






# Nuclear protein in testis (NUT) carcinoma in the public sector of the Free State province, South Africa



## Authors:

Antoinette E. Roets<sup>1,2</sup>   
 Shireen Pretorius<sup>2</sup>   
 Gina Joubert<sup>3</sup>   
 Nicholas Pearce<sup>4</sup>   
 Jacqueline Goedhals<sup>1,2</sup> 

## Affiliations:

<sup>1</sup>Department of Anatomical Pathology, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa

<sup>2</sup>Department of Anatomical Pathology, National Health Laboratory Service, Bloemfontein, South Africa

<sup>3</sup>Department of Biostatistics, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa

<sup>4</sup>Department of Surgery, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa

## Corresponding author:

Jacqueline Goedhals,  
 gnmbjg@ufs.ac.za

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**Background:** Nuclear protein in testis (NUT) carcinoma (NC) is a rare tumour easily mistaken for a number of other tumours if a NUT immunohistochemical stain is not performed, and there is no high index of suspicion. This tumour is exceptionally aggressive, with only isolated survivors. Early identification and aggressive treatment are required. No research on NC has been conducted in South Africa and only one case has been reported from the rest of Africa. The incidence of this tumour in South Africa is, therefore, unknown.

**Aim:** The aim of this study was to determine the incidence of NC over a 12-year period and describe the demographic features of any patients identified.

**Setting:** Department of Anatomical Pathology, University of the Free State and National Health Laboratory Service (NHLS) in Bloemfontein, South Africa.

**Methods:** In this retrospective study, all undifferentiated malignant tumours and tumours with evidence of squamous differentiation from the head, neck and thorax seen between 01 January 2005 and 31 December 2016 were included. Nuclear protein in testis immunohistochemical staining was performed on all specimens. The stain was regarded as positive if speckled nuclear staining was observed in more than 50% of the tumour cells.

**Results:** In total, 498 cases were investigated, of which 424 (85.1%) belonged to male patients. The mean age of the patients was 58.6 years. Only one positive case, a 30-year-old woman with a lung mass and lymph node metastases, was identified.

**Conclusion:** Our findings confirmed the rarity of NC. Additional research in other provinces and the private sector is recommended to provide a comprehensive patient profile of NC in South Africa.

**Keywords:** NUT midline carcinoma; NUT carcinoma; tumour; Free State; South Africa.

## Introduction

Nuclear protein in testis (NUT) midline carcinoma (NMC) was first described in 1991.<sup>1</sup> It is a rare form of poorly differentiated squamous cell carcinoma caused by a translocation involving the *NUT* gene.<sup>1,2,3,4</sup> In most cases, it fuses with *BRD4*, but other genes such as *BRD3* can also be involved.<sup>3</sup> It was previously thought to occur only in young patients in midline locations. However, research has shown that NMC can occur at any age and in locations away from the midline, and the name has been changed to NUT carcinoma (NC).<sup>2,5,6,7,8</sup>

Nuclear protein in testis carcinoma is an aggressive tumour that has a very poor prognosis with a median survival of 6.7 months.<sup>6,9</sup> Conventional chemo- and radiotherapies have proven unsuccessful in most cases and only isolated survivors have been documented.<sup>10,11,12,13</sup> Consequently, numerous targeted therapies are under investigation in the hope of finding a cure.<sup>14,15,16,17,18</sup> As this is a translocation-associated tumour with a simple karyotype, these targeted therapies are aimed towards epigenetic components, including histone deacetylase inhibitors, bromodomain and extra-terminal motif (BET) inhibitors or specific components of the cell cycle.<sup>19,20</sup>

Because of the rarity of this entity, a lack of awareness on the part of pathologists and its undifferentiated appearance, NC has been misdiagnosed in the past as poorly differentiated squamous cell carcinoma or undifferentiated carcinoma.<sup>2,3,6,21</sup> The typical morphological appearance is that of an undifferentiated carcinoma with foci of abrupt keratinisation, with varied and sometimes unexpected staining with a number of immunohistochemical markers such as CD99, FLI1, CD45, CD56, CD138, TTF1, S100 and CD117.<sup>21</sup>

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Identification of patients with NC is important for the provision of counselling for families, surveillance for other metachronous carcinomas and early, more aggressive treatment.<sup>7</sup> Limited research has been conducted on NC, and most of the identified patients to date have been from the United States of America (USA) and Europe, with limited data from other continents.<sup>6,21,22,23</sup> Additional research can aid in building the NC international registry, identifying more patients for clinical trials in the development of novel treatments and in the overall demographic profiling of patients.

