ACCSCIENCE PUBLISHING

Tumor Discovery

EXPERT CONSENSUS

Expert consensus and current landscape of NUT carcinoma: A comprehensive strategy from diagnosis to treatment

Supplementary File

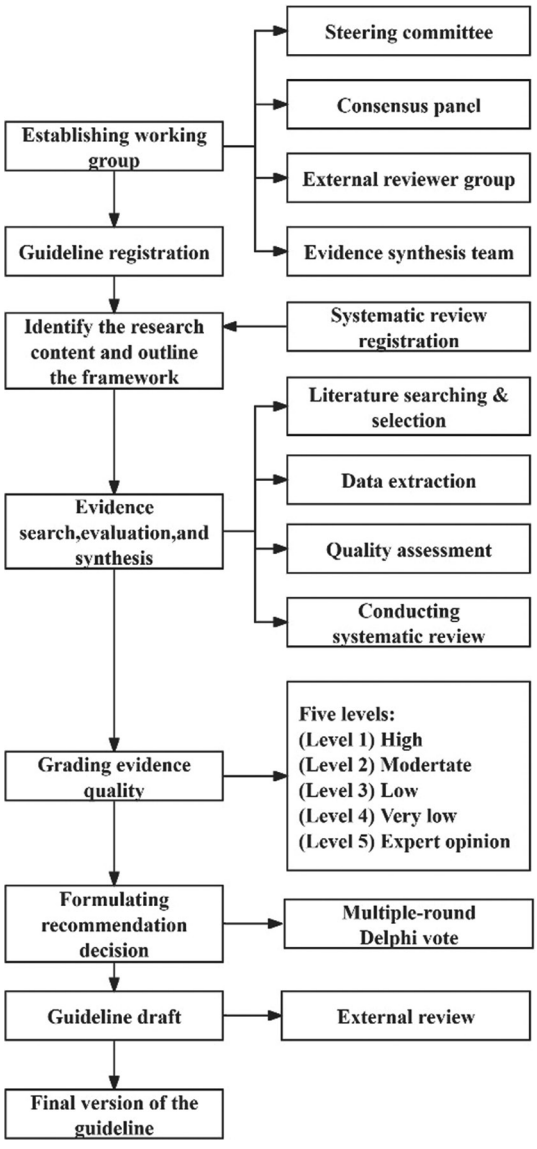

Figure S1. The full development process of the expert consensus

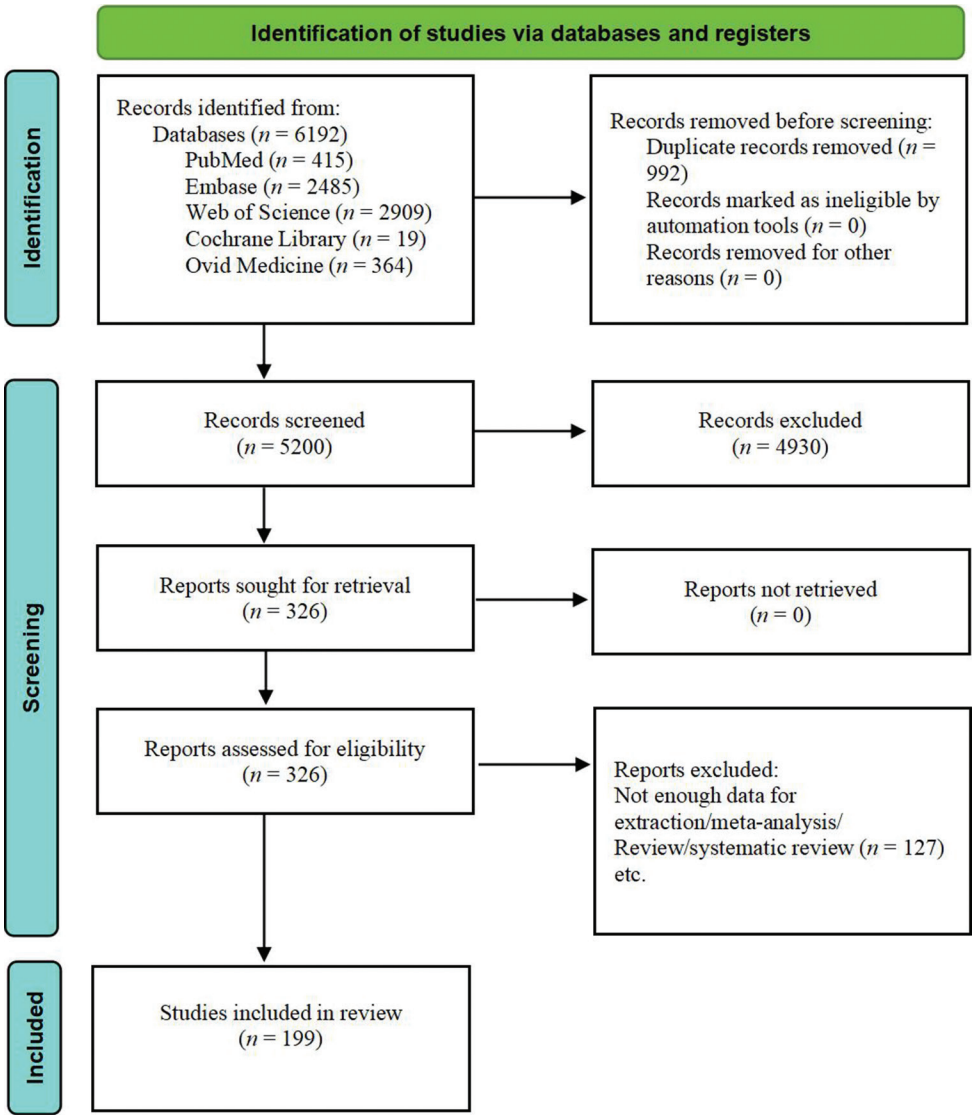

Figure S2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram
