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Intensive treatment and survival outcomes in NUT midline carcinoma (NMC) of the head and neck (HN)

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Abstract

Background—NUT midline carcinoma (NMC) is a rare and aggressive genetically characterized subtype of squamous cell carcinoma frequently arising from the head and neck (HN). HNNMC characteristics and optimal management are unclear.

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Methods—We performed a retrospective review of all known cases of HNNMC in the International NMC Registry, data as of December 31, 2014. Of 48 consecutive patients treated from 1993–2014, clinicopathologic variables and outcomes from 40 patients were available for analyses, the largest cohort of HN NMC studied to date. Overall survival (OS) and progression-free survival (PFS) according to patient characteristics and treatment were analyzed.

Results—We identified a five-fold increase in diagnosis of HNNMC from 2011 to 2014. Median age was 21.9 years (range 0.1–81.7), male:female was 40%:60%, and 86% had *BRD4-NUT* fusion. Initial treatment was initial surgery (S) +/− adjuvant chemoradiation (CRT) or adjuvant radiation (RT) (56%), initial RT +/− chemotherapy (C) (15%), or initial C +/− S or RT (28%). Median PFS was 6.6 months (range 4.7–8.4). Median OS was 9.7 months (range 6.6–15.6). Two-year PFS was 26% (95% CI, 13%–40%). Two-year OS was 30% (95% CI, 16%–46%). Initial S +/− post-operative CRT or RT (p=0.04), and complete resection with negative margins (p=0.01) were significant predictors of improved OS even after adjustment for age, tumor size and neck lymphadenopathy. Initial RT or C, and *NUT* translocation type were not associated with outcome.

Conclusions—HNNMC portends a poor prognosis. Aggressive initial surgical resection +/− post-operative CRT or RT was associated with significantly enhanced survival. C or RT alone is often inadequate.

Keywords

NUT protein; BRD4; BRD3; NUT midline carcinoma; head and neck cancer

Introduction

NUT midline carcinoma (NMC) is a rare and aggressive genetically defined subtype of squamous cell carcinoma characterized by chromosomal rearrangement of the *NUT* gene (a.k.a. *NUTM1*, *Chr15orf55*).[1] The characteristic somatic t(15:19) translocation that positions *NUT* in-frame with *BRD4*, a ubiquitously expressed transcriptional coactivator, was first identified in 2003.[2] About 30% of NMCs lack *BRD4* rearrangement and are termed *NUT* variants, whereby *NUT* is often fused to *BRD3*,[3] or *NUT* is fused to a non-*BRD* gene such as *NSD3*.[4] NMCs are poorly differentiated tumors that display variable degrees of squamous differentiation. Diagnosis is made by demonstration of *NUT* rearrangement by molecular analysis, including reverse transcriptase-PCR (RT-PCR), fluorescence in situ hybridization (FISH), or cytogenetic analysis.[1] Alternatively, an immunohistochemical (IHC) stain with monoclonal antibody to NUT (C52, Cell Signaling) has been shown to be 100% specific and 87% sensitive[5] for the diagnosis of NMC. Thus, a positive NUT IHC stain by itself is diagnostic of NMC.[6]

NMC is considered the most clinically aggressive type of squamous carcinoma and the majority of patients will succumb to rapid disease progression with early metastases to locoregional and distant sites. Over 80 % of patients will die within one year of diagnosis despite intensive treatment, underscoring the need for effective treatment of this disease.[7] NMC typically arises from the midline structures of the thorax, or from the head and neck (HN). NMC was initially described in children and adolescents, however in recent years there appears to be an increasing diagnosis in adults.[7] The actual NMC incidence is unclear,

and is almost certainly under diagnosed. Up to 18% of undifferentiated carcinomas of the head and neck are in fact NMC.[8, 9]

In vitro studies of NMC have demonstrated that NUT fusion proteins drive tumor growth and blockade of differentiation through aberrant histone acetylation in a manner dependent on the targeting of *MYC* and *TP63* genes by BRD bromodomains.[3, 10–12] In a unique mechanism, the acetyl-histone binding bromodomains of BRD4 tether NUT to chromatin, driving acetylation of massive regions of chromatin through recruitment of p300, a histone acetyl-transferase, by NUT. These so-called 'megadomains' trigger transcription of underlying genes both directly and through activation of their entire regulatory domains, including enhancers, enforcing the expression of key oncoproteins such as MYC, p63, and MED24.[10] Small molecule BET bromodomain inhibitors targeting BRD4-NUT are in development and are enrolling NMC patients in clinical trials. While an initial report indicates that at least one of these these drugs, OTX015 (OncoEthix/Merck), appears to have some efficacy as single agent in human NMC, it is unclear at this stage, due to limited patient numbers and lack of clinical trial data, whether this drug class alone is more effective than other conventional strategies.[13]

