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Current radiotherapic procedures and preservation of salivary function in patients with head and neck cancer

Recenti procedure radioterapiche e di preservazione della funzione salivare in pazienti affetti da carcinoma della testa e del collo

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Summary

Head and neck tumours have poor prognosis: with surgery and radiotherapy, local control is achieved but is associated with damage to speech and swallowing function. Conventional 2-D radiotherapy is based on one fraction of 1.8-2.0 Gy per day; increasing the number of fractions, a higher dose can be administered, with an increase in local control. Today, conventional treatment can be replaced by new techniques: with 3-D Conformal Radiotherapy, higher doses of radiation can be delivered to cancer cells while reducing the amount of radiation received by surrounding healthy tissues; Intensity Modulated Radiation Therapy permits an irregular dose distribution that conforms exactly to the volume of the target, increasing local tumour control and survival and decreasing radiation-induced side-effects.

Riassunto

In generale i tumori della testa e del collo hanno una prognosi poco favorevole: con la chirurgia e la radioterapia spesso si ottiene un buon controllo locale a discapito però della funzione fonatoria e deglutitoria. La radioterapia convenzionale si basa su un frazionamento di 1,8-2,0 Gy al giorno; aumentando il frazionamento, è possibile somministrare dosi più elevate, ottenendo un miglior controllo locale della neoplasia. Oggi come oggi il trattamento radioterapico convenzionale può essere sostituito dall'utilizzo di nuove tecniche: con la 3-D Conformal Radiotherapy più alte dosi di radiazioni possono essere somministrate alle cellule tumorali, riducendo la quantità di radiazioni ricevuta dai tessuti sani circostanti; l'Intensity Modulated Radiation Therapy permette una distribuzione irregolare della dose somministrata, che si conforma esattamente al volume del bersaglio, aumentando il controllo locale del tumore e riducendo gli effetti collaterali indotti dalle radiazioni.

Introduction

Patients with head and neck cancer require complex multidisciplinary care, on account of the great differences in these tumours. The treatment options include: radiotherapy, surgery or a combination of both and the end-point of any new treatment is minimizing the high morbidity related to the treatment itself [1-3].
Therefore, it is necessary to evaluate the quality of life (QoL) of these patients, analysing the side-effects of radiotherapy, particularly as far as concerns salivary deficit, and new therapeutic strategies which can modify this kind of sequence.

Radiation therapy: from 2-D to Intensity Modulated Radiation Therapy

Conventional radiotherapy techniques encompass the primary tumour site with a 1-2 cm cuff of normal tissue and the associated lymphatic drainage.
2-D treatment [2] is based on two lateral fields and, to achieve a homogeneous dose distribution, a compensatory filter or wedge can be used for each individual patient; the prescribed irradiation dose is 60-70 Gy, delivered at 1.8-2.0 Gy per fraction.
Several Authors have suggested the advantage of hyper-fractionation in radiotherapy of head and neck carcinoma [4].
The rationale for hyper-fractionation is based on exploiting differences in the radiobiology of the tumours, which respond quickly, and the late-responding normal tissues; these differences depend upon three phenomena: differences in repair capacity, differences in the effect of division cycle redistribution and an increase in the relative "biological" dose rate to the tumour [5]. Thus a higher dose can be administered at the same time as the conventional treatment,

increasing the number of fractions, hence using at least two fractions per day with a lower dose per fraction. In a randomised study on patients with oro-pharyngeal neoplasia, it was observed that local control is significantly higher in hyper-fractionation (80.5 Gy in 70 fractions with 2 daily fractions, delivered at 1.5 Gy per fraction) than in a single fraction per day (70 Gy, in 35 fractions in 7 weeks) resulting in a 5-year local control of 59% *vs* 40%. There was no difference in late normal tissue damage between the two treatment modalities [5].

Today, conventional radiotherapy can be replaced by a new technique that delivers the prescribed dose to the tumour or target volume, minimizing the dose to the surrounding critical structures.

Three-dimensional conformal radiotherapy (3-D CRT) is a complex process that begins with the creation of individualized, 3-D digital data sets of patient tumours and normal adjacent anatomy.

These data sets are then used to generate 3-D computer images and to develop complex plans to deliver highly “conformed” (focused) radiation while sparing normal adjacent tissue. Since higher doses of radiation can be delivered to cancer cells while significantly reducing the amount of radiation received by the surrounding healthy tissues, the technique should increase the rate of tumour control while decreasing side-effects [6].

The use of more precise ways to deliver the dose to the target volumes and protect the normal tissues at risk obviously requires an excellent knowledge of the volumes to be irradiated and an accurate delineation of these volumes on a 3-D basis.

New guidelines for the selection and definition of Clinical Target Volumes (CTV) in the neck of patients with head and neck carcinomas are, therefore, necessary, particularly in deciding which neck lymph nodes are to be included in the CTV.

Typically, in the head and neck region, lymphatic drainage remains ipsilateral, but structures, such as the soft palate, tonsil, base of the tongue, posterior pharyngeal wall and particularly the naso-pharynx have bilateral drainage.

