Genetic mutations in recurrent and/or metastatic nasal carcinoma: A pathological comparison based on the Japanese national genomic profiling database

Hiromi Nagano[ABCDEF], Satoshi Kiyama[BCDEF], Kyutoku Takayuki[BCDEF], Hayato Matsumoto[BCDEF], Masaru Yamashita[AD]

Department of Otolaryngology Head and Neck Surgery, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan

ABSTRACT:

Introduction: Comprehensive genome profiling (CGP) has been reimbursed under Japan's national health insurance since 2019 for patients with advanced solid tumors, including head and neck cancers. Despite this, genomic insights into rare nasal carcinoma subtypes remain limited, hindering subtype-specific therapeutic strategies.

Aim: To characterize the genetic mutational profiles of recurrent and/or metastatic nasal carcinoma across histological subtypes using data from the Japanese National Genomic Profiling Database.

Materials and methods: Genomic data from 135 patients with nasal carcinoma were analyzed, including squamous cell carcinoma (SCC) (n = 48), neuroendocrine tumor (NET) (n = 52), adenocarcinoma (n = 20), and undifferentiated carcinoma (n = 15). All cases were registered in the Center for Cancer Genomics and Advanced Therapeutics (C-CAT), National Cancer Center Japan, between June 2019 and May 2025. Mutations were identified via FoundationOne CDx next-generation sequencing. Survival analysis employed the log-rank test and Cox proportional hazards model.

Results: *TP53* and *KMT2D* were frequently mutated across all subtypes. In SCC, *KMT2D* ($p = 0.03$), *EGFR* ($p = 6.4 \times 10^{-3}$), and *RICTOR* ($p = 0.03$) mutations correlated with poor prognosis. No significant differences were found among subtypes in mutation count or tumor mutational burden (TMB).

Discussion: Shared and distinct mutational patterns were observed, with prognostic relevance in SCC. These findings underscore the importance of genomic stratification in rare nasal carcinomas.

Conclusions: CGP reveals key genetic drivers in nasal carcinoma, supporting its role in precision oncology and informing future subtype-specific therapeutic approaches.

KEYWORDS: cancer genomic profiling tests, *EGFR*, genetic mutations, *KMT2D*, nasal carcinoma, *RICTOR*

STRESZCZENIE:

Wprowadzenie: Od 2019 r. kompleksowe profilowanie genomowe (CGP) u pacjentów z zaawansowanymi guzami litymi, w tym nowotworami głowy i szyi, podlega refundacji w ramach japońskiego krajowego ubezpieczenia zdrowotnego. Pomimo tego wgląd w genomikę rzadkich podtypów raka nosa pozostaje ograniczony, co utrudnia opracowanie strategii terapeutycznych swoistych dla podtypu.

Cel: Celem badania jest scharakteryzowanie profili mutacji genetycznych nawracającego i/lub przerzutowego raka nosa w różnych podtypach histologicznych w oparciu o dane z japońskiej krajowej bazy wyników profilowania genomowego.

ORIGINAL ARTICLE

Received: 25.08.2025
Accepted: 28.10.2025
Published: 23.02.2026

CITE THIS ARTICLE AS:
Nagano H., Kiyama S., Takayuki K., Matsumoto H., Yamashita M.: Genetic mutations in recurrent and/or metastatic nasal carcinoma: A pathological comparison based on the Japanese national genomic profiling database; Otolaryngol Pol 2026; 80 (2): 31–38; DOI: 10.5604/01.3001.0055.5235

AUTHORS' CONTRIBUTION:
A. Conceptualization
B. Data Curation
C. Formal Analysis
D. Funding Acquisition
E. Investigation
F. Methodology
G. Project Administration

CORRESPONDING AUTHOR:
Hiromi Nagano (ORCID: 0000-0002--9080-7259); Department of Otolaryngology Head and Neck Surgery, Kagoshima University Graduate School of Medical and Dental Sciences; 8-35-1 Sakuragaoka, Kagoshima, 890-8520, Japan;
Phone: +81 992648296; E-mail: nagano@m.kufm.kagoshima-u.ac.jp

COPYRIGHT:
Some rights reserved: Polish Society of Otorhinolaryngologists Head and Neck Surgeons. Published by Index Copernicus Sp. z o.o.

OPEN ACCESS:
The content of the journal „Polish Society of Otorhinolaryngologists Head and Neck Surgeons" is circulated on the basis of the Open Access which means free and limitless access to scientific data.

CREATIVE COMMONS CC BY:
This material is available under the Creative Commons – Attribution NonCommercial 4.0 International (CC BY-NC 4.0). The full terms of this license are available on: https://creativecommons.org/licenses/by-nc/4.0/Legalcode

COMPETING INTERESTS:
The authors declare that they have no competing interests.

Materiały i metody: Przeanalizowano dane genomowe od 135 pacjentów z rakiem nosa, w tym rakiem płaskonabłonkowym (SCC, n = 48), guzem neuroendokrynnym (NET, n = 52), gruczolakorakiem (n = 20) i rakiem niezróżnicowanym (n = 15). Wszystkie przypadki zostały zarejestrowane w *Center for Cancer Genomics and Advanced Therapeutics* (C-CAT), *National Cancer Center Japan*, w okresie od czerwca 2019 r. do maja 2025 r. Mutacje zidentyfikowano za pomocą sekwencjonowania nowej generacji FoundationOne CDx. W analizie przeżycia zastosowano test log-rank i model proporcjonalnych zagrożeń Coxa.