For over a decade, we have served as the primary diagnostic center for NMC, and in 2010 we established an international NMC Registry to analyze clinical and pathologic data in aggregate to inform natural history, therapeutic interventions and outcomes. We previously reported on 63 cases of NMC in which the overall median survival was 6.7 months.[7] Slightly better outcomes were observed for patients with HNNMC (n=19) compared to thoracic NMC in that cohort.[7] Since 2012 the registry has accrued more NMC cases, particularly arising from the head and neck (n=29). To define preferred management strategies, we sought to determine the clinical presentation, treatment and outcome of 48 patients with HNNMC from the Registry. The clinico-pathologic features, treatment regimens and outcomes of 40 evaluable patients with HNNMC are reported herein.

Materials and Methods

NUT midline carcinoma registry

The International NMC Registry was created in 2010, and NMC patients in this study who were enrolled were identified by referral as part of consultation for clinical care either for diagnosis or treatment. Patients were not identified by literature searches or added from published cases. NMC patients prior to 2010 were identified similarly through referral, or through screening of archival pathology specimens at one of our institutions,[9, 14] and retrospectively enrolled into the NMC Registry. The number of patients retrospectively enrolled before 2010 is 19, and patients prospectively enrolled 2010 or later is 29. The Registry is international; enrolled patients have come from North America, South America, Europe, Asia, and Australia. There are no geographic restrictions to enrollment in the Registry.

Patients

From January 1993 to December 2014, we identified 48 patients with HNNMC amongst a total of 107 patients (45%) in the International NMC Registry. HNNMC patients were defined as those with tumors originating in the head and neck, exhibiting aberrant NUT expression demonstrated by IHC, *NUT* rearrangement shown by fluorescent in situ hybridization (FISH), *BRD4-NUT* fusion by reverse transcriptase (RT)-PCR, or cytogenetic t(15;19) in the setting of carcinoma.[1] Histology and immunohistochemistry was reviewed for all cases by Dr. French. Of these 48 patients, 19 were reported in our previous study[7] and 29 were not previously reported.

A registry questionnaire was sent to treating physicians inquiring about demographic, clinical, treatment, and outcome variables. Outcome data were provided for 40 patients. Approval for the International NMC Registry (www.nmcregistry.org), including the retrospective and prospective analysis of NMC patient data, was obtained from the Institutional Review Board of the Dana-Farber Cancer Institute (Boston, MA). Written informed consent was obtained from all study participants.

Patient data including demographics, clinical staging data (site of primary tumor, lymph node involvement, and location of metastasis), therapeutic interventions, and response to treatment were abstracted from questionnaires completed by the treating physician and analyzed in aggregate. Initial therapy was defined as treatment administered from initial diagnosis until first relapse or progression. Surgical extent was classified as complete resection with negative margins (R0 resection), gross total resection (resection of all gross visible disease however microscopic residual disease present), debulking (gross residual disease present). Chemotherapy was categorized into regimens containing either platinum, or regimens containing anthracyclines and nonplatinum alkylating agents. Progression-free survival (PFS) was measured as the time from initial diagnosis of NMC until the time of first disease relapse, progression or death, or until last contact if none of these events occurred. Overall survival (OS) was defined as the time from diagnosis until the time of death or until last contact. Clinical responses to initial therapies were classified as complete or partial responses, stable disease, or progressive disease according to the clinical judgment of the treating physician. Confirmation of diagnosis was obtained by pathology reports and actual histology was reviewed when available. Cases were classified into 3 histopathologic categories: carcinoma with squamous differentiation, carcinoma without squamous differentiation, and other histology.

Statistical analysis

Analyses were conducted to investigate factors potentially associated with PFS or OS, using Kaplan Meier plots and log-rank tests. Two-year PFS and OS point estimates were reported with 95% confidence intervals (CI). Cox proportional hazards regression modeling to predict PFS and OS was conducted to generate unadjusted and adjusted results where individual predictors of PFS and OS were analyzed with and without simultaneously including age and tumor size in the model. Hazard ratios and 95% CI's were reported. SAS version 9.4 was used.