To date, no research on NC is available from South Africa, and only a single case report documenting an Egyptian patient is available from the rest of Africa.<sup>13</sup> Because the incidence and demographic profile of patients from Africa are unknown, the aim of this study was to determine the number of cases of NC seen over a 12-year period by the Department of Anatomical Pathology, University of the Free State (UFS) and National Health Laboratory Service (NHLS), and to describe the demographic features of any patients identified.

## Methods

A retrospective descriptive study was performed. A Systematised Nomenclature of Medicine (SNOMED) search of the NHLS electronic databases was performed to identify all malignant tumours of the head, neck and chest diagnosed by the Department of Anatomical Pathology, University of the Free State (UFS) and NHLS, over a 12-year period from 01 January 2005 to 31 December 2016. Prior to this, there was no electronic laboratory information system. The department provides diagnostic surgical pathology services to all public-sector hospitals and clinics in the Free State province of South Africa.

Cases that were selected included all undifferentiated malignant tumours and tumours showing squamous differentiation. Males and females of all ages were included. Seven cases were excluded from the study as the wax blocks contained insufficient tissue for immunohistochemical studies. Furthermore, tumours were excluded if they showed neuroendocrine or glandular differentiation, had specific diagnoses, such as Ewing sarcoma or lymphoma, or had evidence of a specific aetiology determined by the presence of p16 and Epstein-Barr virus encoded RNA *in situ* hybridisation (EBER-ISH) positivity, although rare cases of NC can show neuroendocrine differentiation and p16 expression. Once the suitable cases had been identified, the slides were retrieved from the departmental archives. All the cases were reviewed and a representative slide was selected.

The wax blocks were then retrieved from the departmental archives, and 4-micrometre ( $\mu\text{m}$ ) sections were cut and stained using an anti-NUT rabbit polyclonal antibody (clone abl22649; Abcam Inc., Cambridge, MA, USA). A dilution of

1:500 was used. Slides were stained using a Benchmark XT automated slide preparation system (Ventana Medical Systems Inc., Tucson, AZ, USA). The slides were then counterstained with Mayer's haematoxylin, dehydrated and covered with a coverslip.

The slides were reviewed by two investigators including an experienced pathologist. Nuclear protein in testis was scored as positive when speckled nuclear staining was evident in 50% or more of the tumour cells. Otherwise, it was scored as negative. Cases with non-specific staining were reviewed by an expert pathologist at Brigham and Women's Hospital in Boston, MA, USA. Additional information including the patient's age, sex, topography of the biopsy and the original diagnosis was also recorded.

Statistical analysis was performed by the Department of Biostatistics, UFS. Results were expressed as frequencies and percentages (categorical variables) and means, standard deviations or percentiles (numerical variables).

## Ethical consideration

Approval to perform the study was obtained from the Health Sciences Research Ethics Committee, University of the Free State (clearance number: UFS-HSD2017/1164). The need for individual patient consent was waived because of the retrospective design, and patient records were anonymised.

## Results

A total of 498 cases that met the inclusion criteria were identified in the 12-year study period. The majority of patients ( $n = 424$ ; 85.1%) were men. The mean age of the patients was 58.6 years (median 59 years; range 17–89 years). Twenty-five (5.0%) patients were under the age of 40 years at the time of diagnosis. As shown in Table 1, the most common locations included the larynx ( $n = 287$ ; 57.6%) and the lungs ( $n = 118$ ; 23.7%). The most common diagnosis was that of squamous cell carcinoma with 447 (89.8%) cases, followed by undifferentiated carcinoma with 40 (8.0%) cases (Table 1).

Only one case was positive with the anti-NUT antibody. The patient was a 30-year-old woman with right middle lobe lung collapse and mediastinal and cervical lymphadenopathy. The histology was characteristic of an undifferentiated carcinoma with focal abrupt keratinisation (Figure 1). The remaining 497 cases were negative. Seven cases showed non-specific staining and were confirmed as negative by an expert pathologist from Brigham and Women's Hospital in Boston, MA, USA.

