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Prognostic significance of cervical lymph nodes density evaluated by contrasted computer tomography in head and neck squamous cell carcinoma treated with hyperthermia and radiotherapy

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Introduction: A correlation between node hypodensity assessed by means of computer tomography (CT) and resistance to both chemotherapy and radiation therapy (XRT) in advanced head and neck tumours has been suggested in the literature. The outcome of a retrospective series of 50 patients with head and neck squamous cell carcinoma (SCC) and cervical nodes metastases treated with combined hyperthermia (HT) and definitive XRT was reviewed to investigate if node density confirmed its prognostic value.
Materials and method: For all patients, a pre-treatment contrasted CT scan performed at the Institution between 1987–1993 was available. The density of the largest node (> 2 cm) was compared to that of adjacent nuchal muscles. Nodes with hypodense areas present in more than one third of the total volume were considered necrotic nodes.
Results: The patients were divided in two groups (with and without nodal necrosis), well balanced in terms of potential prognostic factors. No significant difference in overall nodal response rate, local control and survival was found in the two groups of patients.
Conclusion: Nodal density assessed by contrasted CT scan in the series did not result in a significant prognostic factor in patients with SCC node metastases treated with HT and XRT. It is suggested that HT could act as a radiosensitizer in the treatment of hypodense (at CT scan) metastatic nodes overcoming the radioresistance of necrotic, presumably hypoxic nodal metastases.

Key words: Hyperthermia, head and neck, node metastasis, radiotherapy, CT scan.

1. Introduction

Metastases to regional lymph nodes are an important prognostic factor in head and neck tumours (Vokes *et al.* 1993). Several node characteristics such as localization, number, size, extracapsular spread and fixation have been found to predict local control and overall survival in different series (Snow *et al.* 1982, Lefebvre *et al.* 1987, Leemans *et al.* 1990). Furthermore, the prognostic significance of cervical nodes appearance on a computer tomography (CT) scan in predicting response to chemotherapy in advanced head and neck cancers has been reported (Munck *et al.*

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1991, Janot *et al.* 1993). More recently, this has been confirmed also for radiation therapy (XRT) (Grabenbauer *et al.* 1998), with findings proving a correlation between node hypodensity and resistance to irradiation.

The appearance of lymph nodes on CT after injection of contrast medium gives information regarding vascularity and, hence, perfusion and oxygenation status inside the node. The areas of hypodensity that are commonly seen inside large cervical nodes are considered to be suggestive of locally impaired angioperfusion resulting in necrosis and hypoxia of metastatic tumour cells (Hermans *et al.* 1997). This phenomenon is caused by both the accelerated growth rate of rapidly-dividing cancer cells and the defective neoangiogenic tumour process. As tumour perfusion is related to tumour oxygenation, perfusion measurement by dynamic computed tomography has also been suggested as a prognostic indicator regarding the outcome of head and neck tumours after XRT (Hermans *et al.* 1999).

It is long well known that hypoxic tumour cells are less responsive to the effect of both chemotherapeutic drugs (Nugent and Jain 1988) and irradiation (Gatenby *et al.* 1988). Drugs need effective perfusion in order to reach and exert their action inside tumour areas, and the importance of the presence of oxygen during irradiation has found confirmation not only in early experimental radiobiological observations (Gray *et al.* 1953), but also in several clinical series (Overgaard and Horsman 1996). The positive results of this meta-analysis (Overgaard and Horsman 1996) based on previous clinical trials were dominated by tumours localized in the head and neck region.

Hyperthermia (HT) is known to be effective on hypoxic tissues, being commonly employed together with XRT in order to overcome hypoxic tumour cells acquired radioresistance (Meyer 1984, Field 1989).

It was investigated whether node density assessed on pre-treatment CT confirmed its role as a relevant prognostic factor on a retrospective series of cervical nodal metastases of head and neck tumours treated with combined hyperthermia and radiation therapy.

2. Materials and methods

The outcome was reviewed of a series of 50 patients with head and neck squamous cell carcinoma (SCC) and cervical nodes metastases treated with combined HT and XRT between 1987–1993. Only patients for whom a pre-treatment CT scan was available were selected. The examens acquired with bolus injection of contrast medium and with a cross-section of the largest node greater than 2 cm were considered for this study. This lymph node size has been chosen since it is considered to be predictive of metastatic invasion (Mancuso *et al.* 1983).

Node density was assessed on CT scans by the radiologist in charge, as reported by Munck *et al.* (1991). Briefly, the density of the neck node was compared to that of adjacent normal nuchal muscles. Nodes with hypodense areas present in less than one third of the volume were classified for the purpose of this study as grade 1. Those with hypodense areas present in more than one third of the total volume were considered necrotic nodes and classified as grade 2.

