Mudança de paradigma no tratamento inicial do câncer de cabeça e pescoço

The change of paradigm in initial therapy of head and neck cancer

RESUMO

Introdução: Devido aos avanços na técnica cirúrgica, radioterapia e quimioterapia, têm ocorrido constantes mudanças na abordagem inicial do câncer precoce e avançado da cabeça e pescoço. Objetivo: Avaliar as mudanças de paradigma ao longo do tempo. Síntese dos dados: A cirurgia evoluiu rapidamente a partir do aprimoramento das técnicas anestésicas, antibióticos, reposição de hemoderivados, novos procedimentos de reconstrução, estratégicas de abordagem das metástases cervicais e tumores laringeos. Reconhecido como um procedimento efetivo de estadiamento e terapêutica, o esvaziamento cervical terapêutico diminuiu as sequelas funcionais e estéticas. Laringectomias parciais e ressecção endoscópica transoral a laser podem preservar a função de fala e deglutição sem a traqueostomia definitiva. Avanços na criação de algoritmos para cálculo e distribuição de doses mais acuradas possibilitaram o desenvolvimento de dosimetria e controle de qualidade na radioterapia, proporcionando uma abordagem mais conservadora. A radioterapia com intensidade modulada tem alta precisão com melhor proteção de órgãos sob risco. Esquemas de fracionamento alterado podem reduzir a toxicidade tardia com benefício na sobrevida. Tomoterapia, arcoterapia volumétrica modulada, radioterapia estereotáctica e FDG-PET CT são recentes abordagens. Quimioterapia de indução e sequencial é um componente-chave no tratamento do câncer de cabeça e pescoço localmente avançado. O anticorpo monoclonal do fator de crescimento epitelial IgG1 (EGFR) mostrou significativa melhor clínica no tratamento do câncer localmente avançado, recorrente e/ou metastático. Conclusão: Assim, o tratamento dos pacientes com câncer de cabeça e pescoço deve ser multidisciplinar e avanços nas estratégias melhoraram os resultados.

Descritores: Neoplasias de Cabeça e Pescoço; Radioterapia; Quimioradioterapia; Quimioterapia.

ABSTRACT

Introduction: Due to advances in surgical techniques, radiotherapy and chemotherapy, there has been constant changes in the initial management of early and advanced head and neck cancer. Objective: To evaluate paradigm changes along the time. Data synthesis: Surgery evolved rapidly from the improvement in anesthetic techniques, antibiotics, blood replacement, new reconstruction procedures, management strategies of neck metastasis and laryngeal cancer. Recognized as an effective staging and therapeutic procedure, elective neck dissection diminished functional and aesthetic sequelae. Partial laryngectomies and endoscopic transoral laser resection could keep the function of speech and swallowing without definitive tracheostomy. Advances in creating algorithms for calculation and distribution of more accurate dose enabled the development of dosimetry and quality control in radiotherapy, providing a more conservative approach. The radiotherapy with intensity modulation has high precision with better protection of organs at risk. Altered fractionation schemes can reduce the late toxicity with survival benefit. Tomotherapy, volumetric modulated archoterapy, stereotactic radiotherapy and FDG-PET CT are recent approaches. Induction and sequential chemotherapy is a key component in the treatment of locally advanced head and neck cancer. The Epidermal Growth Factor IgG1 monoclonal antibody (EGFR) showed significant clinical benefits in the treatment of locally advanced, recurrent and/or metastatic cancer. Conclusion: Thus, the treatment of head and neck cancer patients should be multidisciplinary and advances in strategies have improved the outcome.

Key words: Head and Neck Neoplasms; Radiotherapy; Chemoradiotherapy; Antineoplastic Combined Chemotherapy Protocols.
INTRODUCTION

Advances in surgical techniques, radiotherapy and chemotherapy modalities carry on for increasing the loco-regional control, survival and quality of life of patients with head and neck cancer. These advances have shifted the focus from curative efforts of radical ablation for the organ and function preservation. At the past Century turn, radiotherapy had just been discovered and surgery was discouraged because of the lack of antibiotics and the anesthesia limitations. As a result, there was a trend toward the use of radiotherapy as primary treatment in the first half of the 20th Century. Then, in the mid 20th Century, advances in perioperative care combined with the recognized adverse local effects and failures in the radiation control of the disease led to the emergence of primary surgery with or without adjuvant radiotherapy for the majority of head and neck cancers.

