Optimal Treatment Strategies for Patients with NUT Carcinoma – A Case Study

**Abstract**

**Background**: NUT carcinoma is a rare, poorly differentiated tumor predominantly affecting teens and young adults. Optimal management for this lethal disease is currently unclear.

**Objective:** To assess the literature along with two patient cases regarding NUT carcinoma in order to increase understanding of optimal management for these patients.

**Discussion:** A literature review was conducted to analyze diagnostic tools and four primary treatment techniques (surgery, chemotherapy, radiation therapy, and targeted therapies) for NUT carcinoma patients, the information was applied to assess two patient cases. In each case, a multi-modality approach of chemotherapy and radiation therapy were used for treatment.

**Conclusions:** Using a multi-modality approach following accurate diagnosis for patient with NUT carcinoma can significantly increase overall survival. Radiation therapists should be aware of this rare and aggressive disease for educated involvement in the treatment process as radiation therapy has become a mainstay in these patients care.

**Introduction**

The body of knowledge surrounding cancer as a biological defect continues to evolve and with this evolution comes about new variations in long treated diseases. NUT carcinoma (NC) is a rare, poorly differentiated tumor that predominantly occurs in the head and neck but can manifest anywhere in the body. This unique genetic abnormality was first characterized in the early 2000’s.1 The mutation itself is caused by a fusion oncogene and is not otherwise known to be associated with risk factors such as: environmental exposure, infections, or familial factors ultimately deeming it unprovoked.2 Optimal management for this disease is unclear at this time, and a standard of care does not exist. Due to this cancer's extreme lethality and tendency to effect teens and young adults more so than other age groups, furthering the understanding of effective treatment options could be life changing for these patients.

 Prior to evaluating the currently utilized treatment regimens, diagnostic tools must be analyzed. Due to similarities with other poorly differentiated tumors, pathology is important but further diagnostic analysis is necessary for these patients. Fundamentally, this paper will focus on four key treatment options: surgery, chemotherapy, radiation therapy, and targeted therapies. Additionally, two patient cases will be assessed in detail through the delineation of case presentation, diagnosis, treatment, and current disease status. Professionals operating in the field of radiation oncology, radiation therapists especially, understand the importance of precise and compassionate care, and the management of NC patient cases are no exception. With further recognition of this rare malignancy will come advancement in treatment schemes, expanded clinical trials, and increased awareness for professionals, patients, and their families. Ultimately, this research aims to positively impact the lives of those affected by this rare, aggressive disease through the continuous search for an optimal treatment regimen while educating others on the current state of care along the way.

**Literature Review**

To analyze the treatment schematics currently utilized for this aggressive disease; it is important to establish an accurate understanding of diagnostic techniques. NC is an identifiable subtype of squamous cell carcinomas defined by a rearrangement of the NUTM1 gene.1,3-6 Traditionally, the gene rearrangement results in a fusion with bromodomain containing protein 4 (BRD4) ultimately producing a BRD4-NUT.1,3-6 Although the BRD4-NUT fusion partners are the most common, there are studied cases of the NUTM1 gene fusing with bromodomain containing protein 3 (BRD3) and other non-bromodomain containing genes.1,3-6 These various identifiable fusion partners are key markers in the diagnosis process for NC and interestingly suggest that the extremely rare and aggressive disease arises from a single disastrous chromosomal event. 1,2 Even though NC uniquely distinguishable, it is lacking in its own precedented research.

Unfortunately, the rarity of this disease creates indisputable challenges for diagnosis. The greatest initial barrier is the overlapping histopathological features with other poorly differentiated/undifferentiated tumors such as squamous cell carcinoma, germ cell tumors, small round blue cell sarcoma, and many more.1,3-6 Patients also traditionally present with non-specific respiratory symptoms including but not limited to: hoarseness, cough, fever, chest pain, shortness of breath, dyspnea, hypopnea and hemoptysis.3 Misdiagnosis for NC patients are all too common and can greatly increases the detrimental effects of the disease showing the true importance of accurate diagnosis for patients. Due to the malignancies structurally similar abnormalities and clinical presentation with other cancers, diagnosis cannot be determined by histopathology or clinical examination alone.1,6 There are several diagnostic tools increasing the prevalence and accuracy of NC diagnosis, immunohistochemistry (IHC) being one of the most documented tools utilized today.