Results

Demographic and Tumor Characteristics

Demographic and tumor characteristics were available for all 48 patients. The diagnosis of HNNMC has increased dramatically since 2012 with an increasing proportion of adult cases (diagnosed at 18 years or older) (Figure 1). Median age was 21.9 years (range 0.1–81.7), and there was a female predominance (1.5:1). Tumor site was sinonasal origin in 57% and other sites included nasopharynx (n=3), oropharynx (n=1), hypopharynx (n=1), larynx (n=1), salivary gland (n=2) and unknown primary (n=5). The *BRD4-NUT* fusion was found in 86%. Histology was classified in 49% of patients as carcinoma with squamous differentiation, whereas 43% had carcinoma without squamous differentiation and 8% had other histology. Regarding NMC diagnosis, we found that 16 of 46 (35%) patients for whom the initial and final diagnoses are known, were in fact initially diagnosed with NMC. The original diagnosis in the remaining 30 (65%) patients are listed in Supplemental Table 1 and included most commonly ‘poorly differentiated carcinoma’ (n=8), ‘poorly differentiated squamous carcinoma’ (n=6) and sinonasal undifferentiated carcinoma (n=5). At diagnosis, 26% had regional nodal metastases, 6% had distant metastases and 12% had both. The average primary tumor size was 5.2cm at diagnosis.

Treatment

Details of treatment were available for 39 of 48 patients. All patients received surgery, radiation or chemotherapy either as single agents, or in combination as part of their initial management. Because no established treatment regimen exists for NMC, treatment was selected based on physician discretion and individual factors. Of the 24 patients who underwent surgery, five patients had complete tumor resection with negative margins, nine had gross total resection, and 10 underwent debulking (subtotal resection). Twenty-nine patients received radiotherapy. Thirty-three patients received chemotherapy, and of these, 27 received a platinum agent.

The majority of patients received intensive initial multimodality therapy (n=28, 72%) consisting of various combinations of surgery, chemotherapy and radiotherapy. For the purposes of this study, treatment was classified into three main categories according to the initial sequencing strategy of therapeutic modalities: 1) Initial surgery (S) with or without adjuvant chemoradiation (CRT) or adjuvant radiation (RT) (n=22, 56%), 2) initial RT with or without concurrent chemotherapy (CRT) (n=6, 15%), or 3) initial chemotherapy alone or followed by S, RT or CRT (n=11, 28%). Of the 22 patients who underwent initial surgery, one patient had surgery alone without adjuvant therapy, 19 received post-operative adjuvant chemoradiation with concurrent chemotherapy utilizing agents such as cisplatin, and two patients received post-operative adjuvant radiation alone. Six patients underwent initial definitive radiation based therapy: three of these patients received radiation alone, and three patients received radiation concurrent with chemotherapy. Eleven patients received initial chemotherapy: seven received chemotherapy alone, two received subsequent surgery, one received subsequent radiation alone, and one went on to receive chemoradiation.

Outcomes

Outcome data were available for 40 of 48 cases (Table 1). Median progression-free survival (PFS) was 6.6 months (range 4.7–8.4). Median overall survival (OS) was 9.7 months (range 6.6–15.6). The 2-year PFS was 26% (95% CI, 13–40). The 2-year OS was 30% (95% CI, 16–46). Median follow-up was 8.3 months (range 2.1–30.0) for the entire cohort, and 19.2 months (range 2.0–79.0) for living patients. There was no statistically significant difference in PFS or OS by age, gender, tumor location, size, histology, presence of neck lymph node involvement, or *BRD4-NUT* translocation (Table 1).

The presence of distant metastases was associated with a 2-year PFS and 2-year OS of 0%. The pattern of treatment failure at first relapse or progression was evaluable for 21 cases; three patients (14%) had isolated locoregional disease, seven (33%) had isolated distant disease, and 11 (52%) developed both locoregional and distant disease.

Clinical response to initial therapy was reported in 38 patients. Best response to initial therapy was complete response in 10 patients, partial response in nine patients, and progressive disease in 19 patients. Of the 10 patients with complete response, eight patients were alive at last follow up with no evidence of disease (NED): one patient had surgery alone (NED at 23 months), one patient had surgery then adjuvant radiation (NED at 72 months), and six patients had surgery followed by post-operative adjuvant chemoradiation (NED at 14, 15, 17, 18, 35, 78 months). The remaining two patients with complete response to initial therapy had progression at 6 months after diagnosis and died from disease (OS 8 and 9 months) and both patients had completed treatment with surgery followed by post-operative adjuvant chemoradiation. By comparison, of the nine patients with partial response, only three were alive at last follow-up, and of the 19 patients with progressive disease, none were alive at last follow-up. Best response to initial therapy was associated with a statistically significantly higher PFS ($p<0.0001$) and OS ($p<0.0001$) (Table 1). Response was not significantly associated with age, gender, tumor histology, *NUT* translocation subtype, tumor location or neck lymph node involvement.