## Discussion

Nuclear protein in testis carcinoma is a highly aggressive translocation-associated carcinoma first described in 1991.<sup>1,2,3,4,6,7,22</sup> It was initially diagnosed using fluorescent *in*

TABLE 1: Number of cases and age of patients according to diagnosis.

| Topography               | No. of cases | Mean age (years) | SD   | Median age (years) | Basaloid squamous cell carcinoma |      | Degenerate malignant cells |      | Sarcomatoid carcinoma |     | Squamous cell carcinoma |       | Undifferentiated carcinoma |      | Verrucous carcinoma |      |
|--------------------------|--------------|------------------|------|--------------------|----------------------------------|------|----------------------------|------|-----------------------|-----|-------------------------|-------|----------------------------|------|---------------------|------|
|                          |              |                  |      |                    | n                                | %    | n                          | %    | n                     | %   | n                       | %     | n                          | %    | n                   | %    |
| Floor of mouth           | 3            | 58.0             | 6.2  | 56.0               | 1                                | 33.3 | -                          | -    | -                     | -   | 2.0                     | 66.7  | -                          | -    | -                   | -    |
| Larynx                   | 287          | 59.2             | 9.4  | 59.0               | 3                                | 1.0  | -                          | -    | -                     | -   | 283.0                   | 98.6  | 1.0                        | 0.3  | -                   | -    |
| Lung                     | 118          | 60.8             | 10.9 | 60.0               | 1                                | 0.85 | 1                          | 0.8  | 1                     | 0.8 | 91.0                    | 77.1  | 24.0                       | 20.3 | -                   | -    |
| Mediastinum              | 6            | 59.5             | 10.8 | 61.0               | -                                | -    | 1                          | 16.7 | -                     | -   | 5.0                     | 83.3  | -                          | -    | -                   | -    |
| Neck                     | 3            | 59.0             | 23.3 | 63.0               | -                                | -    | -                          | -    | -                     | -   | 2.0                     | 66.7  | 1.0                        | 33.3 | -                   | -    |
| Nose                     | 8            | 55.1             | 13.1 | 54.0               | -                                | -    | -                          | -    | -                     | -   | 7.0                     | 87.5  | -                          | -    | 1                   | 12.5 |
| Oesophagus               | 2            | 54.0             | 9.9  | 54.0               | 1                                | 50.0 | -                          | -    | -                     | -   | 1.0                     | 50.0  | -                          | -    | -                   | -    |
| Paranasal sinuses        | 22           | 53.0             | 11.3 | 56.5               | -                                | -    | -                          | -    | -                     | -   | 21.0                    | 95.5  | 1.0                        | 4.5  | -                   | -    |
| Pharynx                  | 44           | 52.4             | 17.3 | 57.5               | 1                                | 2.3  | -                          | -    | -                     | -   | 30.0                    | 68.2  | 13.0                       | 29.5 | -                   | -    |
| Submandibular lymph node | 3            | 62.7             | 10.0 | 62.0               | -                                | -    | -                          | -    | -                     | -   | 3.0                     | 100.0 | -                          | -    | -                   | -    |
| Tongue                   | 2            | 51.0             | 9.9  | 51.0               | -                                | -    | -                          | -    | -                     | -   | 2.0                     | 100.0 | -                          | -    | -                   | -    |
| Mean age (SD) (years)    | -            | -                | -    | -                  | 61                               | 17.4 | 56                         | 2.8  | 61                    | -   | 59.3                    | 9.7   | 50.4                       | 19.3 | 66                  | -    |
| Median age (years)       | -            | -                | -    | -                  | 61                               | -    | 56                         | -    | 61                    | -   | 59.0                    | -     | 57.0                       | -    | 66                  | -    |
| Total                    | 498          | -                | -    | -                  | 7                                | 1.4  | 2                          | 0.4  | 1                     | 0.2 | 447.0                   | 89.8  | 40                         | 8.0  | 1                   | 0.2  |

SD, standard deviation.

