ORIGINAL

Clinical evaluation of normal tissue toxicity induced by ionizing radiation in cases of laryngeal carcinoma

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Abstract

Laryngeal cancer is the second most frequent head and neck cancer in the Brazilian male population. For treatment, radiotherapy combined with chemotherapy is now used in substitution for total laryngectomy, becoming the standard treatment for advanced larynx cancer cases, with the aim of organ preservation. However, this method needs assessment of the side effects caused to normal tissue and organ functionality after treatment and the relation of these clinical factors to the individual characteristics of patients. Thus, the clinical characteristics of 229 patients with laryngeal cancer treated with radiotherapy were evaluated by medical records analysis in relation to normal tissue radiosensibility. Significant relations between smoking (p = 0.018) and combined chemoradiotherapy assistance (p = 0.03) were identified with high frequency of treatment suspension cases. The application of combined chemoradiotherapy also resulted in a higher incidence of oral mucositis (p = 0.04), xerostomia (p = 0.001) and treatment side effects to GIT (p = 0.04). Advanced clinical staging was associated with worse prognosis (p = 0.002) and a higher occurrence of treatment failure (p < 0.001). Radiotherapy was also less effective depending on the primary tumor location (p = 0.001).

Keywords: adverse effects, ionizing, laryngeal neoplasms, radiation, radiation tolerance, toxicity.

INTRODUCTION

Throughout the world, there is a high incidence of head and neck tumors. In Brazil, the estimates are 6.110 new cases of laryngeal cancer in 2012, with an estimated risk of 6 cases per 100.000 men, and the most recent global estimate pointed to the occurrence of about 129.000 new cases per year, responsible for the death of approximately 70.000 people per year[1]. The incidence of laryngeal cancer is greater in men over the age of 40 years[1].

In lieu of total laryngectomy, radiotherapy combined with chemotherapy has become the standard treatment for advanced laryngeal cancer (except for bulky T4) since the publication of two clinical studies: the first in 1991 (Wolf et al.) and the second in 2003 (RTOG 91-11 study)[2-3]. From these, combined radiotherapy and chemotherapy has begun to be used as primary treatment in an attempt to preserve the organ, maintaining surgery as salvage treatment. Given this, new concerns have emerged, such as treatment toxicity and functional outcome of organ preservation strategies since there is a very important interpatient variation in relation to the results obtained with these therapies, particularly concerning side effects that prevent some patients from completing treatment as initially prescribed[4].

The need to better stratify cases even before the start of radiotherapy may determine which patients will not only respond to therapeutic response, but who will have good tolerance to the previously proposed treatment, and the identification of molecular prognostic factors is one of the stratification solutions that has been identified[5]. Another line of research includes genetic evaluation in order to determine the genetic profile from normal tissue radiosensitivity[6]. A third approach, due to the heavy investment in the technical developments of radiotherapy in recent years, has enabled a more individualized treatment for smaller volumes of organs at risk receive high doses of radiation[7].

However, it is important not to underestimate the influence of the clinical characteristics of patients according to their relationship with the different normal tissue responses to radiation: smoking, age, hypertension, diabetes mellitus are among the studied variables[8-10]. Nonetheless, there are few current studies in head and neck tumors with this specific focus.

The present study aimed to analyze the clinical parameters of patients with laryngeal cancer treated with radiotherapy in the period from 2004 to 2010 in relation to the radiosensitivity of normal tissue.

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MATERIAL AND METHODS

This was a retrospective study of clinical information contained in the teletherapy records of patients with laryngeal cancer treated with radiotherapy from 2004 to 2010 in Hospital Araújo Jorge (HAJ) in Goiânia - GO, Brazil. The study was approved by the Ethics Committee in Human Research of the Association Against Cancer in Goiás (ACCG) under number 035/2007. The variables assessed were: age, sex, smoking, alcohol use, primary tumor site, staging, grade of tumor differentiation, treatment performed, length of radiotherapy suspension, treatment response, clinical outcome and acute actinic reactions classified according to criteria of the Radiation Therapy Oncology Group (RTOG)[11].

From a total of 343 records of patients with laryngeal cancer treated at the Radiotherapy Department of HAJ between January 2004 and February 2010, 229 patients were included to be part of this study. We included patients undergoing adjuvant radiotherapy with surgery and concomitant and well as exclusive chemotherapy. We excluded patients who did not undergo follow-up at HAJ and those lost to follow-up.

The patients underwent conventional radiotherapy with a dose of 200 cGy per day, five days a week. The total median dose was 70 Gy for patients undergoing radiotherapy concurrent with chemotherapy, 60 to 66 Gy for patients undergoing adjuvant radiotherapy to surgery and 70 to 74 Gy for patients undergoing radiotherapy exclusively.