Impact of Therapy

Surgical resection, the extent of surgical resection, negative margins, and best response to initial treatment strategy were significantly associated with improved PFS and OS (Table 1) in our retrospective analysis of this small patient cohort. Patients who underwent surgery had a 2-year OS of 50%, whereas those who did not had a 2-year OS of 7%, $p=0.003$. Notably, the extent of surgical resection was significantly associated with PFS and OS (Table 1) in a graded fashion; the 2-year OS for patients who achieved negative margins was 80%, gross total resection with positive margins was 44%, debulking was 37% and no surgery was 7% (Table 1). Radiotherapy and chemotherapy, including the type of chemotherapy (anthracycline or cisplatin), was not associated with differences in PFS or OS.

The sequencing of the initial treatment strategy was also statistically significantly associated with survival. Patients who underwent initial surgery with or without subsequent radiation based therapy had a 2-year OS of 50% (11/22) (95% CI 27–79%), whereas patients who had initial chemotherapy followed by subsequent surgery or radiation had a 2-year OS of 18%

(2/11) (95% CI 3–44%), and patients who underwent initial radiation with or without chemotherapy had a 2-year OS of 0% (0/6) (p=0.04) (Figure 2).

To identify factors independently prognostic of PFS and OS, a multivariate analysis of selected predictors of PFS and OS was performed with and without adjustment for age and tumor size (Table 2). The initial treatment strategy incorporating initial surgery remained predictive of OS even after adjustment for age and tumor size (HR=0.35 (95% CI 0.13–0.90) p=0.03) (Table 2). Initial surgery was also independently prognostic for OS (HR=0.36 (95% CI 0.15–0.83) p=0.01) and PFS (HR=0.24 (95% CI 0.09–0.68) (p=0.007) after adjustment for neck lymph node involvement. Complete resection with negative margins was also independently predictive of PFS and OS after adjustment for age and tumor size (Table 2).

In an exploratory analysis, we examined the interaction between initial surgery and tumor size to determine if the effect of surgery may depend on the size of the tumor. An interaction between initial surgery and tumor size was present for PFS (p=0.06) and OS (p=0.02), indicating that the impact of initial surgery depended on tumor size. In our patient cohort, initial surgery appeared beneficial for smaller tumors but not for larger tumors. For example, for tumors under 6 cm in size, initial surgery was associated with significantly higher PFS (HR=0.21 (95% CI 0.06–0.69) p=0.01) and OS (HR=0.13 (95% CI 0.03–0.5) p=0.005) (Figure 3). For tumors 6 cm and larger, initial surgery was not associated with a significant protective effect on PFS (HR=1.17 (95% CI 0.27–5.16) p=0.83) or OS (HR=1.2 (95% CI 0.26–5.13), p=0.84) (Figure 3). While intriguing, we recognize that strong conclusions cannot be drawn due to the small sample size.

Discussion

NMC is an extremely aggressive and rare genetically defined subtype of squamous carcinoma arising from the head and neck in approximately 45% of cases. To define clinical presentation and optimal treatment approaches, we performed a retrospective analysis of all HNNMC cases in the International NMC Registry. Our study represents the largest cohort of HNNMC reported to date, as the existing literature regarding HNNMC has been primarily restricted to isolated case reports with limited treatment or follow up data.[15–21] The frequency of diagnosis of HNNMC appears to be increasing, particularly since 2012, and the proportion of adults with this diagnosis is also rising. This may be an effect of reporting bias since the recent description of NMC in the head and neck[8, 9, 22] and improved diagnostic availability of a simple highly sensitive and specific, immunohistochemical stain for the NUT gene product using a commercially available clinical antibody.[5] The increasing diagnosis, coupled with the fact that nearly two-thirds of HNNMC cases in this cohort were initially misdiagnosed, suggests that NMC remains under recognized. We found that the most common incorrect initial histologic diagnoses preceding the subsequent diagnosis of HNNMC were poorly differentiated carcinoma (n=8) and poorly differentiated squamous carcinoma (n=6). This suggests that clinicians should consider NMC in any HN carcinoma with a poorly differentiated component, or with clinically aggressive behavior. Most HNNMC patients present with locally advanced disease and the average tumor size is over 5cm at the time of diagnosis. Unlike most HN cancers, HNNMC appears to affect women

more than men for unclear reasons. Survival outcomes are poor with a median survival of 9.7 months, although this appears to be better than thoracic NMC by historical comparison.[7]

Survival appears to be impacted by treatment selection and initial therapeutic sequencing strategy. Initial surgical resection, and the extent of surgical resection (negative margins), was significantly associated with progression free and overall survival. In our cohort, surgical resection appeared to be beneficial for survival for most patients, particularly those with tumors less than 6 cm in size, and this association was independent of patient age and neck lymph node involvement. This data should be interpreted with caution given the limited size of this cohort, and lack of prospective comparison. It is possible that, because enrollment in the International NMC Registry is voluntary and does not involve systematic testing of all HN squamous cell carcinomas for *NUT* rearrangement, patients in this registry cohort may not fully represent the behavior of all HNNMCs.

