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Head and neck cancer survivors patients and late effects related to oncologic treatment: update of literature

R. TAIBI[1,2], A. LLESHI[1], L. BARZAN[3], F. FIORICA[4], M. LEGHISSA[2], E. VACCHER[1], P. DE PAOLI[5], G. FRANCHIN[6], M. BERRETTA[1,7], U. TIRELLI[1]

[1]Department of Medical Oncology, CRO Aviano National Cancer Institute, Aviano, Italy
[2]Department of Specialized Surgery, ORL Unit, Pordenone General Hospital, Pordenone, Italy
[3]Department of Surgery, CRO Aviano National Cancer Institute, Aviano, Italy
[4]Department of Radiation Oncology, University Hospital Ferrara, Italy
[5]Scientific Directorate, CRO Aviano National Cancer Institute, Aviano, Italy
[6]Department of Radiation Oncology, CRO Aviano National Cancer Institute, Aviano, Italy
[7]Euro-Mediterranean Institute of Science and Technology (IEMEST) Palermo, Italy

Abstract. – Cancer survivorship represents a new challenge in the third Millennium. In Europe the number of cancer survivors was estimated to be 17,8 million in 2008 and this number is growing. Recent improvements in cancer survival are largely due to earlier diagnosis and advancements in treatment. Despite having favorable effects on cancer survival, radiation therapy, surgery treatment and combination chemotherapy regimens can also cause long-term organ damage and functional disabilities.

In this paper we review the most important aspects of long-term toxicities in otolaryngology cancer survivors patients.

Key Words:
Cancer, Survivors, Chemotherapy, Radiation therapy, Head and neck cancer survivors.

Introduction

According to the American definition of cancer survivors[1], we are facing two different populations of patients. Many cancer survivors live with active or advanced disease, while a large and growing number of them live extended and cancer-free lives. We believe that a better definition for this patients population could be persons living with cancer.

In the European Union the number of cancer survivors was estimated to be 17.8 million in 2008[2] and this number is growing[3-6]. Recent improvements in cancer survival are largely due to earlier diagnosis and advancements in treatment. Despite having favorable effects on cancer survival, radiotherapy, surgery treatment and combination chemotherapy regimens can cause long-term organ damage and functional disabilities. These long-term toxicities, or late effects, defined as 'unrecognized toxicities that are absent or subclinical at the end of therapy' can manifest as new diagnoses months to years after the completion of primary cancer treatment[7]. Late effects related to treatment are widely variable and are linked to characteristics of the cancer, the modality and intensity of treatment and the underlying health status of the individual experiencing cancer. Some late effects are predictable, for example, the effect of radiotherapy treatment on adjacent organs. This may result in the increased occurrence of hypothyroidism and mucosities in head and neck cancer (HNC) patients[8].

The late effects of chemotherapy are less easy to predict and are often drug specific. For example, cognitive impairment is a well-recognized late effect of chemotherapy[7]. A conceptual framework of its etiology proposes interactions between treatment effects on clotting in small blood vessels and endogenous hormones, in addition to chemotherapy mediating depression and fatigue[9-11] through cytokine involvement leading to cognitive impairment[12]. Finally, some associations are difficult to explain with current knowledge. Therefore, public health policies are needed to define and direct services to these survivors, many of whom will become part of the population of long-term survivors. Unlike cancer patients in earlier times, those who survive today may not only have had a cancer but often have one, two and more concurrent chronic diseases,

Corresponding Author: Rosaria Taibi, SLPs; e-mail: rostai@libero.it

such as diabetes, cardiovascular disease or thyroid dysfunction. Integrated treatment decisions and management structures are required for these more complex cases.

Nearly 650,000 people per year worldwide are newly diagnosed with HNC. Malignancies of the upper aero digestive tract are varied in terms of etiology location, presentation, and pathology. Anatomically, they include cancers of the paranasal sinuses and nasal cavity, nasopharynx, oropharynx, oral cavity, hypopharynx, and larynx. Although a marked variety of malignant processes can present in this region of the body, however, over 90% of HNC are squamous cell carcinoma[13].

HNCs have had a strong association with tobacco and alcohol abuse. Tobacco and alcohol consumption are not only independent risk factors for the development of HNCs, but their concurrent use has a multiplicative, rather than additive, effect on the risk of developing laryngeal cancer[14]. The use of smokeless tobacco has also been linked to cases of oral cavity cancer. The incidence of HNC also tends to increase with age.

The importance of correctly evaluating and minimizing the morbidity of therapy for HNC has become even more relevant with this changing epidemiology of HNC.