Abbreviation: CNKI: China National Knowledge Infrastructure. This diagram is adapted from Page *et al.*[1]

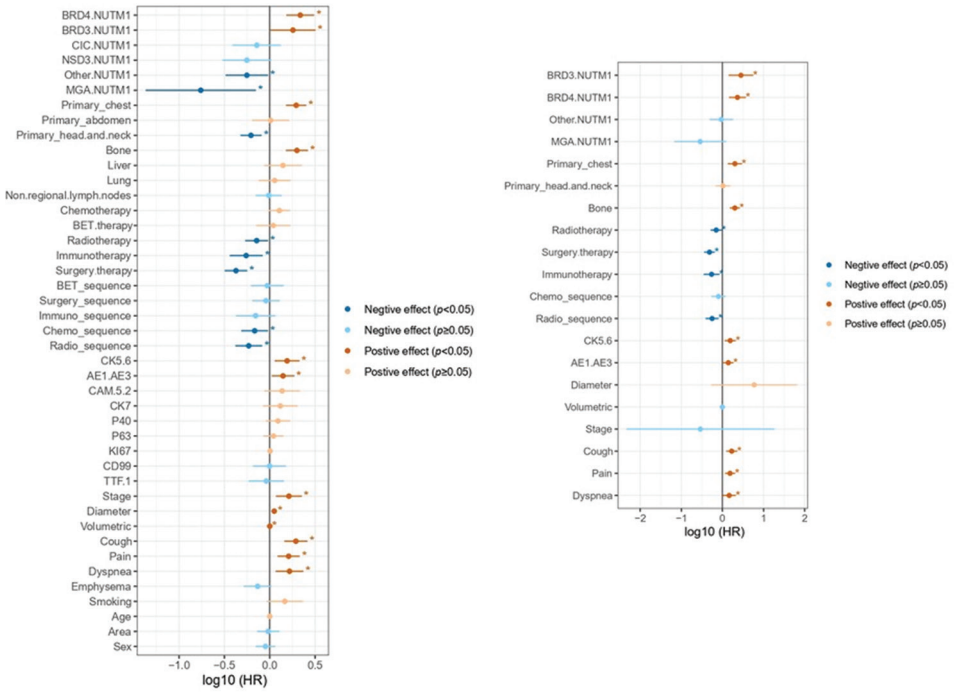

Figure S3. Univariate and multivariate analyses for demographic, clinical parameters, treatments, and fusion partners. (A) Univariate analysis. (B) Multivariate analysis
Abbreviation: HR: Hazard ratio.