Wyniki: We wszystkich podtypach obserwowano częste mutacje genów *TP53* i *KMT2D*. W SCC mutacje genów *KMT2D* (p = 0,03), *EGFR* (p = 6,4×10–3) i *RICTOR* (p = 0,03) korelowały ze złym rokowaniem. Nie stwierdzono znaczących różnic pod względem liczby mutacji lub obciążenia mutacyjnego nowotworu (TMB) między poszczególnymi podtypami raka.

Dyskusja: Zaobserwowano zarówno wspólne, jak i odrębne wzorce mutacji mające znaczenie prognostyczne w SCC. Uzyskane wyniki podkreślają znaczenie stratyfikacji genomowej w przypadkach rzadkich raków nosa.

Wnioski: Analiza CGP ujawnia kluczowe czynniki genetyczne w raku nosa, co potwierdza rolę tego podejścia w precyzyjnej onkologii i dostarcza danych dla opracowania swoistych dla podtypu podejść terapeutycznych w przyszłości.

SŁOWA KLUCZOWE: *EGFR*, *KMT2D*, mutacje genetyczne, rak nosa, *RICTOR*, testy profilowania genomowego nowotworu

ABBREVIATIONS

C-CAT – Center for Cancer Genomics and Advanced Therapeutics
CGP – comprehensive genome profiling
CI – confidence interval
ECOG-PS – Eastern Cooperative Oncology Group Performance Status
HNSCC – head and neck squamous cell carcinoma
HR – hazard ratio
NET – neuroendocrine tumor
OS – overall survival
RICTOR – Rapamycin-Insensitive Companion of mTOR
SCC – squamous cell carcinoma
SEM – standard error of the mean
TKIs – tyrosine kinase inhibitors
TMB – tumor mutational burden

INTRODUCTION

Comprehensive genome profiling (CGP) was introduced in Japan's national health insurance system in June 2019 as part of advanced healthcare services [1, 2]. CGP-based gene panel testing is covered for patients with solid tumors who have no remaining standard therapeutic options, or for whom standard treatment has been completed due to local progression or metastasis. Head and neck cancers are included among the indications for CGP.

While genetic alterations have been reported in head and neck malignancies such as thyroid cancer, nasal melanoma, and nasopharyngeal carcinoma [3–5], there remains a paucity of data regarding nasal squamous cell carcinoma (SCC), neuroendocrine tumors (NET), adenocarcinomas, and undifferentiated carcinoma [6].

This study aims to characterize the mutational landscape of recurrent and/or metastatic nasal carcinomas using genomic profiling assays, with an emphasis on identifying mutations associated with prognosis and comparing the genomic features across histopathological subtypes. Data were extracted from the Japanese National Genomic Profiling Database.

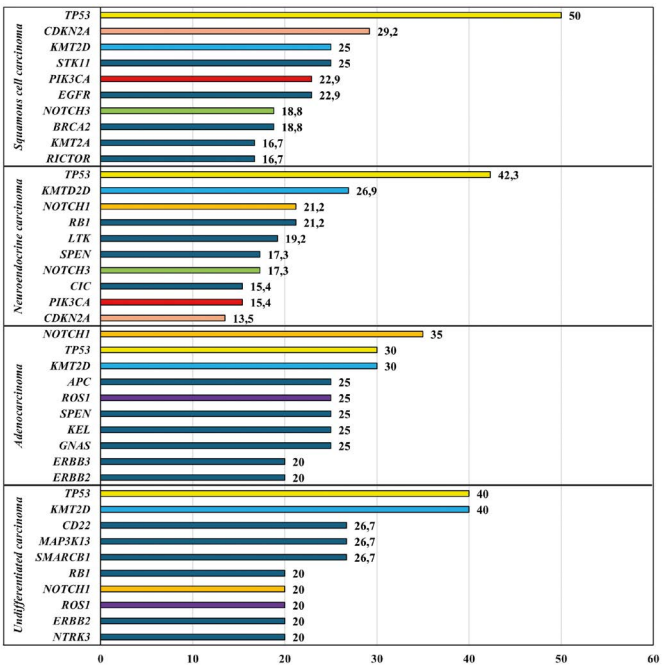

Fig. 1. Top 10 mutations in nasal carcinoma.

Data were analyzed for 135 consecutive patients with nasal carcinoma registered at the Japan National Cancer Center in C-CAT between June 2019 and May 2025.

TP53 – tumor protein p53; *CDKN2A* – cyclin-dependent kinase inhibitor 2A; *KMT2D* – lysine methyltransferase 2D; *STK11* – serine/threonine kinase 11; *PIK3CA* – phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *EGFR* – epidermal growth factor receptor; *NOTCH3* – notch receptor 3; *BRCA2* – BRCA2 DNA repair associated; *KMT2A* – lysine methyltransferase 2A; *RICTOR* – RPTOR independent companion of MTOR complex 2; *RB1* – RB transcriptional corepressor 1; *LTK* – leukocyte receptor tyrosine kinase; *SPEN* – spen family transcriptional repressor; *CIC* – capicua transcriptional repressor; *APC* – APC regulator of WNT signaling pathway; *ROS1* – ROS proto-oncogene 1 receptor tyrosine kinase; *KEL* – Kell metallo-endopeptidase; *GNAS* – GNAS complex locus; *ERBB3* – erb-b2 receptor tyrosine kinase 3; *ERBB2* – erb-b2 receptor tyrosine kinase 2; *CD22* – CD22 molecule; *MAP3K13* – mitogen-activated protein kinase kinase kinase 13; *SMARCB1* – SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily b, member 1; *NTRK3* – neurotrophic receptor tyrosine kinase 3.