The patients were retrospectively restaged using the criteria of the 1997 TNM-UICC staging system. There were 45 men and five women; the median age was 62 years (range: 45–83 years). Patients, tumour and node characteristics are reported in table 1. The two groups of patients were homogeneous and well balanced in terms of clinical and therapeutic characteristics. The characteristics of CT scan of the two

Table 1. Patients and tumour characteristics.

	Grade 1 group	Grade 2 group
No of patients	22	28
Median age	61 years	62 years
(range)	(47–83)	(45–80)
Sex	males 20, females 2	males 26, females 2
Karnofsky PS	90	90
(range)	(80–100)	(70–100)
Median basal Hb level	11.6 g/dl	10.9 g/dl
(range)	(9.6–16.1)	(9.8–14.4)
Primary head and neck site		
oral cavity	4	7
oropharynx	6	5
hypopharynx	4	6
larynx	3	6
other	5	4
T-stage		
*T*x	2	3
*T*1–*T*2	6	7
*T*3–*T*4	14	18
Mean max. node diameter	4.85 cm	5.1 cm
(range)	(3–7)	(3–8)
Nodal stage N2a	10	14
N2b	6	7
N2c	2	1
N3	4	6
No of pts treated with DDP	6	8

groups of patients were related to the response to treatment, evaluated 3 months after therapy, to local control and survival.

All the patients received radical XRT on primary tumour and cervical nodes according to the protocols in use at the time of treatment. Irradiation was administered by a 6 MV linear accelerator or a 60 Co teletherapy unit, using conventional fractionation schedule with daily fraction size of 2.0–2.5 Gy, five fractions weekly, with or without concomitant weekly i.v. infusion of cisplatin (20 mg/m^2), or with a hyperfractionated regimen with two daily fractions of 1.2 Gy. The characteristics of the radiation protocols combined with HT have previously been reported (Valdagni *et al.* 1986, 1988, Amichetti *et al.* 1993). Opposed lateral fields were used initially to treat one large clinical target volume including both primary tumour and all cervical nodes; field reduction was planned at 40–45 Gy in order to exclude the spinal cord. Electron beams of energies varying between 7–12 MeV were employed when deemed necessary to boost the dose on neck nodes.

Hyperthermic treatment was delivered with a BSD 1000 Unit (BSD Medical Corporation, Salt Lake City, USA) with the same applicator (MA150, aperture size 10×13 cm), at operating frequencies of 280–300 MHz. Heat was delivered 20–25 min after irradiation twice a week (Monday–thursday or tuesday–friday) for a total of two or six sessions. The goal for each session was to attain a tumour temperature of at least 42.5°C per 30 min at the periphery of the target volume. Tumour temperatures were monitored with intra-peritumoural single-point Bowman probes, generally positioned at the tumour–normal tissue interface and in the tumour. Skin temperatures were measured with superficially placed thermal

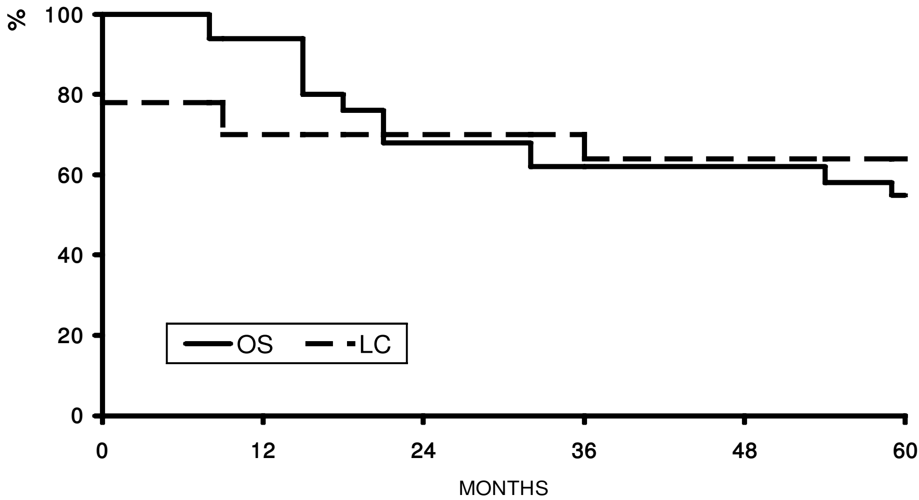

Figure 1. Kaplan-Meier representation of the probability of survival (solid line) and local control (dotted line) at 5 years in patient with grade 1 node density at CT scan.

sensors. Usually, thermal probes with a nodal periphery/nodal core ratio of 4:1 were positioned; one probe was inserted at the centre of the node and four at the boundary with normal tissue (two lateral, one deep, one superficial). Two or more maps were taken at different times during the treatment course. The hyperthermic procedure has been described in details elsewhere (Valdagni *et al.* 1988, Amichetti *et al.* 1991).