Table S1. Detailed list of panel members and their corresponding groups in the development of the guidelines

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(Cont'd...)

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Vishal Shelat	Tan Tock Seng Hospital, Novena, Singapore
Alexander Shtil	Blokhin National Medical Research Center of Oncology, Ministry of Health, Moscow, Russian Federation
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Shaoquan Zheng	Breast Disease Center, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Table S2. Literature search strategy PubMed (January 20, 2024)

Search number	Query	Search details	Results
8	(((((“NUTM1 protein, human” [Supplementary Concept]) AND (“Neoplasms”[Mesh])) OR (NUT midline carcinoma[Title/Abstract])) OR (Nuclear protein of the testis midline carcinoma[Title/Abstract])) OR (Nuclear protein in testis carcinoma[Title/Abstract])) OR (Nut Carcinoma[Title/Abstract])	(“Nutm1 protein human”[Supplementary Concept] AND “Neoplasms”[MeSH Terms]) OR “nut midline carcinoma”[Title/Abstract] OR “nuclear protein of the testis midline carcinoma”[Title/Abstract] OR “nuclear protein in testis carcinoma”[Title/Abstract] OR “nut carcinoma”[Title/Abstract]	415
7	(“NUTM1 protein, human” [Supplementary Concept]) AND (“Neoplasms”[Mesh])	“Nutm1 protein human”[Supplementary Concept] AND “Neoplasms”[MeSH Terms]	177
6	NUT midline carcinoma[Title/Abstract]	“Nut midline carcinoma”[Title/Abstract]	200
5	Nuclear protein of the testis midline carcinoma[Title/Abstract]	“Nuclear protein of the testis midline carcinoma”[Title/Abstract]	7
4	Nuclear protein in testis carcinoma[Title/Abstract]	“Nuclear protein in testis carcinoma”[Title/Abstract]	1
3	Nut Carcinoma[Title/Abstract]	“Nut carcinoma”[Title/Abstract]	201
2	“Neoplasms”[Mesh]	“Neoplasms”[MeSH Terms]	3,920,921
1	“NUTM1 protein, human” [Supplementary Concept]	“Nutm1 protein human”[Supplementary Concept]	179

Web of Science (January 20, 2024)
(((TS=(Nut Carcinoma)) OR TS=(Nuclear protein in testis carcinoma)) OR TS=(Nuclear protein of the testis midline carcinoma)) OR TS=(NUT midline carcinoma)

Embase			
Number	**Query**	**Results**	**Date**
6	#1 OR #2 OR #3 OR #4 OR #5	2485	January 20, 2024
5	‘nutm1 gene’	111	January 20, 2024
4	‘nut midline carcinoma’	372	January 20, 2024
3	nuclear AND protein AND of AND the AND testis AND midline AND carcinoma	184	January 20, 2024
2	nuclear AND protein AND in AND testis AND carcinoma	641	January 20, 2024
1	(‘nut’/exp OR nut) AND (‘carcinoma’/exp OR carcinoma)	2063	January 20, 2024

Cochrane Library (January 20, 2024)
Search Name:
Date Run: 20/01/2024 12:36:56
Comment:
ID Search Hits
#1 (Nut Carcinoma):ti,ab,kw OR (Nuclear protein in testis carcinoma):ti,ab,kw OR (Nuclear protein of the testis midline carcinoma):ti,ab,kw OR (NUT midline carcinoma):ti,ab,kw OR (NUTM1):ti,ab,kw (Word variations have been searched) 19

Ovid Medline (January 20, 2024)			
# ▲	Search results	Results	Search methods
1	Nut Carcinoma.ab.	159	Advanced
2	Nuclear protein in testis carcinoma.ab.	8	Advanced
3	Nuclear protein of the testis midline carcinoma.ab.	16	Advanced
4	NUT midline carcinoma.ab.	156	Advanced
5	NUTM1.ab.	134	Advanced
6	1 or 2 or 3 or 4 or 5		

Table S3. Agency for Healthcare Research and Quality assessment of the included studies