AIM

The aim of this study is to characterize the genetic mutational landscape of recurrent and/or metastatic nasal carcinomas (SCC,

Tab. I. Characteristics of patients.

CHARACTERISTICS OF PATIENTS								
		Squamous cell carcinoma		Neuroendocrine carcinoma		Adenocarcinoma		Undifferentiated carcinoma	
Characteristics		n = 48		n = 52		n = 20		n = 15	
Age, median (range)		57.8 (39–80)		58.7 (38–80)		55.8 (35–77)		54.5 (30–73)	
Sex	Male	32 (66.7%)		34 (65.4%)		14 (70.0%)		9 (60.0%)	
	Female	16 (33.3%)		18 (34.6%)		6 (30.0%)		6 (40.0%)	
Observation period (days), median (range)		1130 (249–4782)		683.7 (49–4401)		1540 (119–4570)		588.6 (88–1605)	
Presence of distant metastasis and lymph node metastasis									
Lymph node metastasis		8 (16.7%)		22 (42.3%)		5 (25.0%)		6 (40.0%)	
Distant metastasis		22 (45.8%)		27 (51.9%)		12 (60.0%)		6 (40.0%)	
None		21 (43.7%)		8 (15.4%)		4 (20.0%)		3 (20.0%)	
Therapy									
		Cisplatin	48/48 (100%)	Cisplatin	51/52 (98.1%)	Cisplatin	12/20 (60.0%)	Cisplatin	9/15 (60.0%)
		Cetuximab	37/48 (77.1%)	Etoposide	50/52 (96.2%)	Fluorouracil	7/20 (35.0%)	Cetuximab	6/15 (40.0%)
		Paclitaxel	37/48 (77.1%)	Carboplatin	18/52 (34.6%)	Pembrolizumab	7/20 (35.0%)	Fluorouracil	6/15 (40.0%)
		Pembrolizumab	26/48 (54.2%)	Dexamethasone	13/52 (25.0%)	Docetaxel	6/20 (30.0%)	Pembrolizumab	6/15 (40.0%)
		Fluorouracil	24/48 (50.0%)	Irinotecan	8/52 (15.4%)	Cetuximab	4/20 (20.0%)	Paclitaxel	5/15 (33.3%)
		Carboplatin	23/48 (47.9%)	Pembrolizumab	7/52 (13.5%)	Paclitaxel	4/20 (20.0%)	Carboplatin	4/15 (26.7%)
		Nivolumab	19/48 (39.6%)	Amrubicin	6/52 (11.5%)	Carboplatin	3/20 (15.0%)	Etoposide	2/15 (13.3%)
		Docetaxel	14/48 (29.2%)	Cetuximab	6/52 (11.5%)	Tegafur/Gimeracil/ Oteracil Potassium	2/20 (10.0%)	Nivolumab	2/15 (13.3%)
		Tegafur/Gimeracil/ Oteracil Potassium	12/48 (25.0%)	Paclitaxel	6/52 (11.5%)	Dexamethasone	2/20 (10.0%)	Other	1/15 (6.7%)
		Dexamethasone	8/48 (16.7%)	Atezolizumab	3/52 (5.8%)	Other	1/20 (5.0%)		

NET, adenocarcinoma, and undifferentiated carcinoma), with a focus on pathological subtype-based comparisons using data from the Japanese National Genomic Profiling Database.

MATERIALS AND METHODS

Study design and Approval

Approval for use of the Center for Cancer Genomics and Advanced Therapeutics (C-CAT) Research-Use Portal site was obtained from the ethics committee at Kagoshima University. An application form for the use of C-CAT data was then submitted for review by the C-CAT Data Utilization Review Board, and once approved, a data access licensing contract was established [1].

Clinical Information

Data were obtained on the following categories: (1) patient information – hospital ID, sex, age, and cancer type; (2) sample information – inspection method, tumor cell content, and site of specimen collection; (3) background information – pathological diagnosis, smoking history, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), and family history; (4) cancer-related information – presence or absence of metastasis, and companion diagnostic test results; (5) treatment regimen (pre-/post-treatment) – drug name, start and end dates of administration, best overall response, and adverse events; (6) clinical outcomes – treatment outcome, last confirmed survival date, date of death, and cause of death [3–5].

Inclusion and exclusion criteria

Data were analyzed for 135 consecutive patients with nasal carcinoma registered at the Japan National Cancer Center in C-CAT between June 2019 and May 2025. Genetic alterations were determined by FoundationOne CDx, (Foundation Medicine, Cambridge, MA) next-generation sequencing. Diagnosis and treatment of each disease were performed at core hospitals for cancer genomic medicine in Japan. Cases were excluded if the CGP test was performed using other methods (NCC OncoPanel, Guardant360 CDx, GenMineTOP). The prognostic analysis included 118 cases for which overall survival (OS) was recorded. Survival time was calculated from the date of nasal carcinoma diagnosis.

Patient background

The cohort included 48 cases of SCC, with a mean age of 57.8 years (range, 39–80). Of these, 32 were male, and 16 were female. Lymph node metastases were noted in 8 cases (16.7%), while distant organ metastases were observed in 22 cases (45.8%).



Fig. 2. Landscape of somatic mutations in nasal carcinoma. (A) Details of SCC genetic mutations; (B) details of NET genetic mutations; (C) details of adenocarcinoma genetic mutations; (D) details of undifferentiated carcinoma genetic mutations are shown in the oncoplot.

