TREATMENT IN OROPHARYNGEAL CANCER- AN UPDATE

Palade O.D.1, Lazăr Andra Sorina1, Oprea Alina2, Toader Miorița2, Toader C.3

1 University of Medicine and Pharmacy “Grigore T. Popa” Iasi
2 Emergency Clinical Hospital for Children “Grigore Alexandrescu”, Bucharest
3 National Institute of Cerebrovascular Disease, Bucharest

Abstract. Oropharyngeal cancer is a common malignancy which includes a wide variety of histopathologic tumors. Unfortunately it affects not only the elderly population, but also young patients, its incidence rising alarmingly in the last decade. The gold standard for the treatment of oropharyngeal cancer is the multidisciplinary approach. The authors present a literature review of the current therapeutic regimens, with an emphasis on the surgical techniques.

Keywords: oropharyngeal cancer, transoral laser microsurgery, robotic surgery, chemoradiation

Introduction

In 2002, the crude incidence rates of carcinoma of the head and neck, including oropharyngeal cancers, in Europe were 36/100 000/year in the male population and 7/100 000/ year for females. This fact became a driving force for the development of new surgical treatment techniques as well as adjustment of the chemotherapy and radiation therapy protocols, in order to battle the disease.

Traditionally, surgery and radiation therapy have been the standards for treatment of oropharyngeal cancers. A pooled analysis of 6,400 patients from 51 reported series who were treated for base-of-tongue oropharyngeal carcinoma between 1970 and 2000 demonstrated local control rates of 79% (surgery ± radiation) and 76% (radiation), (P = .087); locoregional control was 60% versus 69% (P = .009); 5-year survival was 49% for surgery with or without radiation therapy versus 52% (P = .2) for radiation therapy with or without neck dissection. Similar findings showed equivalent overall and cause-specific survival between surgery versus radiation for tonsil carcinoma; however, 23% overall and cause-specific survival for severe complications in the surgery group versus 6% overall and cause-specific survival in the radiation therapy group (P < .001).[4]

Surgical techniques of oropharyngeal cancer treatment

For patients with early-stage disease, single-modality treatment, usually radiation therapy alone is preferred, however, new surgical techniques, including transoral surgery and transoral robotic surgery, are currently growing. Nonrandomized comparisons are starting to suggest superior quality of life with minimally invasive surgical techniques.[4]

Surgical innovation may occur by applying new technology to a procedure or with new anatomic approaches to accomplish existing surgical goals. New technologies from different fields like optics, ultrasonography, radiology and robotics as well as new instruments, drugs and materials, have been introduced in medicine and changed the head and neck surgery techniques.

Important technical improvements facilitating visualization, both in the areas of lighting and magnification, have been realized which is an important part of surgical visualization. The application of surgical loupes for open procedures improves visualization considerably by magnifying vital structures.

Magnification and superior illumination combined with endoscopic telescopes with a camera system provide an excellent two-dimensional view. Current telescope technology allows for high-definition images and digital magnification. [5]

Improvements in intraoperative monitoring, especially with respect to anaesthesia, cardiac and respiratory systems monitoring, have been critical in enhancing the safety of surgical procedures in general, as well as in head and neck surgical approaches.

New techniques are also facilitated by improvements in instrumentation. In some cases, reducing the size of standard instruments or altering the mechanism of action will assist the use of standard instrument designs through smaller incisions or remote locations. Laparoscopic instrumentation offers a set of innovative tools that may be used and potentially modified. Additionally, the development of manual and robotic articulating instrumentation offers the potential to improve dexterity in less accessible areas. With robotic technology, tremor filtration, scaling, and augmented movement can also be achieved [6].
Haemostasis is crucial to performing safe surgery. Improvements in cautery, vessel ligation, surgical clips, and haemostatic dressings have allowed surgery to be accomplished more quickly, with less blood loss, and without surgical drains. [5]

Different approaches are used for oropharyngeal surgeries. Transoral approach may be used for limited tumours since it doesn’t produce external scars, and transcervical/visor flap approach may be considered for large tumours of the base of tongue or tonsil but both provide a poor exposure. Mandibulectomy is indicated for larger lesions, but has a risk of malocclusion and plate extrusion. Mandibulotomy spares mandible and may be approached laterally or midline with a lip-splitting incision. Osteotomy is performed to create a favourable repair followed by rigid fixation. The technique provides exceptional exposure and less risk of malocclusion. Lateral Pharyngotomy may be considered for small base of tongue or posterior pharyngeal wall tumours. The technique has limited exposure field, but spares mandible and avoids lip-splitting incision. Transhyoid Pharyngotomy may be considered for small base of tongue or posterior pharyngeal wall tumours without significant superior or tonsillar extension. The surgeon enters pharynx above or through hyoid bone. The technique spares mandible, avoids lip-splitting incision, but has a poor exposure superiorly. Each of these technologies have benefits and drawbacks that need to be understood, particularly when incorporated into more complicated approaches. [5]

Transoral laser microsurgery
Laser is an acronym for light amplification by stimulated emission of radiation. Since their development in 1960, lasers as surgical tools have evolved and now play an important role in the diagnosis and treatment of cancer. It is precise, decreases the risk of infection, and reduces healing time, bleeding, swelling, and scarring.