The study sample was characterized by analysis of central tendency and dispersion. The software package Statistical Package for the Social Sciences for Windows® (SPSS 20.0: Chicago, Illinois, USA) was used for statistical analysis of retrospective data, including Student's *t* test, chi-square and Fisher's exact test.

RESULTS

The mean age of the study population was 63.4 ± 11.3 years. Clinical characteristics are summarized in Table 1. Of the 229 patients, 57 (24.9%) had radiotherapy suspended due to side effects of treatment (median 7-day suspension). Side effects and therapeutic response of those patients are briefly described in Table 2.

The variables of age, smoking, alcohol use and concomitant treatment with chemotherapy were analyzed in relation to the suspension of radiotherapy for adverse events and the occurrence of the following secondary side effects to radiation: actinic dermatitis (RTOG: skin), xerostomia, oral mucositis (RTOG: oral mucosa), dysphagia and odynophagia (evaluated by RTOG of the upper gastrointestinal tract). Age and alcohol use did not show relationship with the studied variables. Smoking led to a higher incidence of treatment suspension among smokers compared to nonsmokers ($p = 0.018$). The use of radiotherapy combined with chemotherapy resulted in a higher incidence of oral mucositis ($p = 0.04$), xerostomia ($p = 0.001$) and side effects of the upper gastrointestinal tract ($p = 0.04$). Among patients undergoing radiotherapy combined with chemotherapy, there was a larger number of treatment suspensions ($p = 0.03$). With respect to prior surgery, the occurrence of upper

Table 1. Demographic variables and clinical characteristics of patients.

Variables	N	Percentage valid* (%)
Sex		
Male	186	81.2
Female	43	18.8
Smoking		
Yes	179	87.3
No	26	12.7
Alcohol use		
Yes	103	51.0
No	99	49.0
Histology		
SCC	228	99.6
Others	1	0.4
Primary tumor site		
Glottic	127	55.7
Subglottic	4	1.8
Supraglottic	32	14.0
Transglottic	65	28.5
Histologic differentiation grade		
Grade I	22	9.6
Grade II	128	55.9
Grade III	43	18.8
Without other specifications	36	15.7
Clinical staging		
Stage I	84	36.7
Stage II	23	10.0
Stage III	47	20.5
Stage IV	75	32.8
Surgery		
Yes	80	34.9
No	149	65.1
Concurrent chemotherapy and RT		
Yes	60	26.2
No	169	73.8
Suspension of RT		
Yes	58	24.6
No	178	75.4
Total	229	100

RT: radiotherapy; * were not included in the calculation of percentage of cases without information.

Table 2. Side effects and therapeutic response of patients (n = 229).

Variables	N	Percentage valid* (%)
RTOG skin		
Grade 0	91	39.7
Grade I	58	25.3
Grade II	45	19.7
Grade III	34	14.8
Grade IV	1	0.4
RTOG oral mucosa§		
Grade 0	84	68.9
Grade I	23	18.9
Grade II	10	8.2
Grade III	5	4.1
RTOG GIT upper (dysphagia and odynophagia)		
Grade 0	109	47.6
Grade I	81	35.4
Grade II	26	11.4
Grade III	13	5.7
Xerostomia§		
Yes	22	18.0
No	100	82.0
Response after RT		
NED	156	79.2
Residual disease	23	11.7
Disease progression	18	9.1
Lost to follow-up	32	-
Disease outcome		
NED	121	72.5
local recurrence	12	7.2
Persistent disease	20	12.0
Distant metastasis	14	8.4
Lost to follow-up	62	-
Total	229	100

RTOG: Radiation Therapy Oncology Group; GIT: gastrointestinal tract; RT: radiotherapy; NED: no evidence of disease. * were not included in the calculation of percentage of cases without information. § were not included in the calculation of glottis I and II tumor cases.

gastrointestinal tract side effects in patients who underwent surgery was less frequent (p = 0.03), however, this may be better explained by the higher dose of radiotherapy received by patients who were not treated with surgery.

An assessment between clinical stage variables, primary tumor site and tumor differentiation grade was made with tumor response to radiotherapy and clinical outcome of the patient after treatment. Differentiation grade showed no relationship with treatment response and clinical outcome (p > 0.05). In relation to clinical stage, the more advanced the stage, the higher rate of treatment failure (p < 0.001) and worse prognosis (p = 0.002). The site of the primary tumor in the supraglottic or transglottic region showed a worse response to radiotherapy (p = 0.001).