Initial radiation or chemotherapy were not associated with significantly improved survival outcomes, however either may be important as adjuvant therapy. The incremental benefit and role of post-operative adjuvant therapy is unclear as all but one patient in our cohort who underwent surgical resection received post-operative adjuvant radiation or chemoradiation. Our findings are in keeping with accepted treatment paradigms used for other aggressive sinonasal tumors, such as sinonasal undifferentiated carcinomas (SNUC), in which better survival outcomes and local control rates are achieved when complete surgical resection is incorporated into multimodality treatment.[23–25] HNNMC appears to be more aggressive (2-year OS rate 30% in our series) compared to SNUC (2-year OS rate of ~47%[24], 5-year OS rate of 45%[26]), highlighting the need for prompt multidisciplinary evaluation in specialized centers (HN surgical, radiation and medical oncology) for all patients diagnosed with HNNMC.

Our findings reveal that initial treatment selection and sequencing in HNNMC is critical based on the observation that response to initial therapy was associated with improved survival. In our cohort, only 10 patients achieved complete response to initial therapy, all of whom underwent initial surgery. The only long term survivors in our series (survival of 35, 72, 78 months) were those who received initial surgery. Again, despite these compelling findings, interpretation should be made with caution given the small size and retrospective nature of the study.

No other clinical or pathologic features including *NUT* translocation type, or treatment approach, including type of chemotherapy regimen, were associated with survival outcomes. The lack of association of outcome with translocation type may be due to lack of sufficient statistical power, because the majority of patients in our series had a *BRD4-NUT* translocation (86%), leaving a minority with *BRD3-NUT* (n=2), *NSD3-NUT* (n=2) and *NUT*-variant (n=2) fusions. Notably two of the three long-term survivors had *BRD3-NUT* tumors, and a borderline statistically significant difference in PFS and OS was observed when comparing patients with *BRD3-NUT* to all other translocation types (p=0.05). In our series, many systemic therapy regimens including platinums, anthracyclines, alkylating agents in various combinations were used, however no agent was associated with improved outcomes.

The overall unsatisfactory treatment outcomes in this genomically driven tumor highlights the rationale for molecularly targeted therapies as a promising therapeutic strategy. Acetyl-histone mimetic drugs, termed BET or bromodomain inhibitors, act by competitively inhibiting binding of BRD-NUT to chromatin, preventing its ability to activate these oncogenic target genes.[10, 27] First-in-class, direct-acting BET inhibitors are active in NMC xenograft models and humans.[13, 27] At least three phase I clinical trials in the U.S. (NCT01587703, NCT01987362, NCT02431260) and Europe (NCT02259114, NCT01587703) are presently evaluating bromodomain inhibitors in patients with NMC. In addition, histone deacetylase inhibitors have exhibited pre-clinical and clinical activity in NMC and there is a clinical trial in the U.S. enrolling NMC patients who fail bromodomains inhibitors (NCT02307240).[12, 28] If deemed effective, it will be critical to incorporate these novel agents into HNNMC treatment paradigms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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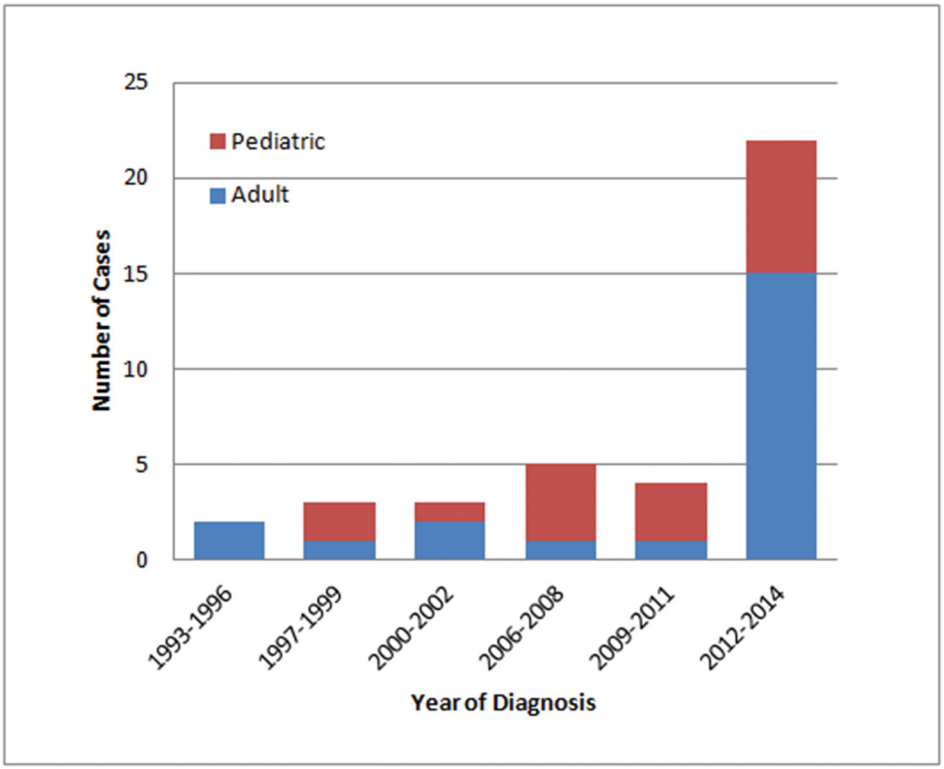