Nowadays, radiation therapy remains an important option for early-stage tumors and plays an important role in the adjuvant setting. In the second half of the 20th Century, the focus on functional outcomes and the increasing role of chemotherapy led to strategies aiming at organ preservation in both surgical and non-surgical approaches. Recently, combinations of chemotherapy and radiotherapy have been increasingly used for cancer in advanced stages, being the primary treatment for adjuvant treatment. Finally, the development of molecular targeted therapy offers new options for the treatment of cancer of the head and neck, which may improve survival and functional outcomes.

Currently, there is a change in the initial management of head and neck cancer, either for early and for advanced disease. Radiotherapy with or without chemotherapy is considered an option in order to achieve oncologic control. On the other hand, it offers better functional and aesthetic outcome. As a result, such approach could be considered the treatment of choice. Furthermore, the ability for probable identification of occult disease through new methods for detection by means of molecular markers would create a new paradigm in this already fetched scenario, determining the paradigm shift. Therefore, head and neck cancer should be understood as a systemic phenomenon instead as a localized condition.

SURGERY

As a tool in the treatment of head and neck cancer, surgery evolved rapidly from the improvement in anesthetic techniques, development of antibiotics, blood replacement and the introduction of new reconstruction procedures. Radical resection, whose primary goal is the potential cure, should always seek to preserve the aesthetic function with lowest possible injury. The technical improvement in management strategies of neck metastasis and for laryngeal cancer is an example of evolution and adaptation of treatment based on the understanding of the phenotypic expression of the disease.

The radical neck dissection was introduced in the late 19th Century\(^3\) and represented the workhorse of treatment of cervical lymph node metastases for many decades. The progress regarding the neck approach is undeniable, since Crile’s publication\(^6\) and through the historical publication of Martin\(^7\) with standardization of radical neck dissection, without preservation of non-lymphatic structures. It is noteworthy that Martin was not adept to elective (prophylactic) neck dissection advocating the conduct of wait and see and intervening after the neoplasm recurrence.

In 1963, Suarez\(^8\) published an article showing the possibility of radical neck dissection with preservation of non-lymphatic structures (internal jugular vein, sternocleidomastoid muscle and XI cranial nerve) based on the fascial compartments of the neck. Thus, the concept of modified radical neck dissection (MRND) was introduced\(^9\), considering the oncological radicality and the functional and aesthetic maintenance. In 1972, the rationale selective neck dissection was established\(^10\) with the identification of the distribution patterns of clinical metastasis according to the subsites within the head and neck. The evaluation of the histological pattern of cervical lymph node metastasis in patients undergoing elective radical neck dissection and treatment for cancer of the head and neck was considered since 1970\(^11,12\). Then, it was created the basis for selective neck dissection to levels with higher risk of metastasis and an alternative for MRND.

Although the movement towards elective neck dissection (END) and MRNI was in order to avoid functional and aesthetic sequelae associated with radical neck dissection (RND), END was useful as a staging procedure and its effectiveness was demonstrated by several studies in the late 1990\(^13,14\). Its use was suggested as a safe alternative in patients with clinically lymph node with limited disease\(^15-17\). Cervical lateral endoscopic approaches were proposed\(^12\) as minimally invasive techniques and may have utility in the future. The ability of identifying probable occult disease has been improved through new methods of detection by molecular markers, which would create a new paradigm in this already fetched scenario when the knowledge of tumor biology determines paradigm shift. The head and neck cancer ceases to be understood as a localized phenomenon and is understood as a systemic one.