IHC is a method that uses a commercially available monoclonal antibody to the NUTM1 gene in order to stain the tumor nuclei within the given sample.1,3,5 This test has proven to be 100 percent specific and 87 percent sensitive with respect to the diagnosis of NC.1,3,5 Additionally, IHC is a proven rapid and cost-effective approach for diagnosis. Other documented tools for the effective diagnosis of NC include fluorescence in situ hybridization (FISH), reverse transcriptase-polymerase chain reaction (RT-PCR), and next generation sequencing (NGS).1,3,6,7 FISH and RT-PCR are proven to be effective instruments in the identification of the NUT gene rearrangement, while NGS has the ability to determine the specific gene that has fused with NUTM1.6 Identification of the specific fusion gene is especially important when considering targeted therapies as a treatment option, which is one of the several treatment techniques used for these patients.

Due to the relatively recent discovery of this disease and its extremely aggressive biological behavior, the optimal treatment strategy has yet to be identified. There is extensive debate on the role that surgery has for these patients, much of which depends on the extent of disease at diagnosis. 1,3,5 Studies conducted by French C1, Chau NG et al5, and Zhang H. et al8 suggest that surgery increases patient progression free survival (PFS) and overall survival (OS). An article published by a conglomerate of authors through the American Cancer Society (ACS)5 found that patients who underwent surgery had a two-year OS rate of 50 percent compared to 7 percent for those who did not undergo surgery. Conversely, studies conducted by Xie XH et al3 and Giridhar P et al4 found no surgical benefit for their patient cohorts. Giridhar P et al4 reported the five-year survival for patients who underwent surgery and those that did not to be less than 5 percent. Factors contributing to surgery consideration included location of primary tumor and stage of disease.4 It was concluded that patients with early-stage disease who have small primary tumors outside of the thoracic cavity benefit from surgery as a treatment option.1,3,5

Subsequently, chemotherapy regimens have been analyzed for their effectiveness. Unlike surgery, chemotherapy has found acceptance as a treatment method in an adjuvant setting, especially when used in tandem with radiation therapy. Studies conducted by Zhang H et al8, Xie XH et al3, and Giridhar P et al4 show substantial increase in OS for patients receiving chemotherapy and radiation therapy together. Clinical Case Reports8 published data showing the only long-term survivors (> 10 years) in their studied patient cohort received this multimodality method, which concurs with the previous studies. Conversely, chemotherapy as a single treatment method is not supported in the literature, resulting in an overall two-year survival of 0 percent for patients.3,5,6 This is where strong support for the use of multi-modality treatments for NC patients begins.

Multi-modality treatments are becoming a mainstay in effective cancer care. While a standard treatment method for NC patients is yet to be adopted, much of the literature is pointing towards radiation therapy with or without chemotherapy as the primary treatment method.1,3,6,8 Specifically, a dose of greater than 50 gray (Gy) has proven to be effective in a clinical setting.4,8 This treatment schematic was implemented for NC patients due to its proven effectiveness in a majority of small cell lung cancers (SCLC).8 Moreover, radiation therapy used with or without chemotherapy is producing an increased OS for patients who would otherwise quickly reach a dismal outcome.3,4,6,8 While surgery, chemotherapy, and radiation therapy have become the key players in cancer care, targeted therapies are becoming an increasingly studied and utilized treatment method and NC patients are no exception to this powerful modality.

Targeted therapies provide the opportunity to act specifically on the associated cancer molecules, BRD4-NUTM1 in most NC cases. The effectiveness of this therapy method is currently difficult to measure as it is still in the development process and is not widely available. There are several clinical trials assessing the effectiveness of bromodomain inhibitors (BETi) and histone deacetylase inhibitors (HDACi) against NC in the United States and Europe.5,6 Both BETi and HDACi have shown notable increased OS for patients in phase I and II trials.6 Specifically, four patients receiving BETi regimens demonstrated OS of 19, 18, seven, and five months, respectively. 6 When compared to the median OS of six months for NC patients overall these results are promising and are driving the continuation of research. 2,6 Although due to BRD4s expression in a majority of tissues toxicity under treatment is a concern, thrombocytopenia specifically.1 There is still a lot to learn about targeted therapy's role in NC treatment, results from the previously mentioned clinical trials may dramatically impact the treatment recommendations but it is too soon to tell.