*situ* hybridisation. An immunohistochemical stain only became available in 2009.<sup>24</sup> The histological features are typical of an undifferentiated carcinoma with foci of abrupt keratinisation, and the diagnosis could be missed if a high index of suspicion is not maintained with confirmation by means of NUT immunohistochemistry.<sup>2,3,6,21,24</sup> Nuclear protein in testis carcinoma also shows positivity for p63, CK5/6 and p40, confirming squamous differentiation.<sup>25,26</sup> Most tumours are CK7 positive and often CD34 positive.<sup>25</sup> No *in situ* component has been identified and the cell of origin is unknown, but they most probably arise from a stem cell.<sup>27</sup> The majority of cases occur in midline locations, such as the upper aero-digestive tract and mediastinum. However, cases involving numerous other sites have also been described, such as pancreas, adrenal gland and bladder.<sup>3,5,7,28</sup> Patients often present with mass-related symptoms and many have metastases at the time of diagnosis.<sup>9,22,25</sup> The most common metastatic sites are lymph nodes, bone and the pleura.<sup>2,25,29</sup>

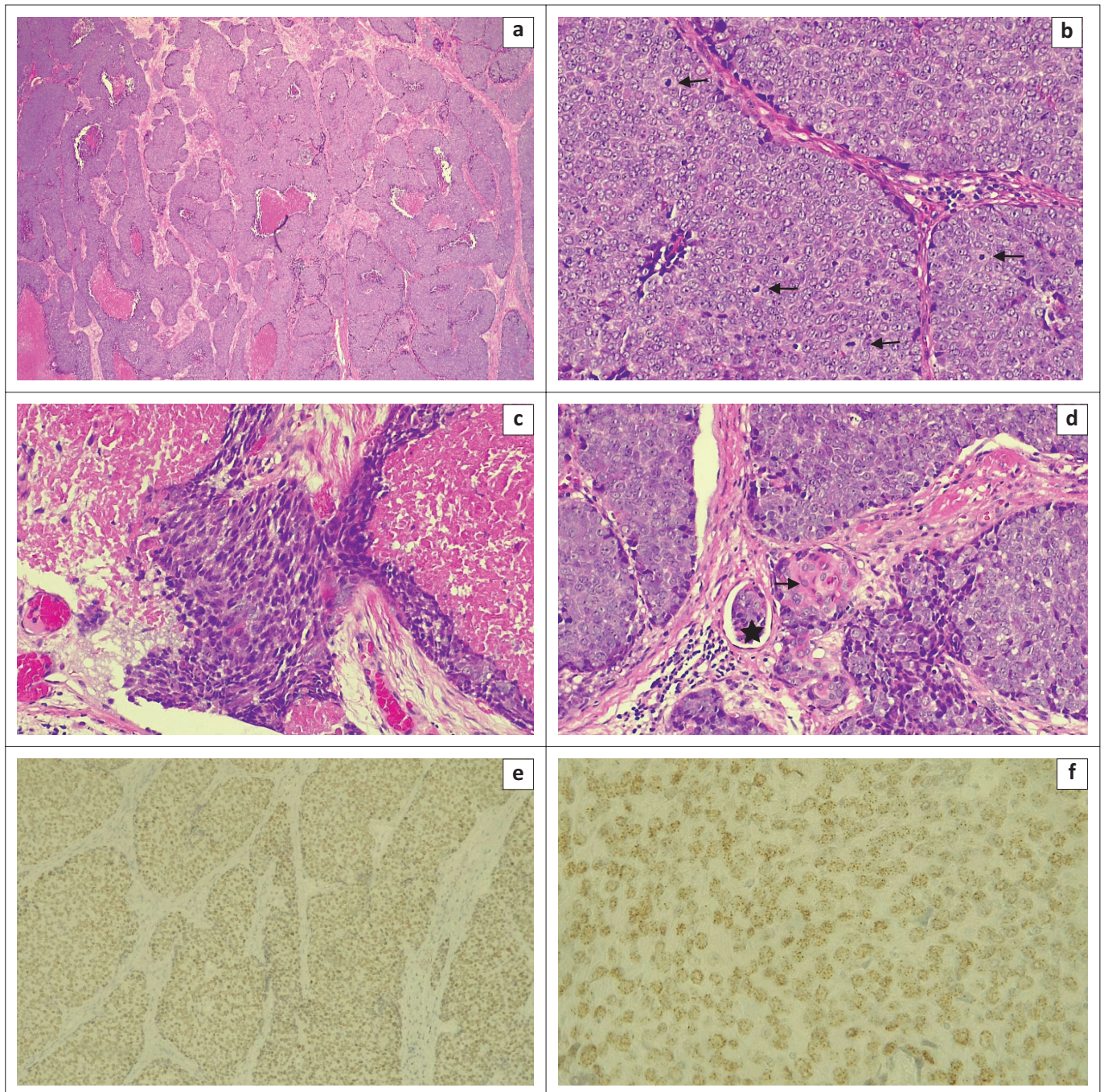
Although specific translocations are associated with a number of sarcomas, NC is one of few translocation-associated carcinomas identified to date. Most carcinomas accumulate numerous mutations with time and have an extremely complex karyotype.<sup>2,4,5,19,30</sup>