M – male; F – female; A – amplification; I – interaction; L – loss; S – small scale variant; TMB – tumor mutation burden.

The cohort included 52 cases of NET, with a mean age of 58.7 years (range, 38–80). Of these, 34 were male and 18 were female. Lymph node metastases were noted in 22 cases (42.3%), while distant organ metastases were observed in 27 cases (51.9%).

The cohort included 20 cases of adenocarcinoma, with a mean age of 55.8 years (range, 35–77). Of these, 14 were male, and 6 were female. Lymph node metastases were noted in 5 cases (25.0%), while distant organ metastases were observed in 12 cases (60.0%). The cohort included 15 cases of undifferentiated carcinoma, with a mean age of 54.5 years (range, 30–73). Lymph node metastases were noted in 6 cases (40.0%), while distant organ metastases were observed in 6 cases (40.0%) (Tab. I.).

Statistical analysis

The Kaplan-Meier method was used to calculate survival probability, with survival curves compared by the log-rank test. A Cox proportional hazards model was used to estimate the hazard ratio (HR) and 95% confidence interval (CI). Statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [7]. All reported P values are two-tailed, and $P < 0.05$ was considered to be significant in all analyses.

RESULTS

Squamous cell carcinoma

The top 10 mutations in recurrent and/or metastatic SCC were *TP53* (24/48, 50.0%), *CDKN2A* (14/48, 29.2%), *KMT2D* (12/48, 25.0%), *STK11* (12/48, 25.0%), *PIK3CA* (11/48, 22.9%), *EGFR* (11/48, 22.9%), *NOTCH3* (9/48, 18.8%), *BRCA2A* (9/48, 18.8%), *KMT2A* (8/48, 16.7%), *RICTOR* (8/48, 16.7%) (Fig. 1.) with 16.1 ±7.5 (mean ±standard error of the mean [SEM]) mutations/individual. Details of SCC genetic mutations are shown in the oncoplot (Fig. 2A.). Mutations were diverse, and no cases had identical mutations.

The HRs for cases with each mutation were as follows: *TP53*, 0.44 (95% CI: 0.13–1.52, p = 0.20); *CDKN2A*, 2.17 (0.48–9.85, p = 0.32); *KMT2D*, 3.18 (0.75–13.40, p = 0.12); *STK11*, 0.20 (0.026–1.62, p = 0.13); *PIK3CA*, 2.96 (0.56–15.81, p = 0.20); *EGFR*, 1.25 (0.18–8.98, p = 0.82); *NOTCH3*, 1.23 (0.24–6.85, p = 0.78); *BRCA2A*, 0.72 (0.19–2.72, p = 0.63); *KMT2A*, 1.95 (0.29–13.14, p = 0.049); and *RICTOR*, 1.80 (0.39–8.34, p = 0.45). No statistically significant differences were observed among these mutations.

Mutations in *KMT2D* (p = 0.03), *EGFR* ($p = 6.4 \times 10^{-3}$), and *RICTOR* (p = 0.03) were significantly associated with poorer prognosis.

The median survival times for cases with *vs.* without each mutation were 686 (95% CI, 384–NA) *vs.* 1712 (732–NA) days for *KMT2D*, 686 (401–1095) *vs.* 1712 (854–NA) days for *EGFR*, 854 (405–NA) *vs.* 1712 (732–NA) days for *RICTOR* (Fig. 3A.–C.).

Neuroendocrine tumor

The top 10 mutations in recurrent and/or metastatic NET were *TP53* (22/52, 42.3%), *KMT2D* (14/52, 26.9%), *NOTCH1* (11/52, 21.2%), *RB1* (11/52, 21.2%), *LTK* (10/52, 19.2%), *SPEN* (9/52, 17.3%), *NOTCH3* (9/52, 17.3%), *CIC* (8/52, 15.4%), *PIK3CA* (8/52, 15.4%), *CDKN2A* (7/52, 13.5%) (Fig. 1.) with 13.6 ±4.8 (mean ±SEM) mutations/individual. Details of NET genetic mutations are shown in the oncoplot (Fig. 2B.). Mutations were diverse, and no cases had identical mutations.

The HRs for cases with each mutation were as follows: *TP53*, 0.47 (95% CI: 0.061–3.62, p = 0.47); *KMT2D*, 0.10 (0.0082–1.32, p = 0.081); *NOTCH1*, 1.12 (0.14–8.76, p = 0.91); *RB1*, 2.74 (0.16–46.9, p = 0.49); *LTK*, 1.35 (0.24–7.64, p = 0.74); *SPEN*, 0.47 (0.06–3.71, p = 0.48); *NOTCH3*, 2.92 (0.16–54.13, p = 0.47); *CIC*, 0.65 (0.10–4.25, p = 0.65); *PIK3CA*, 1.21 (0.20–7.24, p = 0.83); and *CDKN2A*, 3.59 (0.34–37.46, p = 0.29). No statistically significant differences were observed among these mutations.

No statistically significant differences were observed for any genetic mutations in the log-rank test.

Adenocarcinoma

The top 10 mutations in recurrent and/or metastatic adenocarcinoma were *NOTCH1* (7/20, 35.0%), *TP53* (6/20, 30.0%), *KMT2D* (6/20, 30.0%), *APC* (5/20, 25.0%), *ROS1* (5/20, 25.0%), *SPEN* (5/20, 25.0%), *KEL* (5/20, 25.0%), *GNAS* (5/20, 25.0%), *ERBB3* (4/20, 20.0%), *ERBB2* (4/20, 20.0%) (Fig. 1.) with 16.3 ±6.2 (mean ±SEM) mutations/individual. Details of adenocarcinoma genetic mutations are shown in the oncoplot (Fig. 2C.). Mutations were diverse and no cases had identical mutations.