**Case Description**

**Case one**

A 14-year-old male was diagnosed with viral bronchitis on 09/11/20, after his symptoms did not resolve he was sent for a chest x-ray which showed an enlarged mediastinum. The patient was directed to the hospital for a CT scan which showed a 4.78 x 6.7 x 7.3 cm mass in the right middle mediastinum. A scapular biopsy was conducted on 09/16/20; NUT immunostaining was performed on the sample showing strongly and diffusely positive results. Additionally, results from FISH analysis were positive for rearrangement of the NUTM1 gene. A PET-MRI was conducted on 9/17/20 verifying his chest mass along with a right adrenal mass, left renal hilar lesion, and widespread bone metastasis (see Figure 1). Official diagnosis of NUT midline carcinoma came on 09/19/20. The presence of a large foci at L4 invading the spinal canal in addition to the lung mass resulted in the recommendation of radiation therapy after extensive conversation in tumor board. The goal of this treatment was to slow the progression of disease, prevent significant complications, and reduce pain. The lead pediatric radiation oncologist was specifically concerned with the risk superior vena cava (SVC) syndrome due to the mediastinal mass and paralysis due to the large lesion invading the canal at L4 leading to emergent radiation therapy.

On 9/19/20 the patient began radiation, receiving 30 Gy in 10 fraction (fx) for the chest mass. The following day the patient began another course of radiation to the lumbar spine lesion, also receiving 30 Gy in 10 fx. Subsequently, the patient underwent a course of palliative radiation to the right and left tibia receiving 20 Gy in 5 fx. During this time the patient received chemotherapy based on the Scandinavian protocol for Ewing’s sarcoma (EWS). This protocol provides data on increased metastasis free survival (MFS) for patients receiving two cycles of VAI (vincristine, doxorubicin, ifosfamide) and two cycles of PAI (cisplatin, doxorubicin, ifosfamide) with radiation therapy leading to its indication for this patient specifically.9 He received his last radiation treatment of 8 Gy in 1 fx on 12/10/20 to the left shoulder region. The radiation therapists and radiation oncology team collectively played a significant role in managing this aggressive disease. The patient was showing a nearly complete response in areas that were irradiated, yet despite the multi-modality treatment approach the patients widespread metastatic was too abundant to control. After intense chemotherapy and multiple courses of palliative radiation the patient passed away on 1/23/2021.

**Case two**

68-year-old female presented to the ophthalmology clinic on 4/10/20 with a swollen right eye, numbness on the right side of the face, and decreased vision and depth perception. The patient was sent to the emergency department for an MRI of the brain and orbit. The MRI showed a mass located centrally in the right ethmoidal air cells measuring 5.4 x 2.5 x 3.9 cm. After meeting with ears, nose and throat (ENT), a biopsy of the mass was taken, and the pathology report came back as poorly differentiated squamous cell carcinoma (SCC) ultimately identified as a stage III T4N0M0 disease. The patient additionally underwent a diagnostic chest, abdomen, and pelvis CT that came back negative for any obvious metastatic disease although two enlarged lymph nodes were noted, one right femoral node and one external iliac node. On 4/23/20 the patient agreed with the plan presented to her as follows: induction chemotherapy, surgery, and post-operative radiation therapy.

After receiving two cycles of TPF (docetaxel, cisplatin and fluorouracil) a follow-up MRI was conducted which showed partial response with tumor enhancement in the left ethmoid sinus. On 06/24/20 the patient was taken to surgery and the pathology from the surgical resection demonstrated NUT carcinoma; NUT immunostaining was performed on the sample showing strongly and diffusely positive results. Subsequently, on 08/04/20 the patient began post-operative radiation therapy receiving 59.4 Gy in 33 fractions concurrent with weekly cisplatin. After receiving thoughtful care from the radiation oncology team her disease continued to worsen. Unfortunately, on 11/5/20 the patient was admitted for an orbital abscess which was surgically removed. After recovering, a PET scan was conducted in January of 2021 showing FDG uptake in the right medial orbital wall, right neck, along with multiple lymph nodes in the right internal iliac, inguinal, and precranial regions resulting in concern for residual/recurring metastasis (see Figure 2). On 02/5/21 a FNA was performed on specified lymph nodes of concern, pathology came back positive for metastatic NUT carcinoma. This patient is continuing with their care, nearly a year after the initial presentation of symptoms.