Although the mortality from HNC has remained relatively constant over the last several decades, nonsurgical organ preservation strategies have been able to achieve oncologic results comparable to traditional radical surgery, while preserving greater function and improving the quality of life (QOL) for patients with HNC.

In the meantime, traditional radical open surgery has been substituted by minimally invasive trans oral surgery that has led to greater functional preservation and good oncologic results. Also reconstructive techniques have improved, giving head and neck surgeons the ability to remove larger tumors and reconstruct key anatomic sub sites important for swallowing and speech.

Oral complications resulting from cancer and cancer therapies cause acute and late toxicities (Table I) that are underreported, under recognized, and undertreated. Recent advances in cancer treatment have led to changes in the incidence, nature, and severity of oral complications. Acute oral complications include mucositis, infection, and saliva and neurosensory changes. Complications in survivors include neurosensory changes; saliva, taste, and functional changes; oral and dental infection; and risk of dental disease and necrosis of the jaw. These complications

Table I. Oral toxicities of cancer treatment.

Complications	Symptoms
Acute	
Mucosal	Mucositis, pain, dysphagia, limited oral function
Saliva alteration	Viscosity, volume
Neurosensory	Taste change, taste loss, neuropathic pain
Infection	
Dental/periodontal	Acute exacerbation of chronic infection
Mucosal	Candida, herpes, other
Limited movement	Opening of the jaw, tongue function
Chronic	
Mucosal pain	Atrophy, neuropathy
Saliva	Viscosity, hyposalivation
Neurosensory	Taste alteration, taste loss, halitosis, mucosal neuropathy, trismus
Limited movement	Lip aperture, mucosa, muscle/TMJ, neck, shoulder, tongue, trismus
Infection	
Mucosal	Pain, halitosis
Dental	Demineralization, caries
Periodontal	Advanced attachment loss, mobility
Risk of mucosal injury	
Necrosis	Soft tissue, bone
Esthetic change	Social withdrawal, low QOL, depression
Speech	Social withdrawal, depression
Mastication difficulty/dysphagia	Impact on energy and nutrient intake

TMJ indicates temporomandibular joint.

impact on QOL. As the number of survivors increases[15], it is becoming increasingly recognized that the aggressive management of oral toxicities is needed to ensure optimal long-term oral health and general well-being. Considering the impact of potential late toxicities on Head and Neck district, with repercussion in private life, social relations and work activity, its mandatory to plan the better treatment approach.

Treatment

All HNC are initially staged according to the tumor-node-metastasis staging system, which varies slightly by sub site, with assignments made based on tumor size and anatomic extent, nodal involvement, and the presence of distant metastases[16]. The three most commonly used modalities to treat HNC are surgical excision, radiation therapy, and chemotherapy (CT). The anatomic location of the tumor, stage, size, involvement of adjacent normal structures, and the expertise available, all determine which modality or combination of treatments is recommended. HNC can have complicated effects on patient QOL and function with respect to speech and swallowing. Many of the structures affected by head and neck tumors are essential for mastication, swallowing, breathing, and communicating. Also, the head and neck is the most visible and noticeable portion of the human body, critical for social interactions and self-image. Treatments aim not only to cure the underlying malignancy, but to do so with as little functional and cosmetic morbidity as possible. Many trials have shown that chemotherapy with radiation is a viable treatment alternative to surgical excision for many sub sites of HNC[17-22].

A recent study showed that induction CT followed by radiation resulted in equivalent survival and good organ preservation compared with radical open surgery followed by radiotherapy for advanced larynged cancer/hypopharynx sub site[18-22].

Surgery: Head, Neck, and Oral Cancer

Surgery has consistently played an upfront role in the treatment of HNCs. The choice of surgical treatment depends on tumor location, size, proximity to bone, and depth of infiltration[23]. Tumors that approach or involve the mandible require an understanding of the mechanisms of bone involvement, and necessitate mandible-sparing approaches such as partial thickness mandibular surgery (marginal mandibulectomy and mandi- bulotomy) for surgical access. In most cases in which bone is involved, a segmental resection of the mandible is necessary with microvascular reconstruction using fibular free flaps to restore mastication and facial contour, and allow for the placement of osteointegrated implants for orofacial and dental rehabilitation[24]. For advanced stage disease, chemoradiation therapy (CRT) offers optimal cancer outcomes and the potential for organ preservation. Minimally invasive surgery with curative intent for HNCs has increased over the last 3 decades[25]. Transoral robotic surgery and transoral laser microsurgery offer a surgical alternative to CRT-based organ preservation strategies, and several series have shown comparable oncologic outcomes with superior functional results using these surgical approaches[26]. This is because robotic technology provides improved visual access and the ability to manipulate the tissue in a way that cannot be accomplished using nonrobotic transoral techniques[27,28]. Regardless of the surgical approach, microsurgical reconstructive techniques have evolved to facilitate restoration of form and function in both the primary and salvage setting. In the primary setting, these approaches facilitate surgical removal of more extensive cancers, and complex head and neck defects can be effectively restored and rehabilitated. Soft tissue free flaps such as the radial forearm or lateral thigh allow for the reconstruction of oral and oropharyngeal soft tissue defects. In the salvage setting, these techniques allow for improved healing by providing a vascular supply to the surgical bed and reducing the risk of fistula formation. They also allow coverage and protection for major blood vessels, preventing exposure and vascular catastrophes.