For mutations such as *NOTCH1*, *TP53*, *KMT2D*, and others, the HRs estimated by Cox regression were either extremely high or low, with 95% CIs spanning from 0 to infinity. The corresponding p-values were all >0.999, suggesting no statistically significant impact on survival outcomes.

No statistically significant differences were observed for any genetic mutations in the log-rank test.

Undifferentiated carcinoma

The top 10 mutations in recurrent and/or metastatic undifferentiated carcinoma were *TP53* (6/15, 40.0%), *KMT2D* (6/15, 40.0%), *CD22* (4/15, 26.7%), *MAP3K13* (4/15, 26.7%), *SMARCB1* (4/15, 26.7%), *RB1* (3/15, 20.0%), *NOTCH1* (3/15, 20.0%), *ROS1* (3/15, 20.0%), *ERBB2* (3/15, 20.0%), *NTRK3* (3/15, 20.0%) (Fig. 1.) with 13.9 ±7.0 (mean ±SEM) mutations/individual. Details of undifferentiated carcinoma genetic mutations are shown in the oncoplot (Fig. 2D.). Mutations were diverse and no cases had identical mutations.

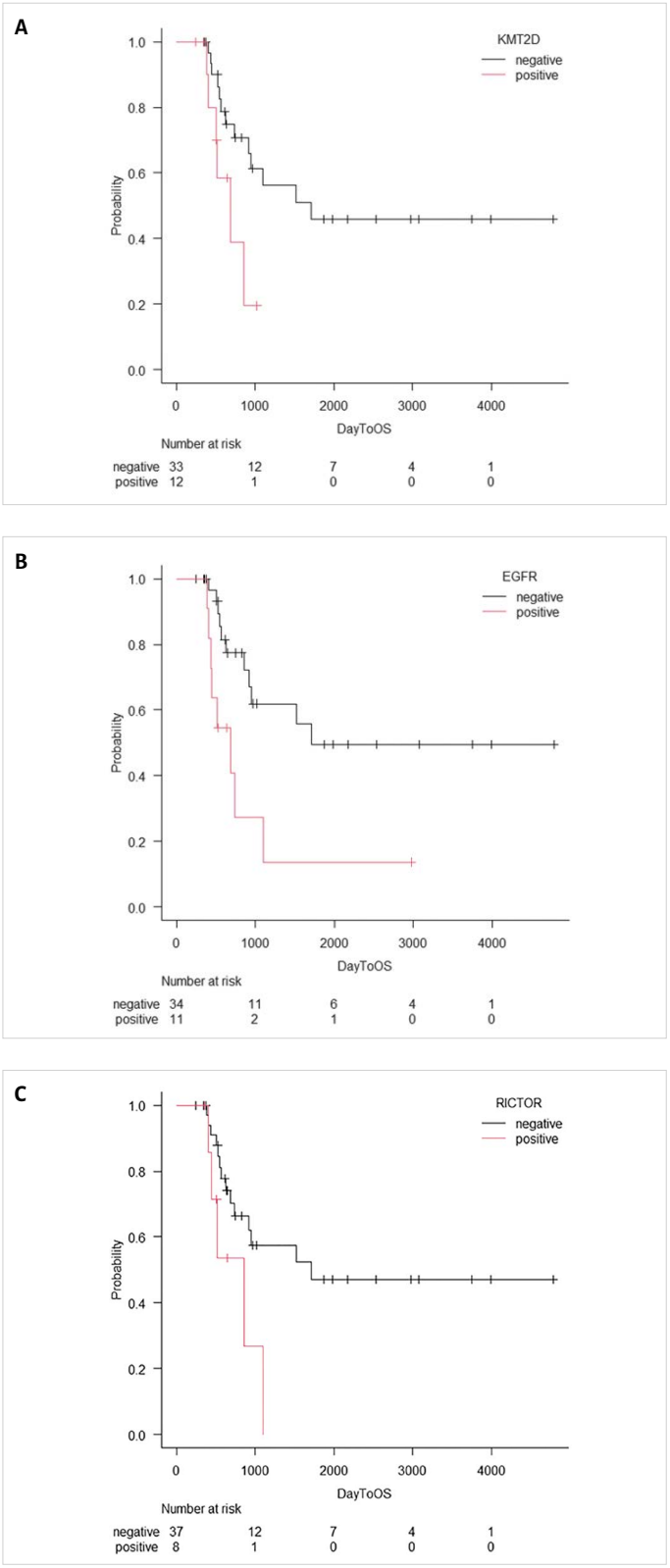

Fig. 3. The median survival times for cases with *vs.* without each mutation.

Mutations in *KMT2D* (p = 0.03), *EGFR* (p = 6.4 × 10^{-3}), and *RICTOR* (p = 0.03) were significantly associated with poorer prognosis. The median survival times for cases with *vs.* without each mutation were 686 (95% CI, 384–NA) *vs.* 1712 (732–NA) days for *KMT2D* (A), 686 (401–1095) vs. 1712 (854–NA) days for *EGFR* (B), and 854 (405–NA) *vs.* 1712 (732–NA) days for *RICTOR* (C).