Of 498 cases evaluated in this study, only one NC case was identified. According to Statistics South Africa (SSA), the Free State province has a population of 2.8 million people, of which 63.5% use public healthcare facilities that send specimens to this department for histology services.<sup>31</sup> This finding confirms the extremely rare nature of this tumour. The case showed the classical histological features with strong positivity on NUT immunohistochemistry, and the diagnosis was made at the time of biopsy.

The other 497 cases included in this study were all negative for NC. This finding is reassuring in the sense that cases are not being misdiagnosed as squamous cell carcinoma or undifferentiated carcinoma. In addition, other tumours, such as Ewing sarcoma, rhabdomyosarcoma, rhabdoid tumour, desmoplastic small round cell tumour, olfactory neuroblastoma, melanoma, lymphoma, synovial sarcoma, undifferentiated nasopharyngeal carcinoma, thymic carcinoma or sinonasal undifferentiated carcinoma (SNUC), can also enter the differential diagnosis depending on the clinical setting.<sup>2,3,6,21</sup> It is also important to note that the NUT antibody can be positive in germ cell tumours, but the pattern of staining differs. Germ cell tumours stain only focally and in a diffuse nuclear manner, whereas NC stains diffusely and in a granular manner.<sup>24</sup>

Seven of the cases showed non-specific staining with the antibody used in this study. Although this might result in incorrect classification as an NC, careful evaluation allowed for accurate interpretation as the speckled pattern of staining was not evident.<sup>24</sup>





**FIGURE 1:** Nuclear protein in testis midline carcinoma. (a) Low-power view shows nests, sheets and trabeculae in a desmoplastic stroma with abundant necrosis; 2.5× magnification. (b) Undifferentiated cells with vesicular nuclei and conspicuous nucleoli. Note the abundant mitotic figures (arrows); 10× magnification. (c) Squamous differentiation noted focally; 10× magnification. (d) Cells with more eosinophilic cytoplasm as evidence of abrupt keratinisation (arrow). Note the lymphovascular invasion (star); 20× magnification. (e) Nuclear protein in testis immunohistochemical stain. Note the diffuse pattern of staining; 40× magnification. (f) Speckled nuclear staining pattern considered positive; 40× magnification.

## Conclusion

Nuclear protein in testis carcinoma is a rare and highly aggressive malignancy that can be misdiagnosed as squamous cell carcinoma or undifferentiated carcinoma if a high index of suspicion is not maintained. In the public sector of the Free State province, as in the rest of the world, NC is a very uncommon tumour, as only one case was identified in a large population group. The extensive differential diagnosis of NC presents a significant challenge to the pathologist, especially in developing countries with

limited access to comprehensive immunohistochemical antibody panels, including anti-NUT. Further studies are needed to establish the frequency in which NC occurs in other provinces of South Africa as well as in the South African private healthcare sector and in the rest of Africa.

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## Competing interests

The authors have declared that no competing interests exist.

## Authors' contributions

The study concept was developed by J.G. and N.P. The protocol was prepared by A.E.R. and J.G. Ethical approval was obtained by A.E.R. Immunohistochemical stains were performed by S.P. Interpretation of the stains and data collection were performed by A.E.R. and J.G. and the data were analysed by G.J. The article was written by A.E.R. and J.G., with input from S.P., G.J. and N.P.

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## Data availability statement

Data are available from the corresponding author upon reasonable request.

## Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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