Medical Oncology

Some traditional chemotherapy drugs, such as fluorouracil, methotrexate, and doxorubicin, are known to cause acute mucositis[29,30]. Mucositis resulting from targeted therapy may present with isolated ulcerations and mucosal pain (even in the absence of mucosal lesions) and, due to a different presentation, different mechanisms of toxicity appear likely[31,32]. Current treatment and symptom management are based on clinical appearance, and initial reports suggest that topical steroids may be useful in the management of isolated ulcerations associated with targeted therapies.[32] Pain management is discussed below. Oral toxicities may be severe and protracted, and thus

preventive and ongoing oral health care is important[33,34]. A better understanding of the critical pathways involved in the development of certain types of cancers has led to the identification of specific molecular therapeutic targets[35,37]. Targeted strategies are appealing because they can be designed to include patients with a specific molecular abnormality, thus, enriching the study population with those patients most likely to respond. This improves the ability to identify effective agents, albeit in select patient populations. Furthermore, patients who are unlikely to benefit are spared unnecessary cost, time delay, and toxicity. The toxicity profile for these agents is also distinct from traditional chemotherapy drugs. In general, targeted agents have a more favorable toxicity profile, with a lower incidence and severity of oral adverse effects[31,38]. In addition to more traditional systemic therapies and targeted therapies, there is an ever-widening variety of agents that work via distinct mechanisms of action. Biotherapeutic agents play a role in the therapy of select tumors. Radiopharmaceutical agents have been designed and tested for diagnostic, palliative, and treatment purposes. Photodynamic therapy, with or without sensitizing agents, may be effective for epithelial skin or mucosal tumors. There are also innumerable areas of active investigation, including the study of vaccine therapy for the treatment and prevention of malignancy and the use of gene therapy for treatment and symptom management.

Chemoradiation Therapy

CRT is commonly used as the primary treatment for locally advanced head and neck cancers or as adjuvant therapy for tumors with poor clinical features. Altered RT fractionation and schedules (doses that differ from 1.8 gray [Gy]-2 Gy/day) have been extensively evaluated to improve treatment outcomes. Altered fractionation (AF) plus concurrent CRT improves tumor control and reduces late toxicity; however, it is associated with more severe acute oral toxicities, primarily mucositis[39-42]. Adding chemotherapy to hyper- fractionation (2 or more small daily doses or 5 or more weekly fractions) also increases acute toxicities to a level that may limit hyperfractionated RT and CRT to selected patients in clinical trials at large institutions. Concurrent chemotherapy with normofractionated RT (2 Gy/day, 5 days/week, for 5-7 weeks) is the most popular approach in current practice. Concomitant boost RT (supplementary daily dose in addition to 2 Gy on a reduced tumor volume at a given time during RT) has also gained popularity with intensity-modulated RT (IMRT) as a simultaneous integrated boost or as simultaneous modulated accelerated RT. This approach offers improved dose conformation to the tumor volume, superior dose rate, and better treatment time delivery compared with other approaches[43]. Volumetric-modulated arc therapy, a form of rotational IMRT, and stereotactic RT, a form of highly focused irradiation using tridimensional tumor targeting, also offer advantages[44]. Arc therapy reduces IMRT delivery time from 20 minutes to fewer than 5 minutes, while optimizing dose homogeneity and normal tissue sparing[45-56], including parotid gland sparing[57]. Stereotactic fractionated RT allows for the generation of x-ray beams from a single electronic source, which can be rotated or moved around a central focus. Linear accelerator-based stereotactic body RT may be used for multisession head and neck irradiation. Stereotactic irradiation generally allows hypofractionation (doses of 2.5 Gy or more) because of the small volume of the treated tumor and the accurate delivery of irradiation. Hypofractionated stereotactic body RT has shown encouraging 2-year overall survival rates of 14% to 41% in the reirradiation setting[58-66], and this approach is being increasingly investigated as a boost of prophylactic volumes after IMRT. Data for proton therapy in rare radioresistant head and neck cancer has shown high local control rates of 78% to 85% at 5 years with less than 5% severe late toxicity. The role of targeted therapies as novel RT sensitizers has also been investigated[67]. The study by Bonner et al showed improved outcomes with cetuximab plus RT when compared with RT alone, with no significant increase in oral complications noted[68]. Conversely, in a recently reported trial comparing RT plus cisplatin with RT plus cisplatin and cetuximab, the addition of cetuximab did not improve outcomes but did add to toxicity[69]. Thus, the role of targeted agents as part of a combined modality treatment approach for locally advanced HNC has yet to be clearly defined. Moreover, since RT has a major role HNC treatment, it is necessary to face its toxicity.