For mutations such as *TP53*, *KMT2D*, *CD22*, and others, the HRs estimated by Cox regression were either extremely high or low, with

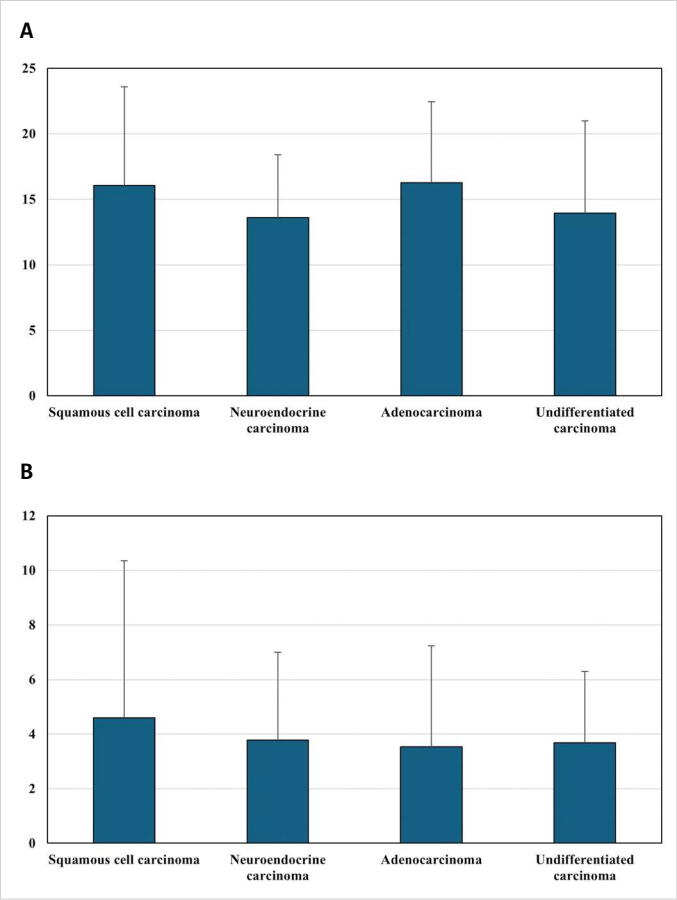

Fig. 4. (A) Number of genetic mutations per individual: mean ±SEM values were 16.1 ±7.5 in SCC, 13.6 ±4.8 in NET, 16.3 ±6.2 in adenocarcinoma, and 13.9 ±7.0 in undifferentiated carcinoma. No statistically significant differences were observed among the four groups; (B) TMB: mean ±SEM values were 4.6 ±5.7 in SCC, 3.8 ±3.2 in NET, 3.5 ±3.7 in adenocarcinoma, and 3.7 ±2.6 in undifferentiated carcinoma. Similarly, no statistically significant differences were found among the four groups.

95% CIs spanning from 0 to infinity. The corresponding p-values were all >0.999, suggesting no statistically significant impact on survival outcomes.

No statistically significant differences were observed for any genetic mutations in the log-rank test.

Number of genetic mutations/individuals

The average number of genetic mutations per individual was 16.1 ±7.5 (mean ±SEM) in SCC, 13.6 ±4.8 in NET, 16.3 ±6.1 in adenocarcinomas, and 13.9 ±7.0 in undifferentiated carcinoma. No statistically significant differences were observed among the four histological subtypes (Fig. 4A.).

Tumor mutational burden

The average tumor mutation burden (TMB) per individual was 4.6 ±5.7 (mean ±SEM) in SCC, 3.7 ±3.2 in NET, 3.5 ±3.7 in adenocarcinomas, and 3.7 ±2.6 in undifferentiated carcinoma. No statistically significant differences in TMB were observed among the four histological subtypes (Fig. 4B.).

DISCUSSION

CGP in the national health insurance system began in Japan in June 2019. CGP data and clinical information for patients are stored at C-CAT with individual informed consent [1, 2]. These data are now open for sharing with cancer genomic medicine hospitals, academic centers, and industry [2, 8]. However, the data do not indicate the pre--treatment stage or whether surgery or radiotherapy was performed.

Although CGP testing for head and neck cancer is now covered by insurance in Japan, there are few comprehensive reports on mutations in nasal carcinoma. There have also been no reports using FoundationOne CDx or Liquid CDx to examine mutations in nasal carcinoma.

The frequency of mutations may differ from other reports due to the different methods used, as well as the variations in patient backgrounds and racial differences. However, FoundationOne CDx and Liquid CDx used in this study cover a wide range of mutations, since they are pan-cancer, cfDNA-based comprehensive genomic profiling assays that detect alterations in a total panel of 324 genes [9].

The diagnosis of sinonasal tumors is challenging due to a heterogeneous spectrum of various differential diagnoses as well as poorly defined, disputed entities such as sinonasal undifferentiated carcinomas [6].

Sinonasal carcinomas harboring *IDH2* mutations exhibit a hypermethylator phenotype and represent a distinct molecular subgroup of tumors arising in this anatomical region [10]. These *IDH2-mutated* sinonasal carcinomas are aggressive neoplasms characterized by unique molecular features, with a predilection for the nasal cavity. Despite frequent recurrence and metastasis, they show better survival than *IDH2* wild-type or *SMARCB1*-deficient tumors [11]. In our study, the frequency of *IDH2* mutations was relatively low. This discrepancy is likely attributable to differences in the diagnostic methods employed, such as panel-based genetic testing versus immunohistochemical approaches.

Whole transcriptome and exome analyses of head and neck adenocarcinomas arising in the nasal and paranasal sinuses identified *MLL3* (*KMT2*) loss-of-function mutations as key oncogenic drivers, highlighting site-specific epigenetic diversity [12].

