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Radiotherapy of NPC

Smoking is a poor prognostic factor for male nasopharyngeal carcinoma treated with radiotherapy

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ABSTRACT

Background and Purpose: To evaluate the effect of smoking on prognosis of male nasopharyngeal carcinoma by comparing the treatment outcomes between smokers and non-smokers.
Materials and Methods: A total of 2450 nasopharyngeal carcinoma patients were enrolled, including 1865 male patients. Matching was performed between smokers and non-smokers in male patients according to age, UICC clinical stage, T stage, N stage and treatment. Survival outcomes were compared using Kaplan–Meier analysis and Cox regression. Smoking index was calculated by multiplying cigarette packs per day and smoked time (year).
Results: In male patients, smokers had significantly lower 5-year overall survival (70.1% vs. 77.5%, $P < 0.001$) and locoregional recurrent free survival (76.8% vs.82.4%, $P = 0.002$) compared with non-smokers. Matched-pair analysis showed that smokers kept a high risk of death compared with non-smokers (HR = 2.316, $P < 0.001$). High degree of smoking index (>15 pack-years) had a poor effect on overall survival (HR = 1.225, $P = 0.016$). When smoking index was more than 45 and 60 pack-years, the risk for death increased to 1.498 and 1.899 fold compared with non-smokers ($P = 0.040$, 0.001), respectively.
Conclusions: Smoking was a poor prognostic factor for male nasopharyngeal carcinoma. The heavier the patients smoked, the poorer prognosis they suffered.
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Nasopharyngeal carcinoma (NPC) presents a high incidence in Southern China and Southeast Asia [1–4]. Smoking, as a non-viral personal factor, was significantly associated with a 2 to 3 fold higher incidence of NPC than non-smoking in a dose-dependent manner [5–9].

In the past decade, great effort had been made in exploring the relationship between tobacco and prognosis of head and neck cancer (HNC) [10–12]. A prospective study, involving 115 advanced HNC patients receiving radiotherapy, reported that smoking during radiation would lead to a lower complete response and overall survival rate [13]. Matched-pair studies concerning head and neck cancer also found that smoking, both before diagnosis and during the treatment could lead to a poor outcome [14,15].

However, rare study specifically focused on the impact of smoking on prognosis in NPC patients. Therefore, in this study, a large database of NPC patients in our center was involved to investigate whether smoking had any effect on prognosis. Moreover, matched-pair analysis between non-smokers and smokers was used to assess the real impact and quantity analysis of ascending smoking index (SI) was performed to dig out the trend and threshold between smoking and prognosis of NPC.

Materials and methods

Patient populations

This work had been approved by the ethics committees of Sun Yat-Sen University Cancer Center (SYSUCC). The medical records of 2820 patients newly diagnosed with NPC without distant metastasis in SYSUCC from November of 2000 to December of 2004 were reviewed. All patients received radical radiotherapy and completed the prescribed course of treatment. The exclusion criteria included: (1) lost follow-up within 5 years from diagnosis, (2) lack of the record of smoking habits. A total of 2450 patients were enrolled.

The information on smoking habits of patients, containing smoking status, packs of cigarettes/day, years that the patient had smoked and years since smoking cessation, was collected by physicians at entry and by nurses during hospitalization at SYSUCC. Only the records from physicians and nurses were consistent, they were considered credible. Smokers were identified as those who said "yes" when asked "smoking/smoked or not". Patients who said "no" were considered as non-smokers. Patient information on smoking cessation defined the smoker as either [14,16,17]: (1) Current smokers, who did not quit before

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presentation, (2) Long-term quitters, who quit longer than 1 year, (3) Recent quitters, who quit no longer than 1 year.

Karnofsky Performance Status Scale (KPS) was used to evaluate general performance of patients [18].

Study design

The flowchart of our study design is shown in Fig. 1. We first analyzed the impact of smoking on outcome in the all 2450 patients. Given female smokers were few (5 females), we took only male patients (1865) into analysis to eliminate the confounding of gender. In order to balance other prognostic factors and validate the real association between smoking and outcomes in male NPC, we performed 1 to 1 match between smokers and non-smokers based on randomization pairing principle for matched-pair analysis. Matching was preformed according to age (±5 years), UICC clinical stage, T stage, N stage and treatment (radiotherapy or chemoradiotherapy). Finally, we got 363 pair matched patients.