Several laser systems, such as the diode, ruby, Ho:YAG, Er:YAG, Nd:YAG, and yellow light lasers, as well as dye lasers for photodynamic therapy, have been used. However, the argon and CO2 lasers were the first laser systems to be clinically used. Most small tumours of the posterior pharyngeal wall can be completely resected without any difficulties. If tumour extension has occurred toward the hypopharynx or nasopharynx is present, the resection is extended accordingly. [7]

Excisions made by transoral laser microsurgery diminishes morbidity by lowering postoperative complications, such as swelling, pain and scarring, and makes assessment of cancer relapse easier.

Endoscopic CO2 Laser resection
The CO2 laser has currently the highest value in otorhinolaryngology. Advantages are that no tracheotomy is required, the preservation of the suprahoid musculature allows more normal swallowing, no reconstruction needed, and hospital stay is decreased with patients returning to an oral diet as early as the first day postoperative. This approach has given extraordinary results for all areas in which it has been applied.

The technique involves using a bivalve laryngopharyngoscope, an operating microscope, and a CO2 laser as the dissecting instrument. Under microscopic vision, tumour margins are taken up to 10 mm and as opposed to conventional open procedures, the tumour is often cut through to provide a direct view of tumour depth and/or to assess cartilage invasion, in this fashion making complete resection possible. Cartilage may be exposed or resected during the surgery and to avoid perichondritis antibiotics are given prophylactically. [1] [6]

TORS- Transoral robotic surgery
The Da Vinci Surgical System is a sophisticated robotic platform which offers a minimally invasive option for major surgery and is designed to expand the surgeon's capabilities. With Da Vinci, small incisions are used to insert miniaturized wristed instruments and a high-definition 3D camera. The surgeon views a magnified, high-resolution 3D image of the surgical site inside the body. At the same time, the latest robotic and computer technologies scale, filter and seamlessly translate surgeon’s hand movements into exact micro-movements of the instruments. The system cannot move or operate on its own the surgeon being in control 100%. The system holds up to three EndoWrist instruments and one 3D camera that may be used by the surgeon to access the target anatomy.

Recently, many reports have reported the importance of TORS in head and neck cancer treatment. The objective of transoral robotic surgery TORS is the removal of pharyngeal and laryngeal cancers and to improve functional and aesthetic outcomes with the same survival rate. [8]

Transoral robotic surgery gives the surgeon access to operate through the mouth – avoiding a large incision through the jaw and throat. TORS allows a clearer and wider view of the surgical field and better 3D visualization of structures in comparison to TOLS (transoral laser surgery), this enabling a way in to the tumour via a smaller approach than the external one.

It has been demonstrated that the Da Vinci Robot enables transoral removal of the tumour while preserving key structures and nerves. In addition, it has been showed that it further allows a complete resection with negative surgical margins and without complications. Another advantage of TORS is the use of miniaturized tools. This allows mimicking standard surgical instruments and arm movements, with tremor filtration. It also offers an advantage through an excellent frontal view and the reach of blind corners of the pharyngolaryngeal complex, due to the possibility to use a 30° telescope. [3] [9]

The possible complications in TORS are bleedings that might be life-threatening, difficulty in swallowing or breathing, with the need of airway security by tracheotomy or tracheostomy, or use of ventilator for a long time, loss of taste, tongue paralysis, difficulty opening mouth, narrowing of throat, vocal cord damage with changes in speech or voice quality, abnormal salivation pathway, difficulty speaking, injury to teeth, lips, or nerves in the tongue. [2]

Negative outcomes of transoral robotic surgery system may be linked with longer operative and anaesthesia times. There is also the risk of the da Vinci robotic surgical system malfunction. This can lead to serious damage or the need to switch to another type
of surgery. Switching to another procedure technique could also result in a longer operation time, a longer time under anesthesia and greater risk of complications.[2]

**Radical neck dissection**

Lymph node metastasis reduces the survival rate of patients with squamous cell carcinoma by half. The survival rate is less than 5% in patients who have a recurrent metastasis in the neck after previously undergoing surgery. Therefore, the control of the neck is one of the most important aspects in the successful management of these tumours.[10]

The number of lymph nodes involved by cancer has been found to correlate with the incidence of cancer recurrence in the neck and survival rates. Patients with four or more involved nodes have significantly worse prognosis than patients with only one node involved.