ID	Literatures	Sample	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Evidence level
1	Thoracic NUT carcinoma: expanded pathologic spectrum with expression of TTF-1 and neuroendocrine markers	6	Y	N	Y	Y	U	U	Y	N	N	U	Y	4
2	Cytological features of NUT-carcinoma harboring an NSD3-NUTM1 fusion	1	N	N	N	N	U	U	U	N	N	U	Y	4
3	NUTM1-fusion positive malignant neoplasms of the genitourinary tract: a report of six cases highlighting involvement of unusual anatomic locations and histologic heterogeneity	6	Y	N	N	N	U	U	Y	N	N	U	Y	4
4	Primary renal NUT carcinoma identified by next-generation sequencing: a case report and literature review	1	Y	N	N	N	U	U	U	N	N	U	Y	4
5	Cytopathologic features of NUT midline carcinoma: a series of 26 specimens from 13 patients.	13	Y	N	Y	U	U	U	Y	N	N	U	U	4
6	Diagnosis of NUT midline carcinoma using a NUT-specific monoclonal antibody	1	Y	N	N	U	U	U	U	U	U	U	U	4
7	Thoracic NUT carcinoma: common pathological features despite diversity of clinical presentations	3	Y	N	N	N	U	U	U	N	N	U	Y	4
8	NUTM1-rearranged colorectal sarcoma: a clinicopathologically and genetically distinctive malignant neoplasm with a poor prognosis	5	Y	N	N	U	U	U	U	U	U	Y	U	4
9	NUTM1 gene fusions characterize a subset of undifferentiated soft tissue and visceral tumors	6	Y	N	Y	U	U	U	N	U	U	U	Y	4
10	A recurrent novel MGA-NUTM1 fusion identifies a new subtype of high-grade spindle cell sarcoma	2	N	N	N	U	U	U	N	U	U	U	Y	4
11	Clinicopathologic features of a series of primary renal CIC-rearranged sarcomas with comprehensive molecular analysis	6	Y	N	N	U	U	U	Y	U	U	U	Y	4
12	CIC-NUTM1 fusion: a case which expands the spectrum of NUT-rearranged epithelioid malignancies	1	Y	N	N	U	U	U	U	U	U	U	Y	4
13	NUTM1-rearranged neoplasia: a multi-institution experience yields novel fusion partners and expands the histologic spectrum	26	Y	N	U	U	U	U	U	U	U	Y	Y	4
14	Clinicopathologic features of CIC-NUTM1 sarcomas, a new molecular variant of the family of CIC-fused sarcomas	6	Y	N	U	U	U	U	U	U	U	U	Y	4

(Cont'd...)

