

# Radiotherapy play an important role in nut carcinoma: a case report

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## Abstract

NUT carcinoma clinical feature as rare, high lethal, and fast development, easy misdiagnose, and no effective therapy, and have a depressed prognosis. We explore the best strategy about the pulmonary nut carcinoma by analyze our case and retrospective study a lots of others case reports clinical features and therapies

Radiotherapy play an important role in nut carcinoma: a case report

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**Abstract** : NUT carcinoma feature as the rearrangement of the nuclear protein in testis (NUT) gene on chromosome 15q14, and its clinical feature as rare, high lethal, and fast development, easy misdiagnose, and no effective therapy, and have a depressed prognosis. We summary clinical features of a real lung nut carcinoma case in the department of thoracic oncology, West China Hospital of Sichuan university, include radiation sensitive, chemotherapy and immunotherapy unsensitive, and fast progressed. We explore the best strategy about the pulmonary nut carcinoma by analyze our case and retrospective study a lots of others case reports clinical features and therapies.

**Key words**: Pulmonary NUT carcinoma; Radiotherapy; chemotherapy

## Background

NUT carcinoma (NC) is a rare and highly aggressive malignant tumor with unknown histologic origin and without any clinical or histomorphological features to distinguish, except genetically defined by the presence of chromosomal rearrangements involving the NUT (also known as NUTM1, Nuclear Protein in Testis) gene.<sup>1-3</sup> In 1991, Kubonishi<sup>4</sup> first reported a case of thymic carcinoma characterized by t(15; 19) translocation. But it was not until the discovery of formation of a BRD4-NUT fusion oncogene in 2003, resulting from the t(15;19) translocation, NC was defined.<sup>1,5</sup>

Although NC can occur in people of any age (0–81.7 years), the majority are adolescents or young adults (median age 16–22 years) and it affects males and females equally.<sup>6,7</sup> It is also known as NMC (NUT middle carcinoma) because it typically arises from midline upper airway locations, such as head and neck and

thorax. However, some cases also occur in areas other than the above organs, including: lungs,<sup>8</sup> salivary glands,<sup>9</sup> pancreas<sup>10</sup> and bladder<sup>1</sup>.

NC is clinically distinctly aggressive, often accompanied by extensive metastases at the time of diagnosis, and rapidly fatal.<sup>3</sup> Because NC often occurs in the mediastinum or lungs and is usually accompanied by distant and lymph node metastases, it is often mistaken for small cell lung cancer in clinical practice, however, NC progresses more rapidly and often affects young people. Despite such a poor prognosis for NC, there are not many effective treatments and not much research on this. Herein, we report a case of pulmonary NC that achieved long-term survival after a combination of chemotherapy, radiotherapy, and immunotherapy.