Several thermal parameters were analysed: T_{min} and T_{max} (the minimum and maximum intratumoural temperature measured during all spatial maps during steady-state conditions), $*T_{\mathrm{min}}$ and $*T_{\mathrm{max}}$ (the average of T_{min} and T_{max} over the applicable treatments), minimum (min Eq 42.5) and maximum (max Eq 42.5) 'thermal dose' in equivalent minutes at 42.5°C (Sapareto and Dewey 1988) for each treatment and total minimum (Total min Eq 42.5) and maximum (Total max Eq 42.5) 'thermal dose' for all treatments.

WHO criteria have been adopted in the evaluation of tumour response (Miller *et al.* 1981). The Kaplan-Meier product limit method (Kaplan and Meier 1958) was used to calculate actuarial survival times and local control. Fisher's exact test (two-tailed) was used to test for statistically significant associations between patient-, tumour-, and treatment-related variables and response. Chi-square tests were used to analyse the association of categorical variables. The log rank test (Mantel 1966) was used for statistical comparison between curves.

3. Results

The data about irradiation and thermal parameters are reported in table 2. The two groups of patients had similar treatment in terms of radiation total dose delivered, number of hyperthermia sessions, and thermal characteristics.

Globally, patients achieved a complete response (CR) rate of 76%. Seventeen out of 22 (76%) patients with grade 1 node density and 21 out of 28 (75%) with grade 2 node density obtained CR ($p =$ not significant). Five-year local control and survival of grade 1 patients was 64 and 55%, respectively (figure 1) 5-year local control and

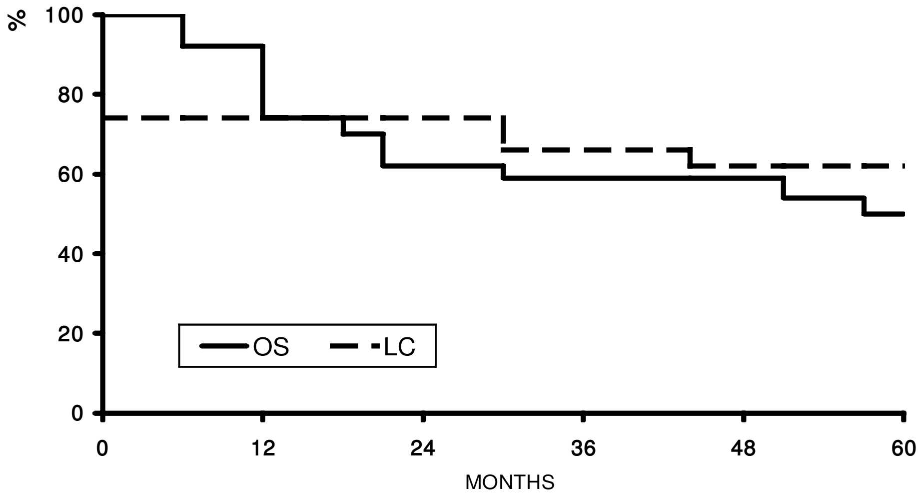

Figure 2. Kaplan-Meier representation of the probability of survival (solid line) and local control (dotted line) at 5 years in patient with grade 2 node density at CT scan.

Table 2. Treatment parameters.

	Grade 1 group	Grade 2 group
Irradiation		
Mean XRT total dose	70.67 Gy	69.52 Gy
(range)	(60–75.90)	(60–74.40)
Thermal parameters		
no of sessions	two: 16; six: 6	two: 17; six: 11
T_{max} (°C)	44.23 (40.3–46)	45.01 (40.8–49.2)
$*T_{max}$ (°C)	43.08 (40.6–45.8)	43.88 (40.9–47.1)
T_{min} (°C)	40.75 (< 40–42.8)	40.24 (< 40–42.0)
$*T_{min}$ (°C)	40.36 (< 40–42.1)	40.05 (< 40–41.4)
Total max Eq 42.5	16.5–1184	9.2–1069
Total min Eq 42.5	0–148	0–196

survival of grade 2 patients was 62 and 50%, respectively (figure 2). The difference between the two groups was statistically not significant.

Nodal density did not result in a statistically significant prognostic factorn similar to the other patient- (age, sex, basal haemoglobin level), tumour- (maximum nodal diameter), and treatment- (XRT total dose, thermal parameters) related variables.

4. Discussion

The prognosis of patients with SCC of the head and neck is greatly influenced by their stage of disease (Dimery and Hong 1983, Vokes *et al.* 1993). Regional lymph node metastases are recognized to be a major determinant in the clinical course and treatment outcome of these patients (Richard *et al.* 1987, Bataini *et al.* 1990, Cerezo *et al.* 1992). The prognostic value of several characteristic of node disease, such as localization, size, and morphologic appearance has been studied by different authors (Snow *et al.* 1982, Lefebvre *et al.* 1987, Leemans *et al.* 1990).