Table S3. ***(Continued)***

ID	Literatures	Sample	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Evidence level
15	Sarcoma with MGA-NUTM1 fusion in the lung: an emerging entity	1	Y	N	U	U	U	U	U	U	U	U	Y	4
16	Epithelioid hyalinizing sarcoma with MGA-NUTM1 fusion	1	Y	N	U	U	U	U	U	U	U	U	Y	5
17	Prolonged disease control on nivolumab for primary pulmonary NUT carcinoma	1	Y	N	N	U	U	U	U	N	N	N	Y	4
18	NUT carcinoma of the mandible in a child: case report and systematic review	1	Y	N	N	N	N	U	U	N	N	N	Y	5
19	Sinonasal NUT carcinoma: delayed diagnosis due to the COVID-19 pandemic and a review of the literature	1	Y	N	N	N	N	U	U	N	N	N	Y	5
20	Thyroid carcinoma with NSD3::NUTM1 fusion: a case with thyrocyte differentiation and colloid production	1	Y	N	N	N	N	U	U	N	N	N	U	4
21	NSD3-NUTM1-rearranged carcinoma of the median neck/thyroid bed developing after recent thyroidectomy for sclerosing mucoepidermoid carcinoma with eosinophilia: report of an extraordinary case	1	Y	N	N	U	U	U	U	N	N	N	Y	4
22	NUT carcinoma of the thyroid: an unusual case with a complete response to treatment.	1	Y	N	Y	N	N	N	N	N	N	Y	Y	4
23	Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers	1	Y	N	U	U	U	U	U	U	U	U	Y	4
24	NUT midline carcinomas and their differentials by a single molecular profiling method: a new promising diagnostic strategy illustrated by a case report	1	Y	N	U	U	U	U	U	U	U	U	Y	4
25	Misleading germ cell phenotype in pulmonary NUT carcinoma harboring the ZNF532-NUTM1 fusion	1	Y	N	N	N	N	N	U	U	U	U	Y	4
26	Ectopic protein interactions within BRD4-chromatin complexes drive oncogenic megadomain formation in NUT midline carcinoma	1	Y	N	N	N	N	N	U	U	U	U	Y	4
27	"Z4" complex member fusions in NUT carcinoma: implications for a novel oncogenic mechanism	1	Y	N	N	N	N	N	U	U	U	U	Y	4
28	Primary malignant epithelioid and rhabdoid tumor of bone harboring ZNF532-NUTM1 fusion: the expanding NUT cancer family	1	Y	N	N	N	N	N	U	U	U	U	Y	4
29	NUT carcinoma of the submandibular gland: a case at this uncommon site with review of the literature	1	Y	N	N	U	U	U	U	U	N	N	Y	4
30	NUT gene rearrangement in a poorly-differentiated carcinoma of the submandibular gland	1	Y	N	N	N	U	U	U	U	N	N	Y	4
31	A case of nuclear protein in testis midline carcinoma arising from the submandibular gland duct in a pregnant patient	1	Y	N	N	U	U	U	U	U	N	N	Y	4
32	Case report of pulmonary NUT carcinoma and literature review	1	Y	N	N	U	U	U	U	U	N	N	U	4
33	Cancer-specific sequences in the diagnosis and treatment of NUT carcinoma	18	Y	N	Y	N	N	N	N	U	N	N	Y	4

(Cont'd...)

Table S3. ***(Continued)***

ID	Literatures	Sample	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Evidence level
34	NUT midline carcinoma of the lung: computed tomography findings in 10 patients	10	Y	N	Y	Y	U	U	U	U	U	U	Y	4
35	NUT carcinoma: a clinical, morphological and immunohistochemical mimicker – the role of RNA sequencing in the diagnostic procedure	1	Y	N	Y	N	N	N	N	U	N	N	Y	4
36	Incidence of NUT carcinoma in Western Australia from 1989 to 2014: a review of pediatric and adolescent cases from Perth Children's Hospital	5	Y	N	Y	Y	N	U	U	U	U	U	Y	4
37	Challenging diagnosis in NUT carcinoma	2	Y	N	N	U	U	U	U	U	N	N	Y	4
38	NUT carcinoma in a patient with unusually long survival and false negative FISH results	1	Y	N	N	N	U	U	U	U	N	N	Y	4
39	NUT midline carcinoma as a primary lung tumor treated with anlotinib combined with palliative radiotherapy: a case report	1	Y	N	N	N	U	U	U	U	N	N	Y	4
40	NUT carcinoma arising from the parotid gland: a case report and review of the literature	1	Y	N	N	N	U	U	U	U	N	N	Y	5
41	Vimentin-positive and alpha-fetoprotein-elevated nuclear protein of the testis midline carcinoma: a case report and review of the literature	1	Y	N	N	N	U	U	U	U	N	N	Y	5
42	NUT midline carcinoma: a neoplasm with diagnostic challenges in cytology	1	Y	N	N	N	U	U	U	U	N	N	Y	4
43	A rare case of NUT midline carcinoma	1	Y	N	N	N	U	U	U	U	N	N	Y	4
44	NUT midline carcinoma mimicking a germ cell tumor: a case report	1	Y	N	N	N	U	U	U	U	N	N	Y	4
45	Alpha-fetoprotein elevation in NUT midline carcinoma: a case report	1	Y	N	N	N	U	U	U	U	N	N	Y	4
46	Nuclear protein in testis midline carcinomas: a lethal and underrecognized entity	1	Y	N	N	N	U	U	U	U	N	N	Y	4
47	A rare Japanese case with a NUT midline carcinoma in the nasal cavity: a case report with immunohistochemical and genetic analyses	1	Y	N	N	N	U	U	U	U	N	N	Y	4
48	NUT carcinoma of the parotid gland: report of two cases, one with a rare ZNF532-NUTM1 fusion	2	Y	N	Y	Y	U	U	U	U	U	U	Y	4
49	NUT midline carcinoma of the parotid gland with mesenchymal differentiation	1	Y	N	N	N	U	U	U	U	N	N	Y	4
50	Usefulness of nuclear protein in testis (NUT) immunohistochemistry in the cytodiagnosis of NUT midline carcinoma: a brief case report	1	Y	N	N	N	U	U	U	U	N	N	Y	4
51	Cytological features of NUT midline carcinoma arising in sino-nasal tract and parotid gland: report of two new cases and review of the literature	2	Y	N	N	N	U	U	U	U	N	N	Y	5
52	First evidence of treatment efficacy in metastatic carcinoma of the parotid gland with BRD4/NUT translocation	1	Y	N	N	N	U	U	U	U	N	N	Y	4
53	NUT carcinoma in children and adults: a multicenter retrospective study	12	Y	U	N	Y	N	U	U	U	U	U	Y	4