Figure 1.
Diagnosis of HNNMC in adult and pediatric patients per year.

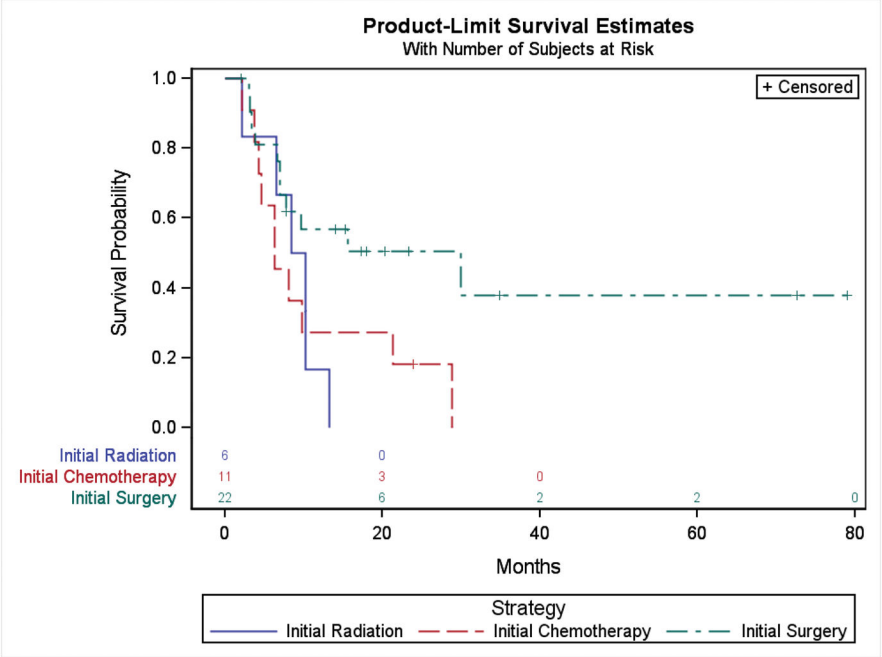
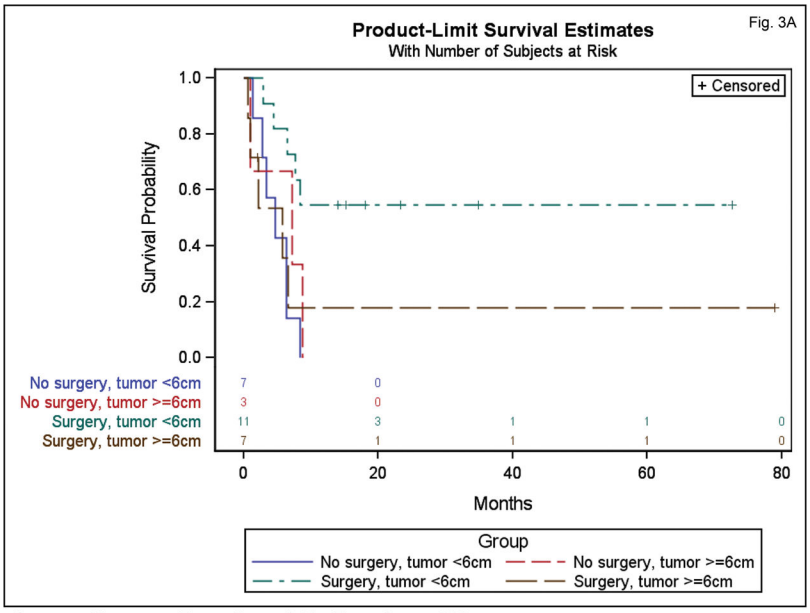
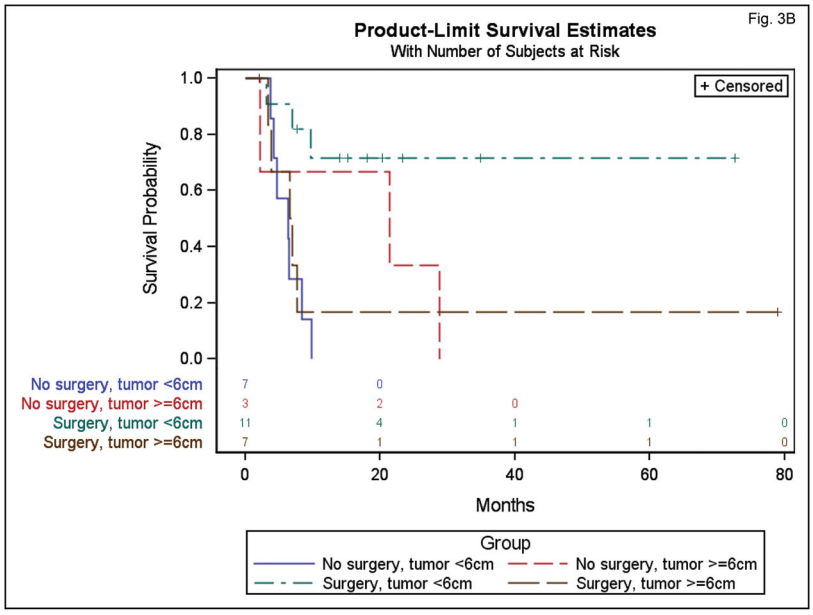