It is known that portions of malignant tumours are hypoxic, probably due to their rapid and disordered growth and the establishment of a defective vasculature (Hall 1994). Tumour oxygenation affects the prognosis of head and neck cancer independently of other known prognostic variables (Brizel *et al.* 1999). Node density estimated by CT scan, considered to reflect oxygenation status inside metastatic nodes, has recently gained a place among prognostic factors of head and neck cancer outcome. Patients with node metastases from head and neck cancers with hypodensity extended to more than one third of the total volume were reported to have a significantly inferior response to either chemotherapy (Munck *et al.* 1991, Janot *et al.* 1993) and/or radiation therapy (Grabenbauer *et al.* 1998).

In a retrospective series of patients with stage IV undifferentiated carcinoma of nasopharyngeal type (UCNT) or SCC treated with chemotherapy and radiation therapy (Munck *et al.* 1991), nodal density was found to be significantly associated in multivariate analysis with both complete response and overall survival rates. The same authors conducted a prospective study that validated these results (Janot *et al.* 1993). The response to neoadjuvant chemotherapy of 36 previously untreated head and neck SCC patients with metastic nodes was significantly correlated to node density.

Controversial results were obtained in a retrospective series of 161 patients with nasopharyngeal carcinoma (Chua *et al.* 1997). In this study, multivariate analysis did not confirm cervical nodal necrosis to be an independent prognostic factor. It is noteworthy that undifferentiated nasopharyngeal tumours are known to be more sensitive to irradiation and chemotherapy compared to SCC, therefore the possible difference in outcome between hypoxic and well oxygenated nodes may require a large study population and very strict evaluation criteria.

Recently, the importance of SCC cervical node density was also reported in a large series of head and neck metastatic nodes treated with radiation therapy alone (Grabenbauer *et al.* 1998). At multivariate analysis, nodal CT density was an independent prognostic factor for overall survival together with age, and the only independent factor predicting locoregional control. It can be underscored that, in most of these series, the prognostic value of node density was superior to that of other prognostic factors extensively reported in the literature, such as the site of primary disease and T and N stage and size (Snow *et al.* 1982, Lefebvre *et al.* 1987).

The results of the above mentioned studies confirm that nodal necrosis, characterized by areas of impaired angioperfusion and tumour hypoxia, adversely affects treatment outcome, confirming the well known concept of radioresistance of hypoxic cells (Hall 1994). Moreover, tumours with a low CT-determined perfusion rate have a trend towards worse local outcome than those with a higher perfusion rate (high vascular density) (Hermans *et al.* 1999). These data suggest that necrotic cervical nodes, at least from SCC, identify a subgroup of patients that may particularly benefit from treatment specifically targeted to hypoxic radioresistant cells.

HT employed in combination with XRT has been shown to improve results in comparison to XRT alone, in two randomized studies (Datta *et al.* 1990, Valdagni and Amichetti 1993). Combining HT and XRT treatment, effective palliation in patients with great metastatic burden or recurrent disease can be obtained, and improved local control and survivals can be expected in the adjuvant treatment of locally advanced lesions (Valdagni and Amichetti 1996). The *in vivo* and *in vitro* effect of heat in killing radioresistant hypoxic cells is well documented (Konings 1996). Besides hyperthermia efficacy on hypoxic cells, a preferential energy deposition inside hypodense-appearing nodes may be postulated, due to the low perfusion rate of necrotic nodes, that may possibly allow one to achieve a therapeutic gain in comparison with adjacent normal tissues that can disperse heat actively.

Radiobiological concepts (Nordsmark *et al.* 1996) prompted the authors to evaluate possible differences in response and local control between metastatic lymph nodes with different grades of density, assuming that the addiction of HT should have reduced or eliminated the difference between necrotic hypodense nodes (poorly radiosensitive) and isodense nodes (radiosensitive).

No significant difference was found in overall nodal response rate, local control and survival in the two groups of patients (with and without CT features of nodal necrosis) treated with HT and XRT. A multivariate analysis was not performed, in consideration of the very similar results obtained in the two groups and the absence of statistically significant differences at the univariate analysis. Moreover, the two groups of patients were well balanced in terms of the other possible prognostic factors (clinical and prognostic characteristics and therapeutic approach).

In conclusion, nodal density assessed by means of pre-treatment contrasted CT scan was not shown to be a significant prognostic factor in patients with head and neck SCC and lymph node metastases treated with HT and XRT, suggesting that hyperthermia can work as a radiosensitizer in the treatment of metastatic lymph nodes, even if necrotic and presumably hypoxic.

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