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Table S3. ***(Continued)***

ID	Literatures	Sample	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Evidence level
54	Pediatric NUT-midline carcinoma: therapeutic success employing a sarcoma based multimodal approach	2	Y	N	N	N	U	U	U	U	N	N	Y	4
55	NUT carcinoma of the salivary glands: clinicopathologic and molecular analysis of 3 cases and a survey of NUT expression in salivary gland carcinomas	3	Y	N	N	N	U	U	U	U	N	N	Y	4
56	HDAC overexpression in a NUT midline carcinoma of the parotid gland with exceptional survival: a case report	1	Y	N	N	N	U	U	U	U	N	N	Y	4
57	NUT carcinoma arising from the parotid gland: a case report and review of the literature	1	Y	N	N	N	U	U	U	U	N	N	Y	4
58	Salivary gland NUT carcinoma with prolonged survival in children: case illustration and systematic review of literature	1	Y	N	N	N	U	U	U	U	N	N	Y	5
59	NUT carcinoma, an under-recognized malignancy: a clinicopathologic and molecular series of 6 cases showing a subset of patients with better prognosis and a rare ZNF532::NUTM1 fusion	6	Y	N	Y	Y	N	U	U	U	U	U	Y	5
60	Primary pulmonary NUT carcinoma: case illustration and updated review of literature	1	Y	N	Y	Y	N	U	U	U	U	U	Y	4
61	A case of metastatic NUT carcinoma of the nasal cavity	1	Y	N	Y	Y	N	U	U	U	U	U	Y	4
62	A NUT carcinoma lacking squamous differentiation and expressing TTF1	1	Y	N	N	N	N	N	N	N	N	N	N	5
63	BRD3-NUTM1-expressing NUT carcinoma of lung on endobronchial ultrasound-guided transbronchial needle aspiration cytology, a diagnostic pitfall	1	Y	N	N	N	U	U	U	U	U	U	Y	4
64	Cytomorphology of primary pulmonary NUT carcinoma in different cytology preparations	10	Y	U	U	Y	U	U	N	N	N	U	U	4
65	Outcome for sinonasal malignancies: a population-based survey	1	Y	U	Y	Y	U	U	U	U	N	N	Y	4
66	Case report: immunovirotherapy as a novel add-on treatment in a patient with thoracic NUT carcinoma	1	Y	N	N	N	U	U	U	U	U	U	Y	4
67	Case report: NUT carcinoma in an elderly woman with unique morphology and immunophenotype highlights a diagnostic pitfall	1	Y	N	N	N	U	U	U	U	U	U	Y	4
68	Clinical and molecular features of pulmonary NUT carcinoma characterizes diverse responses to immunotherapy, with a pathologic complete response case	6	Y	N	Y	N	U	U	U	U	U	U	Y	4
69	Clinical imaging of primary pulmonary nucleoprotein of the testis carcinoma	6	Y	N	Y	N	U	U	U	U	U	U	Y	4
70	Uncommon somatic mutations in metastatic nut midline carcinoma	1	Y	N	N	N	U	U	U	U	U	U	Y	4
71	Staging and evaluation of neoadjuvant chemotherapy response with 18F-FDG PET/CT in NUT-midline carcinoma in a child: a case report and review of the literature	1	Y	N	N	N	U	U	U	U	U	U	N	4