Figure 2.

Overall survival according to initial treatment strategy. The probability of OS is presented for patients with HNNMC according to the initial treatment strategy consisting of either initial radiation, initial chemotherapy or initial surgery.



Surgery vs No surgery: Tumor<6cm: p=0.01; Tumor≥6cm: p=0.83



Surgery vs No surgery: Tumor<6cm: p=0.005; Tumor≥6cm: p=0.84

Figure 3.

Influence of surgical resection on PFS (A) and OS (B) for patients with HNNMC according to primary tumor size (smaller than 6cm, or greater than or equal to 6cm).

Table 1

Estimated two-year PFS and OS by patient characteristics and treatment

		N	2y PFS % (95% CI)	P*	2y OS % (95% CI)	P*
	Overall	40	26 (13, 40)		30 (16, 46)	
Age	17 years or younger	16	31 (11, 54)	0.35	41 (17, 65)	0.11
	18 years or older	22	19 (6, 38)		21 (7, 41)	
Sex	Female	24	31 (14, 50)	0.41	38 (18, 57)	0.42
	Male	16	19 (5, 40)		23 (7, 46)	
Site	Nasal cavity & Paranasal sinus	17	26 (8, 48)	0.24	23 (7, 46)	0.08
	Other	12	42 (15, 67)		49 (15, 77)	
Size	Less than 6cm	18	33 (14, 55)	0.17	42 (20, 64)	0.24
	6cm or greater	10	12 (1, 40)		22 (3, 51)	
Histology	Carcinoma with squamous diff	14	36 (13, 59)	0.61	36 (13, 59)	0.84
	Carcinoma without squamous diff or other histology	14	8 (1, 29)		8 (0.5, 29)	
NUT translocation	BRD4-NUT	29	18 (7, 34)	0.25	20 (7, 37)	0.28
	BRD3-NUT	2	100 (100, 100)		100 (100, 100)	
	NSD3-NUT	2	0		50 (1, 91)	
	NUT-variant	1	0		0	
Distant metastases at diagnosis	Absent	30	31 (16, 48)	0.02	36 (18, 54)	0.06
	Present	5	0		0	
Neck lymph nodes at diagnosis	Absent	24	35 (17, 54)	0.26	39 (20 58)	0.54
	Present	13	15 (3, 39)		23 (4, 51)	
Initial Treatment strategy	Surgery +/− subsequent chemoradiation or radiation	22	43 (22, 63)	0.07	50 (27, 79)	0.04
	Chemotherapy +/− subsequent surgery or radiation	11	9 (1, 33)		18 (3, 44)	
	Radiation +/− concurrent chemotherapy	6	0		0	
Surgery	Yes	24	44 (23, 63)	0.005	50 (28, 69)	0.003