The treatment of laryngeal cancer also demonstrates the conservative spirit or a tendency to functional surgical conservatism notwithstanding the oncological radicalism based on the understanding of the disease expression. In the early 20th Century, the lack of early diagnosis, limitation of anesthesiology and high mortality rate of laryngeal cancer, the situation was hopeless and most patients refused to undergo major procedures because of the low hope of surviving after the perioperative period and also the low cure rates\(^18\). In such a scenario, radiotherapy...
was welcome to the therapeutic arsenal and became the primary treatment of choice for laryngeal cancer. The limitations of the initial radiotherapy techniques have been recognized and an advance in surgical techniques and perioperative care led to a reverse situation in which surgery became once again the treatment of choice for cancer of the larynx.19

In parallel, extensive experimental and observational studies identified the anatomical basis for the cancer spread in the larynx as well as their pattern of lymph node metastasis. This knowledge provided the possibility of developing surgical techniques so as to perform partial laryngectomies.20-22. The purpose of these procedures was to obtain healing by means of less radical approaches, since they could keep the function of speech and swallowing without definitive tracheostomy.23 Subsequently, techniques for endoscopic resection and transoral laser resection were developed and listed as forms of conservative treatment.24-27. Functional laryngeal preservation with adequate oncologic control can be achieved employing the conservative surgery.

More recently, other advances in the operative domain continued to be developed in considering the functional and aesthetic consequences as reconstruction techniques, especially microvascular free flaps, endoscopic endonasal access for resection of anterior skull base tumors with minimally invasive approaches and transoral resection, especially for cancer of the oropharyngeal and supraglottic tumors.32

RADIOThERAPY

The discovery of X-ray by Roentgen (1895), the description of the natural radioactivity32 and subsequent isolation of two new radioactive elements by the Curies, in 1898, laid the foundation for the start of radiation therapy either external (source away from the patient) and brachytherapy (source in the patient). After six months of the Roentgen’s discovery, the first cancer radiation treatment was performed in a patient with gastric cancer.34 The undesirable effects of radiation were related and safety concerns become the object of several studies.

In the first decades of the 20th Century, with the development of ionizing chambers, radiation began to be measured. Brachytherapy was liable for the treatment of some cancers such as base of tongue and uterus tumors.35 In the 1920s, a larynx cancer was cured for the first time without the need for surgery and tracheostomy.36 At this time, it was showed that there was radiosensitivity difference according to the cellular types and dose fractionation (2Gy per fraction) was proposed.37

With the spread of radiotherapy, in 1928 the International Commission on Radiological Protection (ICRP) was created for controlling the safe use of the radiation, creating the concept of radioprotection38. In 1948, the first unit of Telecobalto therapy was installed in Canada. This new technology allowed doses above 50Gy for the treatment of deeper tumors, radically expanding the use of radiotherapy. On the other hand, the use of Co60 radioactive source could lead not only potentially exposed workers, but also the general population to unnecessary and harmful radiation exposure.

The evolution of the radar during the World War II, concerning the use of microwave tubes, enabled the construction of the first linear accelerator, which produced X-ray megavoltage (6mV and 20mV) without the need of using radioactive sources. In 1953, London was the first city to have a linear accelerator. As a result, doses from 60 to 70Gy began to be used even deeper in the development of tumors without unacceptable toxicity to adjacent organs at risk. In this period, the planning of radiotherapy and the location of the fields was done through bony landmarks and treatment was limited primarily to rectangular fields in composition forming “cubes” high dose which involved “target” treatment.

After the second half of the 20th Century, the combination of radiotherapy computers has enabled the creation of software (System Planning), creating algorithms calculation and distribution of more accurate dose, enabling the development of dosimetry and quality control in irradiating treatments.41

Those developments made radiation therapy play a key role in cancer treatment with the possibility of curative treatments in different types of tumors and a significant increase in local control allowing the development of more conservative treatments.42

The last 20 years have been no less extraordinary in the evolution of radiotherapy than that achieved in the 20th Century. The development of tomography43 and the immense development of computing have made the planning of radiotherapy evolve planar radiographs, two-dimensional treatment planning and volumetric tomography based on the three-dimensional technique.