Radiation therapy-related toxicity effects may be defined by the time course of occurrence. Acute toxicity occurs during or shortly after the RT whereas long-term toxicity can manifest itself months to years after the completion of the treat-

ment. Acute toxicity occurs by direct cytotoxic effect to rapidly proliferating normal tissue cells, instead exact etiology behind long-term radiotherapy toxicity is more complex involving depletion of stem cells, changes in vasculature, and alterations in cellular factors including cytokines, small molecular mediators, and others.

Both, short- and long-term effects of RT can have a significant impact on the QOL. Langendijk et al[70] analyzed 458 patients, alive and disease free 6 months after RT and evaluated association between radiation-induced morbidity and health-related QOL. Clearly, the study demonstrated association between health-related QOL and radiation-induced morbidity.

Xerostomia and swallowing dysfunction had a large impact on health related QOL, particularly the second one. Kotz et al[71], performing post-RT videofluoroscopic swallow function studies, observed a decreased base of tongue retraction resulting in reduced propulsion of the bolus into the pharynx, a reduced laryngeal elevation with residue in the valleculae and the pyriform sinus after the swallow and a decreased pharyngeal contraction with bolus residue in the pharynx after the swallow and to further reduce the effectiveness of bolus propulsion into the esophagus. To the same results, Eisbruch et al[72], who performed serial (pre-RT, at 1-3 months post-RT and at 6-12 months post-RT) swallowing studies.

Therefore, radiation can generate damages on nerves and muscles that can change patients' swallowing mechanism. Swallow maneuvers were used to improve tongue base posterior motion and pressures generated at the tongue base-pharyngeal wall after treatment is completed[73,74]. A recent randomized clinical trial[75] showed an improved swallowing function at 3 and 6 months after chemotherapy in patients who performed prophylactic swallowing exercises. Beyond research with maneuvers to rehabilitate or to prevent swallowing disorders, radiation dose to anatomical structures responsible for swallowing function appears to play a role in disorder genesis[76]. Thus, when possible, target volume delineation for radiotherapy of HNC should be optimized on an individual basis to spare the swallowing apparatus. In addition, swallowing dysfunction may be become worse by xerostomia. This sequela following radiation treatment alone have a negative impact on QOL[77], resulting in serious functional impairment and patient discomfort HNC survivors. Several strategies have been implemented in an attempt to minimize radiation-induced xerostomia, however important predictors are: radiation dose, technique, and irradiated volume of glandular tissue. Introduction in clinical practice of intensity-modulated radiotherapy has permitted a salivary gland sparing treatment, leading a lower rates of xerostomia than conventional treatment and an equivalent loco-regional control rate[78].

Conclusions

The initial evaluation and development of a plan for treating the patient with HNCs requires a multidisciplinary team of health care providers with expertise in caring for these patients. Similarly, managing and preventing sequelae after radical surgery, RT, and chemotherapy (e.g., pain, xerostomia, speech and swallowing problems, depression) requires professionals familiar with the disease. Adequate nutritional support can help to prevent severe weight loss in HNCs patients receiving treatment; therefore, patients should be encouraged to see a dietician[79].

Patients should also be encouraged to stop smoking and to modify alcohol consumption if excessive, because these habits may decrease the efficacy of treatment and adversely affect other health outcomes[80,81].

Health-related QOL issues are paramount in HNCs. These tumors affect basic physiologic functions (i.e., the ability to chew, swallow, and breathe), the senses (taste, smell, hearing), and uniquely human characteristics (i.e., appearance, voice). Health status describes an individual's physical, emotional, and social capabilities and limitations. Function and performance refer to how well an individual is able to perform important roles, tasks, or activities. QOL differs, because the central focus is on the value (determined by the patient alone) that individuals place on their health status and function[82].

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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