It has been proposed that treatment of N0 patients with head and neck squamous cell carcinoma is warranted if the probability of occult cervical metastases exceeds 5-10%; similar guidelines could also be recommended for N1 patients without suspected extra-capsular infiltration. For N2c patients, each side of the neck can be considered separately and for N3 patients, treatment of the neck is likely to be dictated by the local infiltration of the node into adjacent structures [7].

Adjuvant radiotherapy is performed in patients with a high risk of lymph node recurrence, with close or positive margins, mass infiltration, capsular rupture, with a metastatic node >3 cm in diameter or with more than one metastatic node.

The new IMRT technique allows dynamic changes to be made in the dose distribution, modulating the intensity of the irradiation through filters as the treatment proceeds, thereby permitting an irregular dose distribution that conforms exactly to the volume of the target.

This technique has a dual impact on cancer treatment, i.e., an increase, both in local tumour control and patient survival, and a decrease in radiation-induced side-effects [8].

Chao et al. made a retrospective comparison of clinical outcomes and radiation treatment-related side-effects in patients with oro-pharyngeal neoplasia treated with IMRT or 3D-CRT. The results showed that the 2-year local-regional control was 88-100% in patients receiving IMRT compared with 68-78% in patients receiving 3D-CRT while the acute toxicity across the two treatment groups was comparable but there was a significantly higher incidence of late xerostomia in patients receiving CRT as compared with those receiving IMRT. IMRT significantly reduced the incidence of xerostomia without any adverse impact on tumour control and Disease-Free Survival in patients with oro-pharyngeal carcinoma [9].

Certainly, IMRT needs to be further analysed, particularly as far as concerns delineation of the target volume [10], but it has all the potentials of becoming one of the greatest improvements in the field of radiotherapy by improving the therapeutic ratio with the escalation of a biologically effective dose.

Side-effects

Radiation therapy to the head and neck area frequently results in permanent, severe salivary gland dysfunction. Saliva production is decreased and its composition is modified. Patients may experience numerous sequelae, including xerostomia, dysphagia, difficulty in chewing and speaking, changes in nutrition, high risk of dental caries and chronic oesophagitis. Albeit, the most invalidating long-term side-effect of radiotherapy is xerostomia [11].

We define xerostomia if the basal salivary flow is <0.1 ml per minute (nv 0.3-0.5 ml/min), with severity depending on extensions of irradiated volume and administered dose.

The salivary glands are highly sensitive to radiation: saliva flow is significantly reduced following 10-15 Gy delivered to most of the gland. While recovery of function is possible over time, following radiation doses up to 40-50 Gy, higher doses to most of the glands cause irreversible hypofunction and permanent xerostomia, which is the most common side-effect and cause of reduced QoL following irradiation of head and neck cancer [12].

According to morphological studies on radiation effects in man and animals, the serous type of gland (parotid gland) is more vulnerable than the mucous type (submandibular gland), and excretory ducts were the least, and acini the most, affected by radiation. After single doses of irradiation, serous acini showed vacuolar degeneration, while mucous acini showed no acute histopathological changes [13]. The latter Authors showed that histological evaluations are not a reliable measure for early radiation-induced salivary gland damage, whereas late histopathological changes (acinar atrophy and chronic inflammation) and the late functional response are comparable between the parotid glands and submandibular/sublingual glands [14].

Evaluation of the relationship between the 3-D dose distributions in parotid glands and their salivary production reveals the existence of threshold values for dose and volume: Eisbruch et al. observed that both parotids should receive a mean dose of 24 Gy to maintain a "non-stimulated" basal flow and of 26 Gy for a "stimulated" flow. Probably, the same threshold dose could be administered on the other salivary glands. In that same study, analysing the threshold exposure volume of the parotid glands, it was observed that 55% of the gland volume should receive a dose <30 Gy [12].

Tsujii indicated that, in the parotids, the volume of the gland irradiated as well as radiation doses were a key factor for the development of salivary dysfunction: more than 50% of the parotids had to be outside the fields to prevent severe dryness and, if any portion of the parotid gland was not irradiated, they could be stimulated to produce saliva [15].

Conclusions

Patients with head and neck cancer have a poor QoL, related not only to the functional deficit caused by the disease but also to the side-effects of therapy.

New therapeutic approaches are being introduced to improve local control and overall survival as well as to preserve gland function and reduce the side-effects of radiotherapy.

Late toxicity is analysed using specific toxicity scales (EORTIC C30, EORTIC HN35, HNRQ, UW-QOL) to evaluate QoL in neoplastic patients; furthermore, during the Late Effects of Normal Tissues Conference, a new system to assess the side-effects of cancer therapies was studied, based on a severity score, ranging from 0 to 5 (SOMA or SOMAS) [16].

Thus an overall evaluation of these patients becomes necessary: each new treatment introduced has to be analysed not only as far as concerns local control but also from a toxicity viewpoint to evaluate how it might influence quality of life.

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