The incorporation of the multileaf collimators to linear accelerators managed by new systems with better planning algorithms calculations and new features (beam-eye-view) provided higher dose on target tissue and protected risk on the surrounding tissues.44-46. Thus, the possibility of dose escalation above 70Gy was possible with proven benefit in prostate tumors.47

After a century of evolution, the gold standard of radiotherapy that would allow an important benefit in the treatment of head and neck cancer was the development of radiotherapy with intensity modulation (IMRT). The IMRT is a type of three-dimensional conformal highly sophisticated radiotherapy, with high precision and controlled by computers which allow non-uniform intensity attributed to a small subdivision of the radiation beam, making it possible to manipulate the beam into several small volumes allowing greater control distribution. It
also used the inverse planning that defines specific doses in healthy adjacent tissue and tumor. So the dose is delivered more accurately on the target, better protection of organs at risk and allows reach different doses in different areas of the same treatment without the necessity of modifying the field (Simultaneous Integrated Boost - SIB).

Recent studies using IMRT demonstrate the superiority of this technique over the others. A randomized study of 60 patients with T1/T2 nasopharyngeal carcinomas showed that IMRT was superior to the conventional two-dimensional treatment in preserving the function of the parotid glands with less late xerostomia after 1 year. The phase II study (RTOG 0225) investigated the feasibility of using IMRT with or without chemotherapy in 68 patients with nasopharyngeal cancer. Grade IV acute mucositis occurred in 4.4% of patients and progression-free survival and overall survival were 72.7% and 80.2% respectively and the rate of grade II xerostomia at 1 year was only 13.5%.

Adaptive radiation therapy is a process in which the treatment plan can be modified and adapted using systematic monitoring of the possible variations that occur during the 5-7 weeks of treatment (tumor volume reduction, weight loss). A new plan tailored the initial course of treatment with the acquisition of new images. In this case, the field margin and treatment dose can be routinely customized for each patient to achieve a dose escalation of security dose.

Another important field of study within the radiotherapy is the altered fractionation schemes. The classic fractionation with an application, once a day for five days a week is commonly used in the treatment of this cancer. In accelerated fractionation, the total treatment time is reduced. This reduces tumor repopulation between the sessions and may allow better local control. Hyperfractionated treatments (two or three applications at lower doses than conventional fractionation) is carried out in one day and can reduce the late toxicity. A meta-analysis of 15 randomized clinical trials enrolled more than 6,000 stage III/IV head and neck cancer patients. In this analysis, there was a small but significant survival benefit of 3.4% associated with altered fractionation radiotherapy in 5 years. The survival benefit was significantly higher with hyperfractionated-accelerated radiotherapy and also among patients under 50 years who had good general condition. The Radiation Therapy Oncology Group (RTOG) has recently completed a phase 3 trial, RTOG 0129, to examine whether the benefit of altered fractionation persisted when combined with chemotherapy. There was no significant difference in acute late toxicity.

The tomotherapy is a type of radiotherapy in which processing is done “slice by slice”, unlike other forms of radiation therapy in which the entire tumor volume is irradiated at a time through a supply of megavoltage X-rays. Constructed with a tomography similar setting, this technique allows a combination of IMRT and image-guided radiotherapy better conformation enabling the beam and maximum dose gradient for the protection of radiosensitive organs. In a comparative study of patients with head and neck cancer treated with IMRT and tomotherapy, the free of loco-regional recurrence survival rates at 1 and 2 years were 61.2% and 58.1% for the conventional RT group, and 89.3% and 80.3% for tomotherapy group. Thus, the outcome for theomotherapy treated group was significantly higher than the conventional group (p = 0.029). There were no significant differences in overall survival and freedom from distant metastases between the groups. Besides the radiation technique, the tumor stage and duration of treatment were significant prognostic factors for loco-regional recurrence-free survival rates.

Volumetric modulated archotherapy (IMAT), another innovation in radiotherapy, allows to change three parameters during treatment: gantry rotation speed; treatment field by modifying the shape of the collimator blades; and the rate dose. This type of treatment allows a reduction in the duration of each treatment session while maintaining the highest compliance standard dose of IMRT. It enables the reduction of monitors (beam time) units during treatment, which decreased scattered patient radiation.