TP53 and *KMT2D* as common drivers across subtypes. In our patients, we found that *KMT2D* ($p = 0.03$), *EGFR* ($p = 6.4 \times 10^{-3}$), and *RICTOR* ($p = 0.03$) mutations were associated with a significantly worse prognosis in log-rank tests in recurrent and/or metastatic SCC.

KMT2D (lysine methyltransferase 2D) is a tumor suppressor gene encoding a histone methyltransferase involved in chromatin remodeling and transcriptional regulation. Somatic mutations or deletions of *KMT2D* are frequently observed in multiple cancers, including follicular lymphoma, diffuse large B-cell lymphoma, lung adenocarcinoma, and gastric cancer. These mutations often result in loss of function and are associated with impaired enhancer activity, deregulated gene expression, and tumor progression. In non-small cell lung cancer, *KMT2D* mutations are linked to poor prognosis and reduced survival [13]. Conversely, in pancreatic cancer, *KMT2D* loss

has been associated with better response to chemotherapy. *KMT2D* alterations may also influence the tumor immune microenvironment and sensitivity to immunotherapy. Thus, *KMT2D* serves as both a biomarker and a potential therapeutic target in cancer.

EGFR mutations and overexpression are frequently observed in head and neck squamous cell carcinoma (HNSCC), contributing to tumor progression, local invasiveness, and resistance to therapy [14]. Although EGFR-targeted treatments such as cetuximab have shown clinical benefit, their efficacy is limited by intrinsic and acquired resistance mechanisms [15]. Moreover, *EGFR* mutations may negatively impact the response to immunotherapy, particularly PD-1 inhibitors, suggesting their potential role as predictive biomarkers [16]. Comprehensive molecular profiling of *EGFR* alterations is essential for optimizing personalized treatment strategies in HNSCC.

RICTOR (Rapamycin-Insensitive Companion of mTOR) is a critical component of the mTORC2 complex, regulating AKT phosphorylation and cytoskeletal dynamics. Genetic alterations in *RICTOR*, particularly gene amplification, have been implicated in various cancers, including lung adenocarcinoma, colorectal cancer, and small cell lung cancer. These alterations are often associated with poor prognosis and resistance to tyrosine kinase inhibitors (TKIs). *RICTOR* amplification enhances PI3K-AKT--mTOR signaling, thereby promoting tumor growth and survival [17]. Preclinical studies suggest that targeting *RICTOR* may overcome drug resistance and improve therapeutic outcomes. *RICTOR* also plays a role in T lymphopoiesis, highlighting its broader biological significance. Its expression may serve as a biomarker for stratifying patients in precision oncology [18]. Ongoing research explores mTORC2-specific inhibitors as potential treatments. Understanding *RICTOR*'s role could inform novel strategies in cancer therapy and immunomodulation [19]. However, to date, no cases of *RICTOR*-altered nasal carcinoma have been reported in the literature.

TMB is defined as the number of somatic mutations per megabase of interrogated genomic sequence, and is a potential predictive biomarker for identification of patients with cancer who are most likely to respond to ICIs. Although reports on nasal cavity SCC and TMB are limited, Kwon et al. reported a TMB of 1.25 mutations per megabase [20]. In our analysis, however, the TMB was higher, at 4.6 mutations per megabase. No significant differences in TMB values and numbers of mutations were observed among the four groups in our study.

DNA methylation-based analysis offers substantial potential to improve diagnostic precision and enable more nuanced classification of tumors arising in this anatomically complex region [6, 10].

In summary, we emphasize the importance of incorporating comprehensive genetic profiling into future clinical management to enable the development of targeted therapies for patients with actionable mutations. As head and neck oncology continues to progress, individualized treatment strategies may become increasingly achievable through pre-treatment pathological evaluation and cancer gene panel testing.

Although our analysis encompassed four distinct cancer types, the pursuit of organ-agnostic therapeutic approaches – guided by specific genetic alterations rather than tumor origin – represents a critical direction for precision oncology.

Study limitations

This study is subject to several limitations. First, the protocol was not uniformly applied across all cases, and left-truncational bias may have influenced mutation detectability, as noted by Mochizuki et al. [21]. Second, the lack of detailed patient background data limits the ability to account for potential confounding variables. Third, the sample size for each histological subtype, particularly adenocarcinoma and undifferentiated carcinoma, was relatively small, potentially impacting statistical power and limiting the generalizability of subtype-specific findings. Additionally, the retrospective design and reliance on data from a single national genomic profiling database may introduce selection bias. While FoundationOne CDx enables comprehensive mutational profiling, it may not detect all genomic alterations, including structural variants or rare mutations outside targeted regions. Finally, clinical outcome data – including survival analyses – may be influenced by heterogeneity in prior treatments and follow-up duration.

Nonetheless, the findings hold meaningful value, given the limited genomic data available on nasal carcinoma. They contribute important insights into the mutational landscape and potential prognostic markers for this rare malignancy.

CONCLUSIONS

This study provides a comprehensive overview of the mutational landscape in recurrent and/or metastatic nasal carcinoma across distinct pathological subtypes. *TP53* and *KMT2D* emerged as recurrently altered genes across all subtypes, underscoring their potential role in nasal carcinogenesis. Importantly, mutations in *KMT2D, EGFR*, and *RICTOR* were significantly correlated with poor prognosis in SCC, suggesting their utility as prognostic biomarkers or therapeutic targets. These findings highlight the value of subtype-specific genomic profiling in guiding precision oncology strategies and lay the groundwork for future studies exploring targeted therapies and molecular classification in this rare tumor entity.