## Case presentation

A 56-year-old male presented to our hospital with "dizziness" and was found to have a 4.2\*3.7 cm occupancy in the lower lobe of the left lung with obstructive atelectasis and enlarged mediastinal and supraclavicular lymph nodes on chest CT (figures 1a1,a2,a3). No distant metastasis was found in the head MRI, abdominal CT and SPECT bone scan. To further clarify the pathological type of the lung mass, a percutaneous puncture biopsy was performed on 01/17/2020. Immunohistochemical demonstrated strong and diffuse expression of PCK, P40 and CK5/6. There was focal expression of TTF-1 and Syn, whereas EBER1/2-ISH, CK7, NapsinA and CgA were negative (figures 2a,b). And no driver mutation was detected. The diagnosis of NC was confirmed following fluorescence in-situ hybridization (FISH) showed BRD4-NUT rearrangement. PD-L1 testing was not performed due to insufficient specimens. He was finally diagnosed as NUT carcinoma of the lower lobe of the left lung with hilar, mediastinal, and supraclavicular lymph node metastases, T3N3M0, stage IIIC (American Joint Committee on Cancer 8th Edition Cancer Staging Form). Patient refuses surgery. Cycle 1 nab-paclitaxel combined with carboplatin chemotherapy was then started on February 12, 2020. Chest CT was done to evaluate the efficacy before next cycle and suggested heterogeneous changes with a shrinking chest lesion and an increasing supraclavicular lymph node lesion (figures 1 b1,b2,b3). Supraclavicular lymph node aspiration biopsy was performed at the same time as the second cycle of chemotherapy. Pathological findings showed poorly differentiated carcinoma in fibrofatty tissue, and FISH detected NUT gene translocation, indicating NC metastasis. Then chest and neck radiotherapy (56Gy/28f) was performed from March 16, 2020 to May 11, 2020, the target volume was preventability lymph node area radiation (accessory figure 1). Radiotherapy was suspended for 5 days for skin erosion of the neck caused by radiation during treatment. The 3rd and 4th cycles of chemotherapy were administered concurrently with radiotherapy. After the completion of radiotherapy, chest CT scan showed significant response of mediastinal and left lung tumors and the comprehensive efficacy evaluation was partial response (PR) (figures 1c1,c2,c3). Four cycles of Durvalumab maintenance immunotherapy were then administered from June to September 2020. However, a new lesion in the right middle lobe and enlarged left lower lobe lesion and right apical lesion were found by chest CT scan on August 15, 2020, which means disease progressed (figures 3a1,a2,a3). Next, second-line treatment was given with chemotherapy of etoposide plus cisplatin combined with anti-vascular therapy of anlotinib. Two months later, chest intensive CT scan showed the mass at low lobe of left lung and left hilus of the lung and the mediastinal obviously progressed, and the comprehensive efficacy evaluation was progressive disease (PD) (figures 3b1,b2,b3). The patient cardio-pulmonary function dramatic decreased because of the large effusion arise in the chest and cardio bag (figures 3c1, c2), and his general condition flow down, the ECOG 3-4. He finally died at 2020/22/15, and the overall survival time was 10 months.

## Discussion

NUT carcinoma is a rare, poor differentiated, high lethal cancer which clinical feature as often occurred on the middle position of the body, and happened on from children to the old, no difference at gender, hard diagnosis, progressed fast, and no effective therapy, disaster ending<sup>6,11-13</sup>. Pulmonary nut carcinoma is a special kind with worse prognosis<sup>14-18</sup>. Recent years, a lots of reports were studied. Such as Xie et al have reported an retrospective study, they found the middle overall survival of 7 pulmonary nut carcinoma patient only were 4.1 months<sup>17</sup>. Sholl et al retrospective reported 8 pulmonary nut carcinoma patients, their middle overall survival time only 2.2 months<sup>15</sup>. However, in our case, the pulmonary nut carcinoma patient got 10 months survival through a series therapy, like chemotherapy, radiotherapy, immunotherapy (figures 4). In

our hospital, another two lung nut cancer patient were diagnosis at march and november 2019, they are 24 years old male, and 22 years old female, whom were both found big mass at their chest, and were definition as local progressed stage T4N2M0 at the first diagnosis(accessory 2,3). The male have through a unilateral lung resection, and chemotherapy with two cycles TP (taxol and cis-platinum) were given after the surgery, and after progressed two cycles AIM (doxorubicin and ifosfamide) were given. Finally, he was died after 6 months later from the first diagnosis. Another female patient only through two cycles chemotherapy with TC (taxol and carboplatin), and she only got 2 months survival.