In a landmark paper from Memorial Sloan-Kettering, Strong reported a series of 204 patients treated by radical neck dissection alone. The recurrence rate in the neck was 36.5% in patients with histologically positive nodes at one level of the neck and 71% in patients with positive nodes at multiple levels. The presence of tumour spread beyond the capsule of a lymph node is a major determinant for prognosis and need for postoperative chemo radiation. [2] [10]

It has also been shown that the recurrence rate in the neck after radical neck dissection is significantly higher when extracapsular spread of tumour is verified. The efficacy of a therapeutic radical neck dissection must be measured in relationship with the adjuvant use of radiation therapy. Studies have shown that the combined use of radical neck dissection and postoperative radiation therapy can reduce recurrence in the ipsilateral neck and prevent recurrence in the contralateral side in patients with cervical lymph node metastases who have one or more of the factors associated with increased risk of recurrence. These include multiple histologically positive nodes and extracapsular extension of tumour.[2]

**Radiation and chemotherapy**

The probability of tumour control correlates with both the dose of radiation and the size of the malignancy. Radiation cell kill is essentially an exponential function of dosage. Thus, the necessary dosage of radiation is approximately proportional to the number of cells in the tumour (tumour volume). Control of microscopic disease in head and neck cancers usually requires a dosage of approximately 50 Gy, while positive margins require 60 Gy, and adequate control of large (stages T3 and T4) tumours requires dosages in the range of 70 Gy.[11]

Altered fractionation achieves better local control and higher overall survival than conventionally fractionated radiation but has not yet been compared with conventional chemoradiation. In the postoperative setting, the addition of concurrent chemotherapy to radiation improves survival in cases with extracapsular extension and/or microscopically involved surgical margins.

External beam radiotherapy was the most frequently used form of radiotherapy but intensity-modulated radiation therapy (IMRT) has evolved over the past decade to become a standard technique for head and neck radiation therapy. IMRT allows a dose-painting technique also known as a simultaneous-integrated-boost (SIB) technique with a dose per fraction slightly higher than 2 Gy, which allows shortening of overall treatment time increasing the biologically equivalent dose to the tumour offering a better tumour control by reducing the constraints on the tumour dose that are due to critical organs that limit the tumour boost doses in conventional radiation therapy. Therefore, the use of intensity-modulated radiation therapy in advanced head and neck cancer may offer sparing of vital organs, including major salivary glands, minor salivary glands dispersed within the oral cavity, mandible, pharyngeal musculature, inner and middle ears, temporomandibular joints, temporal brain lobes, and optic pathways.[11]

Chemotherapy may be given with a curative intent, or it may aim to prolong life or to reduce symptoms - palliative chemotherapy. Concurrent chemoradiation is superior to radiation therapy alone and is used for locally advanced disease, emphasizing organ preservation and functionality.

In a randomized trial of locally advanced head and neck cancer patients, curative-intent radiation therapy alone (213 patients) was compared with radiation therapy plus weekly Cetuximab (211 patients). At a median follow up of 54 months, patients treated with Cetuximab and radiation therapy demonstrated significantly higher progression-free survival (hazard ratio for disease progression or death, 0.70; P = .006). [9]

Depending on pathological findings after primary surgery, PORT or postoperative chemoradiation has proven its use in the adjuvant setting for T4 disease, perineural invasion, lymphovascular invasion, positive margins or margins less than 5 mm, extracapsular extension of a lymph node, two or more involved lymph nodes.

**References**

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To update the Memorial Sloan-Kettering Cancer Center’s experience with intensity-modulated radiotherapy (IMRT) in the treatment of oropharyngeal cancer (OPC). Methods and materials: Between September 1998 and April 2009, 442 patients with histologically confirmed OPC underwent IMRT at our center. There were 379 men and 63 women with a median age of 57 years (range, 27-91). The disease was Stage I in 2%, Stage II in 4%, Stage III in 21%, and Stage IV in 73% of patients. A total 404 patients (91%) received chemotherapy, including 389 (88%) who received concurrent chemotherapy, the majority of which was platinum-based. RESULTS: Median follow-up among surviving patients was 36.8 months (range, 3-135). Oropharyngeal cancer, that is, cancer of the mouth and/or throat, can be caused by tobacco smoking or exposure to the human papilloma virus (HPV). Treatment includes surgery, radiation, chemotherapy, and targeted therapy. Learn about the signs and symptoms of oropharyngeal cancer. What Is Oropharyngeal Cancer? Oropharyngeal cancer is a disease in which malignant (cancer) cells form in the tissues of the oropharynx. The oropharynx is the middle part of the pharynx (throat), behind the mouth. The pharynx is a hollow tube about 5 inches long that starts behind the nose and ends where the trachea (windpipe) and esophagus (tube from the throat to the stomach) begin. Since the updated staging system for oropharyngeal cancer now also includes the p16 status of the tumor, the stages may be higher or lower than previous staging systems. Whether or not treatment strategies will change with this new staging system are yet to be determined. You should discuss your stage and treatment options with your physician. Most experts agree that treatment in a clinical trial should be considered for any type or stage of cancer in the head and neck areas. This way people can get the best treatment available now and may also get the new treatments that are thought to be even better. Stage 0 (carcinoma in situ).