ACKNOWLEDGEMENTS

This work was not supported by any grant or foundation. We give our deepest thanks to the patients with cancer in Japan who contributed to the C-CAT database.

REFERENCES

1. Mukai Y., Ueno H.: Establishment and implementation of Cancer Genomic Medicine in Japan. Cancer Sci., 2021; 112(3): 970–977. doi: 10.1111/cas.14754.
2. Kohno T., Kato M., Kohsaka S. et al.: C-CAT: The National Datacenter for Cancer Genomic Medicine in Japan. Cancer Discov., 2022; 12(11): 2509–2515. doi: 10.1158/2159-8290.CD-22-0417.
3. Nagano H., Matsumoto H., Ando Y., Nakajo M., Yamashita M.: Mutations in Anaplastic Thyroid Carcinoma: An Analysis of the Japanese National Genomic Database. Laryngoscope Investig Otolaryngol., 2025; 10(2): e70110. doi: 10.1002/lio2.70110.
4. Matsumoto H., Nagano H., Kyutoku T., Yamashita M.: Genetic Analysis of Melanoma Types Using Japanese Genomic Database. Laryngoscope., 2025; 135(1): 134–139. doi: 10.1002/lary.31676.
5. Nagano H., Matsumoto H., Ando Y. et al.: Genetic mutations in recurrent and/or metastatic nasopharyngeal carcinoma – an analysis of the Japanese national genomic profiling database. Otolaryngol Pol., 2025; 79(4): 34–39. doi: 10.5604/01.3001.0055.1903.
6. Jurmeister P., Glöß S., Roller R. et al.: DNA methylation-based classification of sinonasal tumors. Nat Commun., 2022; 13(1): 7148. doi: 10.1038/s41467--022-34815-3.
7. Kanda Y.: Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant., 2013; 48(3): 452–458. doi: 10.1038/bmt.2012.244.
8. Ebi H., Bando H.: Precision oncology and the Universal Health Coverage System in Japan. JCO Precis Oncol., 2019; 3: PO.19.00291. doi: 10.1200/PO.19.00291.
9. Woodhouse R., Li M., Hughes J. et al.: Clinical and analytical validation of FoundationOne Liquid CDx, a novel 324-Gene cfDNA-based comprehensive genomic profiling assay for cancers of solid tumor origin. PLoS One., 2020; 15(9): e0237802. doi: 10.1371/journal.pone.0237802.
10. Dogan S., Vasudevaraja V., Xu B. et al.: DNA methylation-based classification of sinonasal undifferentiated carcinoma. Mod Pathol., 2019; 32(10): 1447–1459. doi: 10.1038/s41379-019-0285-x.
11. Alzumaili B., Sadow P.M.: *IDH2*-Mutated Sinonasal Tumors: A Review. Adv Anat Pathol., 2023; 30(2): 104–111. doi: 10.1097/PAP.0000000000000391.
12. Bell D., Bell A.H., Weber R.S., Hanna E.Y.: Intestinal-Type Adenocarcinoma in Head and Neck: Dissecting Oncogenic Gene Alterations Through Whole Transcriptome and Exome Analysis. Mod Pathol., 2024; 37(1): 100372. doi: 10.1016/j.modpat.2023.100372.
13. Ardeshir-Larijani F., Bhateja P., Lipka MB., et al.: KMT2D Mutation Is Associated With Poor Prognosis in Non-Small-Cell Lung Cancer. Clin Lung Cancer., 2018 Jul;19(4):e489-e501. doi: 10.1016/j.cllc.2018.03.005.
14. Nair S., Bonner J.A., Bredel M.: EGFR Mutations in Head and Neck Squamous Cell Carcinoma. Int J Mol Sci., 2022; 23(7): 3818. doi: 10.3390/ijms23073818.
15. Zhou J., He M., Zhao Q. et al.: EGFR-mediated local invasiveness and response to Cetuximab in head and neck cancer. Mol Cancer., 2025; 24(1): 94. doi: 10.1186/s12943-025-02290-1.
16. Dou S., Zhang L., Wang C. et al.: EGFR Mutation and 11q13 Amplification Are Potential Predictive Biomarkers for Immunotherapy in Head and Neck Squamous Cell Carcinoma. Front Immunol., 2022; 13: 813732. doi: 10.3389/fimmu.2022.813732.
17. Zhao D., Jiang M., Zhang X., Hou H.: The role of RICTOR amplification in targeted therapy and drug resistance. Mol Med., 2020; 26(1): 20. doi: 10.1186/s10020-020-0146-6.
18. Tang F., Wu Q., Ikenoue T. et al.: A critical role for Rictor in T lymphopoiesis. J Immunol., 2012; 189(4): 1850–1857. doi: 10.4049/jimmunol.1201057.
19. Sakre N., Wildey G., Behtaj M. et al.: RICTOR amplification identifies a subgroup in small cell lung cancer and predicts response to drugs targeting mTOR. Oncotarget., 2017; 8(4): 5992–6002. doi: 10.18632/oncotarget.13362.
20. Kwon S., Kim J.W., Kim E.S. et al.: Assessment of TP53 and CDKN2A status as predictive markers of malignant transformation of sinonasal inverted papilloma. Sci Rep., 2024; 14(1): 14286. doi: 10.1038/s41598-024-64901-z.
21. Mochizuki T., Ikegami M., Akiyama T.: Factors predictive of second-line chemotherapy in soft tissue sarcoma: An analysis of the National Genomic Profiling Database. Cancer Sci., 2024; 115(2): 575–588. doi: 10.1111/cas.16050.