DISCUSSION

Substantial interpatient variety is observed in the response of normal tissues to radiation in daily medical practice. The various clinical factors that may influence this response need to be adequately identified so that together with radiogenomic studies and development of new and more precise radiotherapy planning techniques, it is possible to accumulate knowledge of the complex network of events that determine the intensity of damage caused by radiation to normal tissue and the ability of each organism to repair this damage.

Wang et al.[12] in 2000 investigated the effect of smoking, sex and age on the radiosensitivity of lymphocytes. That study concluded that men were more radiosensitive than women, as well as the cells of smokers were more sensitive than that of nonsmokers. No difference regarding age was found, which agrees with our findings in relation to this variable in this study and in the most recent studies[13-14]. In relation to smoking, our study showed similar results with a higher incidence of treatment suspension among smokers compared with nonsmokers (p = 0.018). In terms of radiotherapy response and clinical outcome, our study found no difference between men and women, similar to the results of other authors[13-14].

Among the results, we found that the use of radiotherapy combined with chemotherapy resulted in a higher incidence of oral mucositis (p = 0.04), xerostomia (p = 0.001) and side effects of the upper gastrointestinal tract (p = 0.04). This higher incidence of oral mucositis was previously shown in the group that underwent conventional radiotherapy exclusively, the incidence of grade 3 and 4 mucositis was 34%, and in the group undergoing concomitant radiochemotherapy, the incidence was 43%[15]. Hey et al.[16] determined the normal tissue complication parameter of the probability model, TD (50), where the required dose of radiotherapy which causes a 50% probability of complication was 32.2 Gy in 4 weeks and 32.1 Gy in 6 months for concomitant radiochemotherapy and 41.1 Gy in 4 weeks and 39.6 Gy in 6 months for radiotherapy exclusively in relation to the function of the parotid gland, which supports our findings as to xerostomia. Concerning the assessment of dysphagia and odynophagia, patients undergoing radiochemotherapy has a higher incidence of these symptoms than those treated with radiotherapy exclusively[17]. Among patients undergoing radiotherapy combined with chemotherapy, there was a greater number of treatment suspension cases (p = 0.03), which is a result of the increased incidence of side effects in this group and may lead to a decrease in the therapeutic response rate in these patients.

Regarding prior surgery, the occurrence of side effects of the upper gastrointestinal tract was more pronounced (p = 0.03). However, a higher dose of radiotherapy received by patients who were not treated with surgery in our study cannot be dismissed.

As for the results found in relation to the variables clinical stage, primary tumor site and tumor differentiation grade, some considerations can be made. In relation to clinical stage, the more advanced the stage, the higher rate of treatment failure (p < 0.001) and worse prognosis (p = 0.002). This association is quite common in general cases of malignant neoplasms and confirmed the findings of Rades[13], who in 2011 compared stage III and IV tumors of the head and neck and category T in relation to local control and overall survival. In their study, the influence of these factors was demonstrated on the clinical outcome of patients (p = 0.035 and p < 0.001). The site of the primary tumor in the supraglottic or transglottic region showed a worse response to radiotherapy (p = 0.001). Papadas et al.[14] who in 2010 evaluated disease-free and overall survival with surgery, also observed worse outcome of disease-free survival for supraglottic tumors compared to glottic tumors (p = 0.045 and p = 0.15, respectively). Involvement of the supraglottic region showed worse response, which may be caused by the region being rich in lymphatic drainage that result in a high incidence of occult cervical metastasis. A retrospective study has shown more than 20% of regional failure after radiotherapy exclusively[18]. Concerning histologic grade, which showed no relationship with treatment response and clinical outcome in our study (p > 0.05), Rades et al.[13] also found no statistical difference in local control, disease-free survival and overall survival in relation to this parameter (p = 0.13, p = 0.11 and p = 0.22, respectively). Nevertheless, a distinct result was observed in 2010 when the greater disease-free survival and overall survival found, the more well-differentiated the tumor was (p < 0.001 and p = 0.003, respectively)[14].

Therefore, faced with the results foun+d, we conclude that the assessment of various clinical factors that may influence the response of normal tissues to radiation should always be observed. Those same factors in clinical practice can determine the need for more frequent outpatient follow-up for patients at higher risk, but also encourage a stricter adjustment of doses received by organs at risk during the planning of radiotherapy. While these results are not sufficient to explain all the differences found between the side effects of patients undergoing similar treatments, radiogenomic studies need to be encouraged. Notwithstanding, the clinical assessment of these factors should always be part of the multivariate analysis of these studies.

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