Cancer/Radiothérapie 20 (2016) 384–390

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Original article

Prognostic significance of Livin expression in nasopharyngeal carcinoma after radiotherapy

Signification pronostique de l'expression de Livin après radiothérapie des carcinomes du nasopharynx

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ARTICLE INFO

Article history:
Received 22 February 2016
Received in revised form 4 May 2016
Accepted 15 May 2016

Keywords:
Livin
Inhibitors of apoptosis proteins
Nasopharyngeal cancer
Protein expression
Radiotherapy
Prognosis
Immunohistochemistry
Kaplan-Meier method

ABSTRACT

Purpose. – This study was designed to investigate the expression levels of the inhibitor of apoptosis protein Livin in nasopharyngeal cancer tissues and its prognostic significance in nasopharyngeal carcinoma after radiotherapy.
Material and methods. – A total of 83 patients with nasopharyngeal carcinoma who received radiotherapy were enrolled in this study from January 2008 to October 2010. Livin expression in nasopharynx pathological specimens extracted from patients was detected by immunohistochemistry. A Kaplan-Meier analysis was conducted to explore the effects of clinicopathological features and Livin expression on the overall survival and progression-free survival of patients with nasopharyngeal carcinoma, and explore its prognosis relevance after radiotherapy.
Results. – Of the 83 patients with nasopharyngeal carcinoma, the overall Livin positive expression rate was 65.1% (54 patients), and the overall response rate of radiotherapy was 81.9% (68 patients). Significant differences in radiotherapy efficacy were found between patients who did not express Livin and those who did ($P < 0.05$). The Kaplan-Meier analysis showed that Livin expression, high clinical staging, cervical lymph node metastasis, high T-staging and high N-staging were significantly correlated with a decrease in the overall survival of patients with nasopharyngeal carcinoma (all $P < 0.05$). A Cox multivariate survival analysis showed that Livin expression, clinical staging and N-staging were independent risk factors for the overall survival of patients with nasopharyngeal carcinoma treated with radiation (all $P < 0.05$). Furthermore, Livin expression and clinical staging were independent risk factors for the progression-free survival of patients with nasopharyngeal carcinoma once radiotherapy was introduced (all $P < 0.05$).
Conclusion. – Expression of Livin, an inhibitor of apoptosis proteins, may be closely linked with poor prognosis of nasopharyngeal carcinoma post-radiotherapy and hence it may be a new therapeutic target in the treatment of the disease.

Mots clés :
Livin
Inhibiteurs de protéines de l'apoptose
Cancer du nasopharynx
Expression des protéines
Radiothérapie
Pronostic
Immunohistochimie
Méthode de Kaplan-Meier

RÉSUMÉ

Objectif de l'étude. – Cette étude a été conçue pour étudier les niveaux d'expression de l'inhibiteur des proteins de l'apoptose Livin dans le cancer du nasopharynx et leur signification pronostique après la radiothérapie.
Matériel et méthode. – Quatre-vingt-trois patients irradiés pour un carcinome du nasopharynx ont été inclus dans cette étude de janvier 2008 à octobre 2010. L'expression de Livin a été détectée par immunohistochimie sur des prélèvements biopsiques. L'influence de l'expression de Livin sur la survie globale et la survie sans progression a été étudiée par la méthode de Kaplan-Meier.
Résultats. – Sur les 83 patients atteints de carcinome du nasopharynx, le taux global d'expression de Livin était de 65,1 % (54 patients) et le taux de réponse global à la radiothérapie de 81,9 % (68 patients). Des

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http://dx.doi.org/10.1016/j.canrad.2016.05.013

différences significatives d'efficacité ont été observées selon que Livin était exprimé ou non ($p < 0,05$). L'analyse de Kaplan-Meier a montré que l'expression de Livin, un fort stade clinique, des métastases ganglionnaires cervicales, un fort T et un fort N étaient significativement corrélés avec une diminution de la probabilité de survie globale des patients (tous $p < 0,05$). L'analyse multifactorielle de Cox a montré que l'expression de Livin et le stade N clinique étaient des facteurs de risque indépendants de survie globale (tous $p < 0,05$). En outre, l'expression de Livin et le stade clinique étaient des facteurs de risque indépendants de survie sans progression après mise en route de la radiothérapie ($p < 0,05$).
Conclusion. – L'expression de Livin peut être étroitement liée avec un pronostic défavorable après la radiothérapie d'un carcinome du nasopharynx ; cette protéine pourrait être une nouvelle cible thérapeutique chez ces patients.