		N	2y PFS % (95% CI)	P*	2y OS % (95% CI)	P*
	No	15	0		7 (0, 26)	
Extent of surgical resection	None	15	0	0.01	7 (0, 26)	0.01
	Debulking (subtotal resection)	10	23 (4, 52)		37 (7, 69)	
	Gross total	9	44 (14, 72)		44 (14, 72)	
	Complete with negative margins (R0)	5	80 (20, 97)		80 (20, 97)	
Extent of margins	No negative margins	18	24 (8, 46)	0.03	30 (9, 55)	0.06
	Negative margins	5	80 (20, 97)		80 (20, 97)	
Radiation	Yes	29	29 (14, 46)	0.37	34 (16, 53)	0.12
	No	10	20 (3, 48)		20 (3, 48)	
Chemotherapy	Yes	33	25 (12, 41)	0.79	30 (14, 48)	0.70
	No	6	33 (5, 68)		33 (5, 68)	
Chemotherapy type	Anthracycline	6	33 (5, 68)	0.76	67 (20, 90)	0.56
	No Anthracycline	25	25 (10, 43)		23 (7, 43)	
	Platinum	27	23 (10, 41)	0.59	25 (10, 45)	0.49
	No Platinum	6	33 (4, 67)		50 (11, 80)	
Best response to initial treatment strategy	Complete Response	10	80 (41, 95)	<0.0001	80 (41, 95)	<0.0001
	Partial Response	9	11 (1, 39)		35 (6, 67)	
	Stable Disease	0	0		0	
	Progression	19	5 (0, 21)		5 (0, 21)	

*by log-rank test

Table 2

Hazard Ratios for selected predictors for PFS and OS, unadjusted and adjusted for age and tumor size

	PFS				OS			
	Unadjusted HR* (95% CI)	**P value**	**Adjusted HR** (95% CI)**	**P value**	**Unadjusted HR* (95% CI)**	**P value**	**Adjusted HR** (95% CI)**	**P value**
Age 17 years or younger	0.70 (0.33, 1.50)	0.36			0.51 (0.22, 1.17)	0.11		
Tumor size 6cm or greater	1.87 (0.76, 4.59)	0.17			1.75 (0.68, 4.49)	0.24		
Neck lymph nodes	1.54 (0.72, 3.32)	0.27	2.09 (0.83, 5.30)	0.12	1.28 (0.58, 2.82)	0.54	1.85 (0.68, 5.05)	0.23
Male	1.35 (0.66, 2.78)	0.41	1.6 (0.52, 4.91)	0.41	1.36 (0.65, 2.86)	0.42	1.32 (0.41, 4.32)	0.64
Nasal cavity & Paranasal sinus location	1.74 (0.68, 4.48)	0.25	2.25 (0.54, 9.28)	0.26	2.48 (0.86, 7.12)	0.09	8.90 (1.27, 62.50)	0.03
Carcinoma with squamous differentiation histology	0.80 (0.34, 1.88)	0.61	1.06 (0.32, 3.57)	0.92	0.92 (0.39, 2.14)	0.84	1.14 (0.33, 3.91)	0.83
Distant Metastases	3.16 (1.14, 8.77)	0.03	2.82 (0.89, 8.92)	0.08	2.74 (0.90, 8.30)	0.08	2.31 (0.62, 8.59)	0.21
Initial surgery +/− subsequent chemoradiation or radiation	0.42 (0.20, 0.90)	0.03	0.44 (0.18, 1.09)	0.07	0.38 (0.17, 0.84)	0.02	0.35 (0.13, 0.90)	0.03
Complete resection with negative margins (R0)	0.27 (0.11, 0.68)	0.005	0.33 (0.12, 0.89)	0.03	0.29 (0.12, 0.74)	0.01	0.32 (0.12, 0.88)	0.03
Partial resection	1.74 (0.65, 4.67)	0.27	2.43 (0.64, 9.19)	0.19	1.59 (0.55, 4.59)	0.39	2.34 (0.46, 11.95)	0.31
Anthracycline chemotherapy	0.77 (0.29, 2.05)	0.6	1.05 (0.24, 4.58)	0.95	0.66 (0.22, 1.97)	0.45	0.87 (0.16, 4.61)	0.88
Platinum chemotherapy	0.79 (0.33, 1.88)	0.6	0.79 (0.19, 3.34)	0.74	1.01 (0.41, 2.53)	0.98	1.13 (0.21, 5.94)	0.89

*Single predictor in the model

**Single predictor plus age and tumor size in the model.