The therapy of nut carcinoma is a hard work, many reports showed us that no matter the traditional chemotherapy or radiotherapy and surgery, or the new method to antitumor, like anti-angiogenesis, immunotherapy both could not improve the prognosis of nut carcinoma<sup>11,12,19</sup>. The molecular mechanism of nut carcinoma have no exactly explanation, and there have no any development of target therapy<sup>20-23</sup>. Though some new agents clinical trials for nut carcinoma have been conducted, but the preliminary result is still unsatisfactory<sup>20,21</sup>. People know nut carcinoma mostly from a lots of case report and review of literature. Giridhar, P et.al analysis 119 nut carcinoma cases from lots of case report, and pneumonia nut carcinoma occupy 42 cases. They analysis the relationship of treatment and prognosis, and they found that nut carcinoma first treat with radiotherapy with a dose exceed 50Gy can significantly improve the overall survival of the patients<sup>19</sup>. Also, they found that the use of pet-ct for the first diagnosis of the disastrous carcinoma may help patient win more time to diagnosis and treatment<sup>19</sup>. In the lung nut cancer case we have reported previously, we can see that the patient recur at many sites over and over again, carefully check the images of different time, the tumor of these recur sites have been there a period time. So, if the pet-ct were given in time, these tiny tumor were been diagnosis as soon as possible, and then give timely and effective therapy like radiation therapy may stop the explosive progression. In addition, we can see from both the previously lung nut cancer case report and this lung nut cancer case that radiation therapy can effectively release the tumor burden at any period<sup>24</sup>. In our previously report, radiotherapy at a dose of 20-40Gy can effectively release tumor burden, and after 40Gy radiation, the tumor seemingly did not recur again at a long time. In this case, the patient only received one time radiotherapy with a dose of 56Gy, but still recured in situ after 3 months later of the radiation, it may relative with the discontinuous radiation. In the before case we have reported, the radiation target volume is involved field irradiation. But in this case, the radiation target volume is elective nodal irradiation, and carefully comparison the images of CT scan, we found that recurrence at the area where radiation target volume did not covered. All in all, patient benefit more from the radiation at the before case than this case. So, both radiation dose and the target volume and the radiation involved time could affect the prognosis of lung nut cancer patient. How to properly use pet-ct and radiation at the disaster cancer is a big question which need us explore deeply.

As far as we can see from the two cases we treated and those cases in other doctors previous reports, the follow few points need we consider carefully when we encounter lung nut cancer. Firstly, it is very important to release tumor burden at the first treatment, surgery, radiation, and chemotherapy should be consider, and the local treatment seem more important. Secondly, radiation should be considered during the whole disease process, so, low dose(<40Gy), accurate target volume should be executed. For repeatedly radiation, lower dose should be considered if the target volume is elective nodal irradiation. And radiation should be got involved timely at every time recur. Thirdly, because of the clinical feature of rapidly progressed, the monthly follow-up visit is very important, and the intensive CT scan or the pet-ct should be considered. Pet-ct could help us make a accurate target volume. As for chemotherapy, anti-angiogenic, and immune therapy, the effective are not sure in many cases. So, it acts according to the circumstances on the condition of guarantee radiation.

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## Data availability statement

All data are presented in the manuscript.

## Author contributions

Xiaoqin Liu and Lin Chen provided care for this patient on hospitalization. Xiao qin Liu prepared the manuscript. Lin Zhou and Yong Mei Liu provided professional opinions regarding patient care and helped to draft the manuscript. All authors read and approved the final manuscript.

## Ethics statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

## Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images and tables. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

## Competing interests

The authors declare that they have no competing interests.

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## FIGURE LEGEND

Fig. 1 Serial abdominal CT scans shows dynamic change from the base line to the radiation. a1 the base line of the metastatic mediastinal lymph nodes a2 a3 the base line of the primary tumor at the left lung. b1 after two cycles of chemotherapy with TC(taxol and carboplatin), the metastatic mediastinal lymph nodes shrink but a new metastatic lymph node occur. b2 b3 the primary tumor partly shrink. c1 after radiotherapy, the all the metastatic lymph nodes obviously shrink. c2 c3 the primary tumor totally shrink.

Fig. 2 Histopathological examination shows poorly differentiated squamous cell mixture TTF1(+) and SYN(+) cells which small neuroendocrine cell carcinoma could not been excepted. A, ( $\times 200$ ); B ( $\times 100$ );

