S. Cooper, C. N. Klabunde, N. Schussler, J. Freeman. (2002). Studying radiation therapy using SEER-Medicare-linked data. Medical care. 40 (8): eIV-e49.

[3] M. B. Barton, S. Jacob, J. Shafiq, K. Wong, S. R. Thompson, T. P. Hanna, G. P. Delaney. (2014). Estimating the demand for radiotherapy from the evidence: a review of changes from 2003 to 2012. Radiotherapy and oncology. 112 (1): e140-e144.

[4] S. Marur, A. A. Forastiere. (2016). Head and neck squamous cell carcinoma: Update on epidemiology, diagnosis, and treatment. Mayo Clinic Proceedings. 91 (1): e386-e396.

[5] D. G. Pfister, K. K. Ang, D. M. Brizel, B. A. Burtness, A. J. Cmelak, A. D. Colevas, F. Dunphy, D. W. Eisele, J. Gilbert, M. L. Gillison, R. I. Haddad, F. Worden. (2011). Head and neck cancers. Journal of the National Comprehensive Cancer Network. 9 (6): e596-e650.

[6] E. R. Fregnani, C. J. Parahyba, K. Morais-Faria, F. P. Fonseca, P. A. Ramos, F. Y. de-Moraes, et al. IMRT delivers lower radiation doses to dental structures than 3DRT in head and neck cancer patient. Radiat oncol 2016; 11:116.

[7] E. Vanetti, A. Clivio, G. Nicolini, A. Fogliata, S. Ghosh-Laskar, J. P. Agarwal, R. R. Upreti, A. Budrukkar, V. Murthy, D. D. Deshpande, S. K. Shrivastava, L. Cozzi. (2009). Volumetric modulated arc radiotherapy for carcinomas of the oro-pharynx, hypo-pharynx and larynx: a treatment planning comparison with fixed field IMRT. Radiotherapy and Oncology. 92 (1): e111-e117.

[8] L. N. Nguyen, K. K. Ang. (2002). Radiotherapy for cancer of the head and neck: altered fractionation regimens. The Lancet Oncology. 3 (11): e693-e701.

[9] H. J. Park, R. J. Griffin, S. Hui, S. H. Levitt, C. W. Song. (2012). Radiationinduced vascular damage in tumors: implications of vascular damage in ablative hypofractionated radiotherapy (SBRT and SRS). Radiation Research. 177 (3): e311-e327.

[10] E. B. Holliday, S. J. Frank. (2014). Proton radiation therapy for head and neck cancer: a review of the clinical experience to date. International Journal of Radiation Oncology*Biology*Physics. 89 (2): e292-e302.

[11] S. Y. Lester, W. Y. Yang. (2012). Principles and management of head and neck cancer. Head and Neck. 30 (11): e617-e623.

[12] B. Lacas, J. Bourhis, J. Overgaard, Q. Zhang, V. Gregoire, M. Nankivell, B. Zackrisson, Z. Szutkowski, R. Suwinski, M. Poulsen, B. O'Sullivan. (2017). Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis. The Lancet Oncology. 18 (9): e1221-e1237.

[13] J. Erlandsson, T. Holm, D. Pettersson, A. Berglund, B. Cedermark, C. Radu, H. Johansson, M. Machado, F. Hjern, O. Hallbook, I. Syk. (2017). Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. The Lancet Oncology. 18 (3): e336-e346.

[14] K. Madhava, A. Hartley, M. Wake, J. C. Watkinson, J. Glaholm. (2006). Carboplatin and hypofractionated accelerated radiotherapy: a dose escalation study of an outpatient chemoradiation schedule for squamous cell carcinoma of the head and neck. Clinical Oncology. 18 (1): e77-e81.

[15] J. S. Tobias, K. Monson, N. Gupta, H. Macdougall, J. Glaholm, I. Hutchison, L. Kadalayil, A. Hackshaw, U. K. Head. (2010). Neck Cancer Trialists Group. Chemoradiotherapy for locally advanced head and neck cancer: 10-year follow-up of the UK Head and Neck (UKHAN1) trial. The Lancet Oncology. 11 (1): e66-e74.

[16] N. Ohri, B. D. Rapkin, D. Guha, H. Haynes-Lewis, C. Guha, S. Kalnicki, M. Garg. (2015). Predictors of radiation therapy noncompliance in an urban academic cancer center. International Journal of Radiation Oncology*Biology*Physics. 91 (1): e232-e238.

[17] A. M. Chen, S. Hsu, J. Meshman, R. Chin, P. Beron, E. Abemayor, M. St John. (2017). Effect of daily fraction size on laryngoesophageal dysfunction after chemoradiation for squamous cell carcinomas of the larynx and hypopharynx. Head Neck. 39 (7): e1322-e1326.