Stereotactic radiotherapy (SBRT) is a new radiotherapy technique that enables the use of high doses in small volumes using highly accurate stereotactic localization devices. In head and neck its use is still being studied and its main role is in the irradiation of recurrent tumors in areas previously irradiated.

The use of FDG-PET combined with CT is a breakthrough in the treatment with radiotherapy. Its use has potential advantages in defining the tumor (GTV) and its banks, distinguishing active disease metabolism. More recently, a prospective study has demonstrated the added planning with the use of 18F-FDG-PET and 18F-FMISO-PET in radiotherapy planning and evaluation of response value.

Chemotherapy and targeted therapy
Chemotherapy is a key component in the treatment of locally advanced head and neck cancer. In a meta-analysis published in 2002 (MACH -NC), in which 93 randomized trials including 17,346 patients were studied, the hazard ratio of death was 0.88 (p < 0.0001) with an absolute benefit for chemotherapy of 4.5% at 5 years and a significant interaction (p <0.0001) between the type of chemotherapy (adjuvant or concomitant induction) and treatment. Both direct (six trials) and indirect comparisons showed a more pronounced benefit of the concomitant chemotherapy compared with induction chemotherapy. For 50 concurrent trials, the hazard ratio was 0.81 (p < 0.0001) and the absolute benefit of 6.5% at 5 years. There was a decreasing effect of chemotherapy with age (p = 0.003).

The role of induction chemotherapy for several authors has been studied. The combination of taxanes, platinum and fluorouracil (Tax-PF) may be superior to...
platinum and fluorouracil (PF). In most studies, the Tax-PF scheme has shown a significant increase in overall survival (OS) and progression-free survival (PFS)\textsuperscript{64-69}. In a metaanalysis\textsuperscript{70}, 5 randomized trials gathering 1,772 patients demonstrated the superiority of Tax-PF scheme compared to PF with significant reduction in progression, loco-regional recurrence and failure to distance, with HR of 0.78 (95% CI, 0.69 to 0.87, p < 0.001), 0.79 (95% CI, 0.66-0.94, p = 0.007) and 0.63 (95% CI, 0.45 to 0.89, p = 0.009), respectively.

The results of Epidermal Growth Factor IgG1 monoclonal antibody (EGFR), Cetuximab showed significant clinical benefits in the treatment of locally advanced, recurrent and/or metastatic cancer. Based on the data from the phase III study\textsuperscript{71}, the European Society for Medical Oncology (ESMO) in its guidelines recommend the use of Cetuximab in combination with radiotherapy\textsuperscript{72}. The use of Cetuximab associated with radiochemo therapy was shown to be feasible in phase II studies and is being investigated in phase III trials. Taken together, these data support an important role in Cetuximab treatment for locally advanced head and neck cancer.

**FINAL COMMENTS**

The advances in strategies for the treatment of head and neck cancer have affected all approaches: surgery, radiotherapy, chemotherapy and targeted therapy. Additionally, the changing of the epidemiological profile seems to determine a group of patients with distinct disease when associated with HPV. Thus, the treatment of these patients should have a multidisciplinary approach, including surgical oncology, radiation oncologists, oncologists, radiologists, dentists, nurses, specialists, psychologists, speech therapist and nutritionists. The experience of the treatment center plays a large and strategic role. A major challenge in treating any type of cancer is to obtain a high cure rate while preserving vital structures and their functionality. This is especially true for tumors of the head and neck due to the anatomic complexity of the region, where major structures and their functions are affected by both the cancer and its therapy\textsuperscript{73,74}. The question to be discussed is that despite these advances, cancer of the head and neck remains a disease under poor prognosis, with the main factor associated with late diagnosis with advanced loco-regional disease and the absence of appropriate biomarkers to detect the progression of the disease. In case of disease control, there is a risk of developing a second primary tumor (4% per year). These primary tumors are considered to result from the field cancerization\textsuperscript{75,76}. Thus, clinical studies to characterize and validate appropriate biomarkers for early detection and specific biomarkers for early tumors at high risk are essential. The characterization of a molecular profile of the patient with head and neck cancer may help in the prediction of tumor behavior and response to therapy culminating with better results.

**REFERENCES**