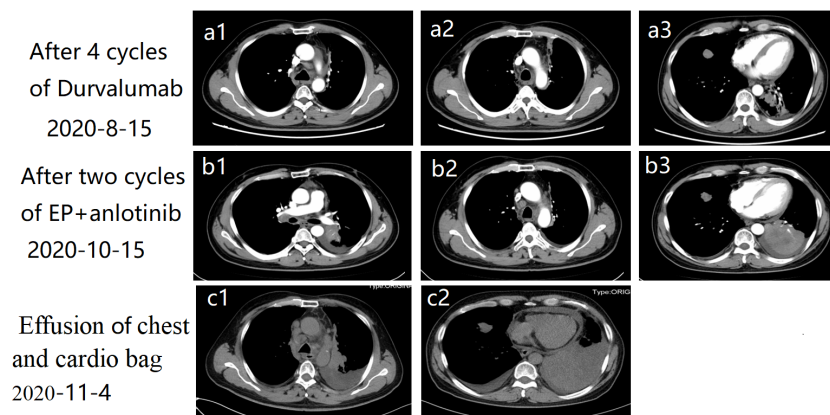
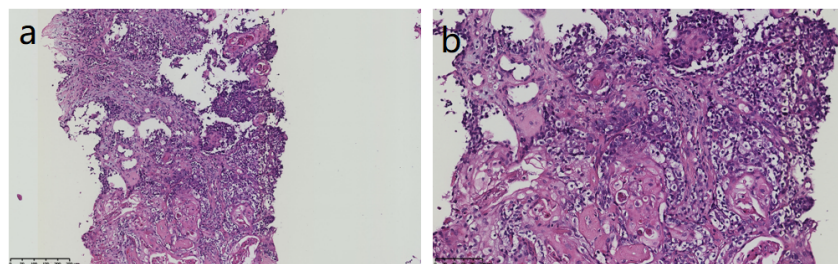
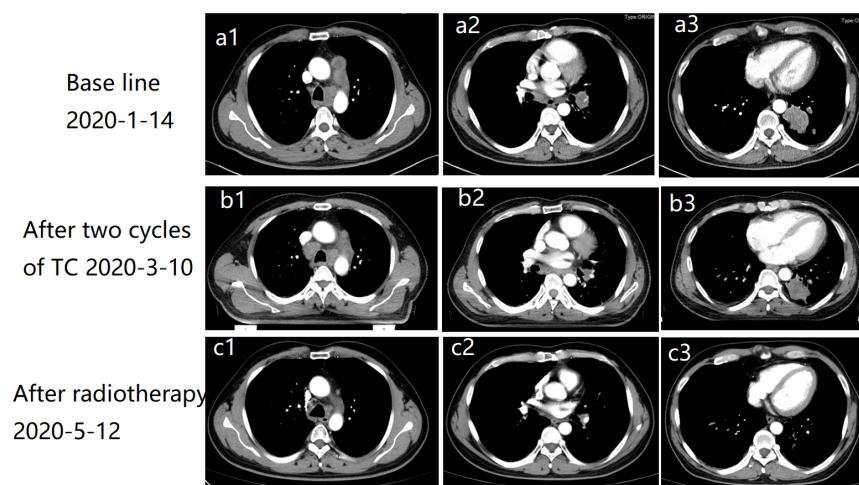
Fig. 3 Serial abdominal CT scans shows dynamic change of the follow-up treatment and the last period. a1 a2 after 4 cycles of immunotherapy with durvalumab, the mediastinal lymph nodes did not recur. a3 the primary tumor at the left lung recur and a new mass occur at the right low lung. b2 after two cycles of chemotherapy with EP(etoposide and cis-platinum) and anti-angiogenesis agent anlotinib, the mediastinal lymph nodes have no change compared before. b1 b3 the primary tumor progressed fastly. c1 c2 at the last period, the pleural effusion and the pericardial effusion appeared.