**Discussion**

Undeniably, the two cases presented manifested themselves in unique ways. Case one presented at a young age with aggressive disease while case two presented later in life with what initially seemed to be a mild and manageable disease. The patients' initial diagnosis, age at diagnosis, clinical presentation, and progression of disease are all key factors illustrating the peculiar development of this cancer. While there are many variations in the presentation of these cases, there are several aspects of each case that fall in line with the current literature. One of which being the importance of fast and accurate detection. The most studied and effective diagnostic tools for NC patients include IHC, FISH, and NGS. For both patients, IHC was the diagnostic tool that produced the answers doctors were looking for. This was following the initial, unspecific, and inaccurate diagnoses of viral bronchitis and SCC, respectively. Although NC is a subtype of SCC, NC is much more aggressive and manifest in a unique way. Ultimately, these cases reiterate the need for accurate diagnosis before optimal treatment can be discussed and delivered.

 In regard to treatments, both patients underwent chemotherapy and radiation therapy. Although their associated regimens and doses varied, both treatments produced measurable impact on disease reduction. Notably, patient one received palliative radiation doses due to the extent of disease at time of diagnosis. The areas irradiated including the mediastinum, left spine, and right and left tibia showed a complete response supporting radiations therapies effectiveness for these patients. The radiation oncologist leading the case shared that the parents were so pleased with the results produced by radiation therapy they continued to come back again and again to seek relief for their son. Subsequently, patient two received a traditional post-operative dose of 55.9 in 33 fx which was in alignment with the literature suggesting a dose of 50 Gy or more. Unfortunately, despite this dose patient two’s disease become metastatic and further treatment options were brought into discussion.

Ultimately, the presented patient cases implicate the need for rapid detection and aggressive, multi-modality treatments. There were several notable limitations for these patients including initial misdiagnosis, availability of targeted therapies, and progression of disease. If these patients would have been properly diagnosed sooner their treatment regimens could have been delivered promptly and more accurately. Patient one underwent foundation testing for targeted therapies but did not survive long enough to receive them. Subsequently, patient two could have been treated more aggressively if the initial diagnosis had shown the presence of the BRD4-NUTM1 fusion gene, the enlarged lymph nodes specifically would have received the necessary attention. In summary, NC patients need precise diagnosis and aggressive treatment to provide them with the best prognostic outlook.

**Conclusion**

To conclude, new discoveries in cancer research inevitably introduce the need for new advancements in cancer care. The recognition of NC as a rare, poorly differentiated tumor has created opportunities for patients whose options were previously limited. Despite the fact that optimal management for this disease is yet to be uncovered, the body of literature surrounding treatment options continues to grow and expand. Creating the ideal treatment regimen begins with an in-depth analysis of reported cases and current literature. Case reports have significantly increased due to the International NUT Midline carcinoma Registry and their efforts to create a central location for healthcare professionals, individuals, and families affected by this disease.10 The registry provides basic information, publications, and clinical trial opportunities specifically and is a resource that can and should be utilized by healthcare professional and patients alike. Radiation therapists play a vital role in patient advocacy and with further education and recognition of this disease will come advancement in treatment schemes, expanded involvement in clinical trials, and increased awareness for healthcare professionals, patients, and their families alike. This growing body of knowledge can be the segue to faster recognition.

Ultimately, optimal treatment must follow accurate diagnosis. IHC is a timely, cost-effective, and precise diagnostic tool supported by both the literature and the discussed patient cases proving itself to be essential for these patients. The ideal treatment for these patients, as suggested by the literature, is a multimodality approach consisting of radiation therapy and chemotherapy. Targeted therapies are another well documented treatment option, although many targeted therapies are still in the early stages of clinical trials and are not widely accessible. With further research on targeted therapies and optimal chemoradiation doses the ideal management for this disease may come to fruition in the near future. Lastly, as radiation oncology professionals it is vital to continue to research, educate, and spread awareness of this lethal genetic abnormality in order to save the lives of patients who otherwise quickly reach a dismal outcome. Radiation therapists specifically should educate themselves and others on this disease as radiation therapy is becoming a mainstay in these patients care. As the body of knowledge surrounding cancer as a biological defect continues to evolve, healthcare professionals must also evolve in their understanding of how to care for patients with these unique diagnoses.

**Figures**

Figure 1. On the left is case one’s initial PET scan, conducted on 09/17/20. On the right is the patients PET scan conducted following radiation therapy and chemotherapy. The effect of chemoradiation on the patient’s disease is notable. Figure courtesy of a Midwest hospital.

Figure 2. On the left is case two’s initial PET scan, conducted on 04/30/20. On the right is the patients most recent PET scan showing the uptake in the right neck pass and pelvic nodes, conducted on 01/19/21. Figure courtesy of a Midwest hospital.

Figure 1.



Figure 2.



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