1. Introduction

Nasopharyngeal cancer is the most common malignant neoplasm originating from the uppermost region of the pharynx. It has significant demographic variations [1–3]. As a common malignancy in the world, approximately 84,000 cases of nasopharyngeal carcinoma are diagnosed every year and most of these cases are reported in South Asia, China, North Africa and Arctic area [4–6]. The incidence of nasopharyngeal carcinoma is estimated to be 25 to 50 cases per 100,000 people. Patients with this disease may experience pain, trismus, otitis media, hearing loss and cranial nerve palsy (paralysis) [7]. The etiology of nasopharyngeal carcinoma is multifactorial, typically including Epstein-Barr virus (EBV) infection, genetic susceptibility, unhealthy lifestyle and environmental hazards such as smoking and exposure to dust contamination [1,6,8–10]. Generally, nasopharyngeal carcinoma can be treated by surgery, anti-cancer drugs, or radiation, among which radiotherapy is regarded as the primary treatment method [11,12]. Improvements in therapeutic effectiveness have been made after radiotherapy was introduced to manage nasopharyngeal carcinoma. However, radiotherapy side effects may trigger distant metastases or tumour progression; thus, understanding the molecular mechanisms of nasopharyngeal carcinoma treatments is urgently needed [13–15].

The inhibitors of apoptosis proteins are a family of proteins that are implicated in cell apoptosis, immunity, inflammation, cell cycle and migration, which are all connected with tumour development [16]. An important member of this family, the Livin protein plays a key role in the inhibition of cell apoptosis by regulating the cell cycle, as well as being involved in tumour angiogenesis and anti-natural killer cells actions [17,18]. Furthermore, Livin has been reported to be undetectable in most normal tissues, while its expression has been found in various cancer tissues such as breast cancer, melanoma, gastric cancer, leukemia, lung cancer, bladder cancer, cervical cancer, prostate cancer, colon cancer, hepatocellular carcinoma and pancreatic cancer [19–23]. The majority of current studies have suggested that Livin expression in cancers appears to be related to various unfavourable clinicopathologic outcomes such as disease recurrence, poor prognosis and lower survival rate [24–26]. It has also been reported that Livin protein, which may be directly involved in apoptosis regulation, is likely to be linked with the radiation sensitivity of lung cancer and the silence of Livin-specific gene may enhance cancer radiation sensitivity [27]. However, it is unclear whether Livin expression correlates with pathological or clinical characteristics and whether it has any relation with the prognosis of the disease after radiotherapy. Hence, we measured the expression of Livin in patients with nasopharyngeal carcinoma after undergoing radiotherapy and observed their 5-year survival rate in order to further explore the relationships among the Livin expression, radiation sensitivity, short-term efficacy and disease prognosis.

2. Materials and methods

2.1. Patients and clinical data

From January 2008 to October 2010, a total of 83 patients with nasopharyngeal carcinoma were enrolled in the present study; they were recruited from the department of oncological radiotherapy of the Fifth Hospital in Wuhan. Of the 83 cases, 64 were male patients and 19 were female patients (median age: 48 years; range: 22 to 69 years). Pathological tissues of the nasopharyngeal region were diagnosed as poorly differentiated squamous cell carcinomas. The conditions of tumour infiltration were confirmed by computed tomography (CT) scans of the nasopharynx before receiving radiotherapy. Enrollment criteria were:

- all cases were pathologically confirmed by biopsy;
- all patients only received radiotherapy, no chemo- or other therapies were involved;
- the Karnofsky Performance Status Score (KPS) of all patients were at least 70 points.

The exclusion criteria:

- patients with poor compliance;
- patients with distant metastasis confirmed by ultrasonography, chest CT scan and bone scan prior to therapy;
- patients with incomplete clinical and pathological data.

Staging nasopharyngeal carcinomas was done according to the 8th edition of the American Joint Committee on Cancer (AJCC) cancer stage classification [28]. Twenty-five lesions were confirmed as stage I–II (stage I, two cases; stage II, 23 cases) and stage III–IV were confirmed in 58 patients (stage III, 47 cases; stage IV, 11 cases). The current study was conducted under the approval of the ethical committee of the Fifth Hospital in Wuhan. All study participants provided written informed consent.

2.2. Radiotherapy method

All enrolled patients underwent conventional radical radiotherapy successfully. All treatments were performed using a Varian CD2100 linear accelerator (dose rate: 30 mu/min; Varian Medical Systems, Palo Alto, CA, USA) with 6 MV X-ray. Radiotherapy was given 5 times a week at 2 Gy per treatment session. The accumulated radiation dosage of the two-lateral facial–cervical fields for the primary tumour was set from 34 to 36 Gy. Then the total dosage was set between 66 and 78 Gy in bilateral preauricular fields