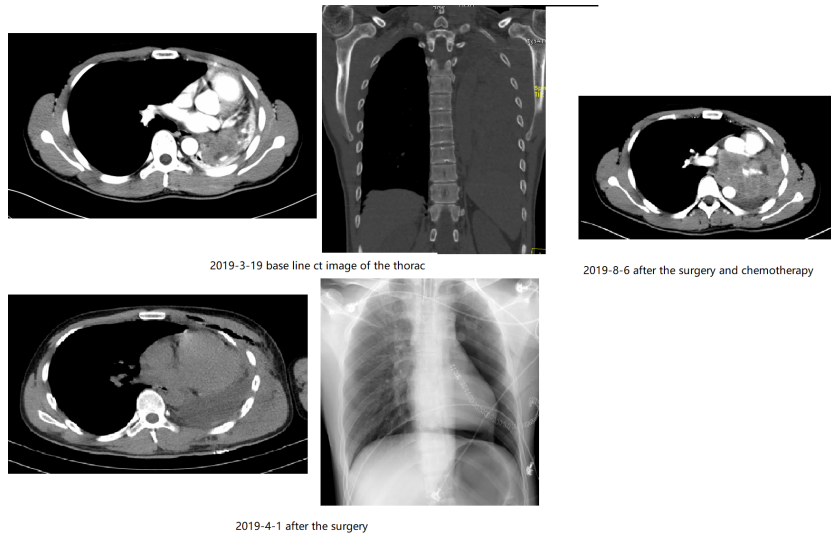
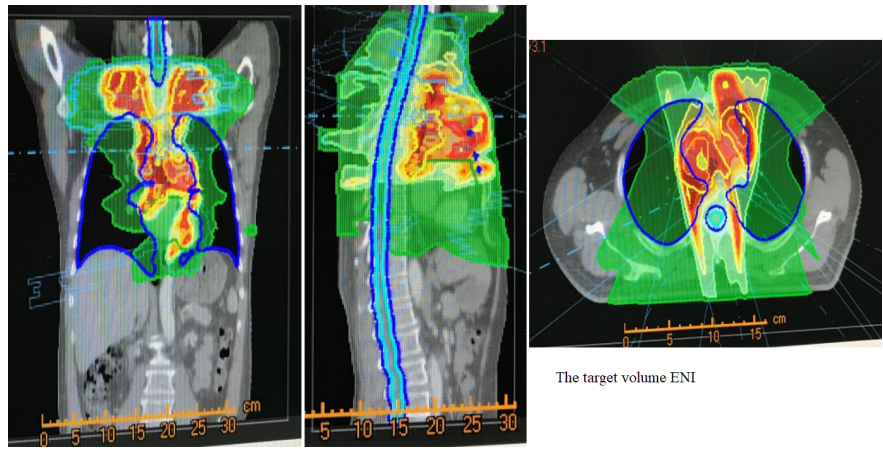
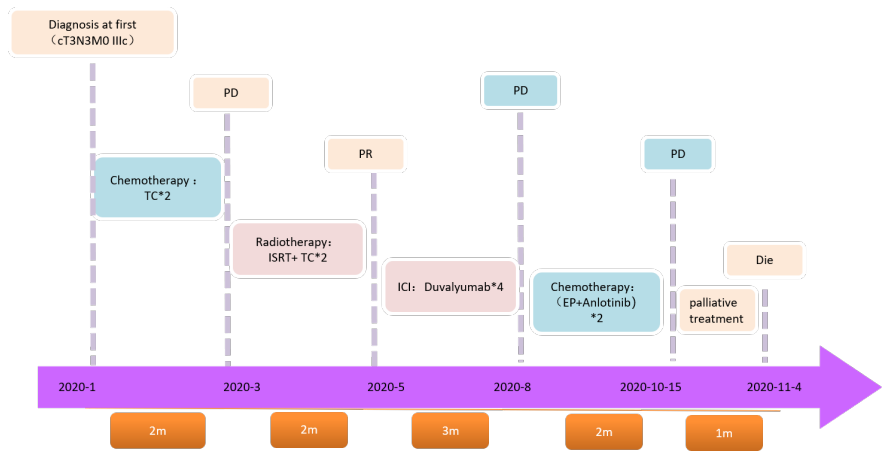
Fig. 4 Overview of the whole treatment process.

Supplement figs1 the target volume of this case was preventability lymph node area radiation.

Supplement figs2 the CT scan images of the male from the base line to the last period.

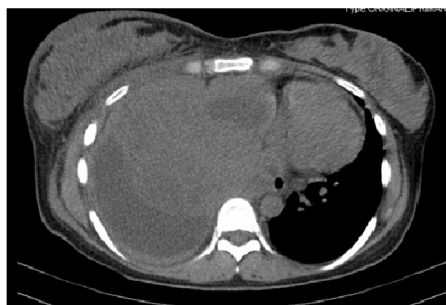
Supplement figs3 the CT scan images of the female from the base line to the last period show the disaster  
nut lung cancer progressed so fast that there is no chance to treat.



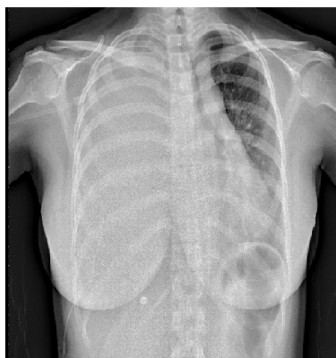




2019-11-9 baseline ct image of the thorac



2019-12-25 After one cycle of TC



Without therapy 2019-11-28