Smoking quantity was evaluated by smoking index (SI), which was calculated by multiplying cigarette packs/day and years that the patient had smoked. A pack contained 20 cigarettes, and 1 pack-year was defined as the equivalent of smoking one pack of cigarettes per day for 1 year [16,19].The receiver operating characteristic (ROC) curve based on data of male patients indicated a best cut-off value of 15.5 pack-year (the sensitivity was 46.8% and the specificity was 65.4%) to divide NPC patients into low degree of SI ($\leqslant$15 pack-years) and high degree of SI (>15 pack-years) groups, with an area of 0.577 (95% CI 0.549–0.605; $P < 0.001$). Furthermore, an interval of 15 pack-years divided the patients as a series of ascending SI groups: (1) SI = 0 pack-year; $n = 697$; (2) $0 < SI \leqslant 15$ pack-years; $n = 447$; (3) $15 < SI \leqslant 30$ pack-years; $n = 464$; (4) $30 < SI \leqslant 45$ pack-years; $n = 144$; (5) $45 < SI \leqslant 60$ pack-years; $n = 61$; (6) SI > 60 pack-years; $n = 52$. The ROC curve was also used to determine the best threshold difference value of age, with a cut-off value of 49.5 year-old (the sensitivity was 54.5% and the specificity was 65.6%).

Treatment

Radiotherapy alone was given for the early stage cases, and radiotherapy combined with chemotherapy was given for the advanced stage cases. All patients were treated with radiotherapy with high energy 6-8 MV X-ray by linear accelerator. Isocenter radiation by face-neck joint field with low melting point lead block was used, and the radiation field included the skull base, nasopharynx and neck. Face-neck joint field and lower cervical anterior tangent field were irradiated, firstly, with anterior nasal field added when the nasal cavity had been invaded, to a dose of 36 Gy, and then followed by bilateral preauricular fields plus anterior tangent field to a total dose of 60 to 78 Gy. Chemotherapy included induction chemotherapy, concomitant chemotherapy, and adjuvant chemotherapy. Chemotherapy regimen was mainly cisplatin (DDP) plus 5-fluorourac(5-FU) for 1 to 3 cycles.

Follow-up

Patients were evaluated by phone and out-patient clinic follow-up. The follow-up mainly included recurrence, distant metastasis and survival status. All recurrence and distant metastasis were confirmed by pathological examination and/or imaging. The last date of follow-up was February 2011. The follow-up time was at least 5 years.

Endpoints and statistical analysis

The primary endpoint was death and the secondary endpoints were recurrence and metastasis. Overall survival (OS) time was defined as time from diagnosis to death from any cause. Locoregional recurrent free survival (LRFS) time was defined as time to the first

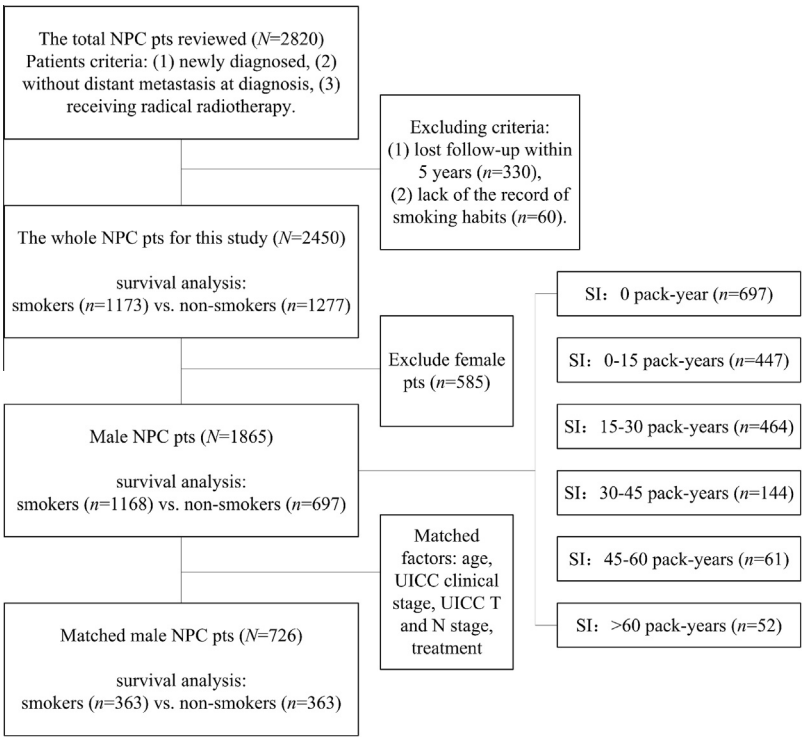

Fig. 1. Flowchart of study design. NPC = nasopharyngeal carcinoma, pts = patients, UICC = International Union Against Cancer, SI = smoking index.