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Table S3. ***(Continued)***

ID	Literatures	Sample	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Evidence level
72	NUT midline carcinoma mimicking tonsillitis in an 8-year-old girl	2	Y	N	N	N	U	U	U	U	U	U	Y	4
73	NUT midline carcinoma: an imaging case series and review of literature	3	Y	N	N	N	U	U	U	U	U	U	Y	4
74	Sinonasal NUT-midline carcinoma - a multimodality approach to diagnosis, staging and post-surgical restaging	1	Y	N	U	N	U	U	N	U	U	U	Y	4
75	Nuclear protein in testis midline carcinoma presenting in an infant as a pericardial mass with staging by (18) F-fluorodeoxyglucose-positron emission tomography/ computed tomography	1	Y	N	U	N	U	U	U	U	U	U	Y	4
76	Metastatic NUT midline carcinoma treated with aggressive neoadjuvant chemotherapy, radiation, and resection: a case report and review of the literature	1	Y	N	U	N	U	N	N	N	N	U	Y	4
77	NUT midline carcinoma in a young pregnant female: a case report	1	Y	N	U	N	U	N	N	N	N	U	Y	4
78	Sinonasal NUT midline carcinoma: a new histological entity	1	Y	N	U	N	U	N	N	N	N	U	N	4
79	NUT carcinoma without upfront surgical resection: a case report	1	Y	N	U	N	U	N	N	N	N	U	Y	4
80	Sinonasal NUT carcinoma: delayed diagnosis due to the COVID-19 pandemic and a review of the literature	1	Y	N	U	N	U	U	U	U	U	U	Y	4
81	NUT carcinoma resulting in SVC syndrome	1	Y	N	U	N	U	U	N	U	U	U	Y	4
82	Multimodality imaging and treatment of paranasal sinuses nuclear protein in testis carcinoma: a case report	1	Y	N	U	N	U	U	N	U	U	U	Y	4
83	Clinical, radiographic, pathologic characterization and survival outcomes of nuclear protein of the testis carcinoma	22	Y	U	Y	Y	U	U	U	U	U	U	Y	4
84	Diagnosis of NUT carcinoma despite false-negative next-generation sequencing results: a case report and literature review	1	Y	N	N	N	U	U	U	U	U	U	Y	4
85	P63-negative pulmonary NUT carcinoma arising in the elderly: a case report	1	Y	N	N	N	U	U	U	U	U	U	Y	4
86	NUT midline carcinoma: case report and review of the literature	1	Y	N	N	N	U	N	N	N	N	N	N	4
87	NUT carcinoma of the thorax: case report and review of the literature	1	Y	N	N	N	U	U	U	U	U	U	Y	4
88	NUT midline carcinoma of the mediastinum showing two types of poorly differentiated tumor cells: a case report and a literature review	1	Y	N	N	N	U	U	U	U	U	U	Y	5
89	The first report of molecular characterized BRD4-NUT carcinoma in Brazil: a case report.	1	Y	N	N	N	U	U	U	U	U	U	Y	4
90	Alpha-fetoprotein elevation in NUT midline carcinoma: a case report	1	Y	N	N	N	U	U	U	U	U	U	N	4
91	NUT midline carcinoma: a series of five cases	5	Y	N	Y	U	U	U	N	N	N	N	N	4

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Table S3. ***(Continued)***

ID	Literatures	Sample	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Evidence level
92	Comprehensive genetic profiling of six pulmonary NUT carcinomas with a novel micropapillary histological subtype in two cases	6	Y	N	Y	U	U	U	N	U	N	N	Y	4
93	Orbital involvement by NUT midline carcinoma	1	Y	N	N	N	U	U	U	U	U	U	Y	4
94	Lung nuclear protein in testis carcinoma in an elderly Korean woman: a case report with cytohistological analysis	1	Y	N	N	N	U	U	U	U	U	U	N	4
95	NUT carcinoma of the nasal cavity that responded to a chemotherapy regimen for Ewing's sarcoma family of tumors	1	Y	N	N	N	U	U	U	U	U	U	Y	4
96	NUT carcinoma of the sublingual gland	1	Y	N	N	N	U	U	U	U	U	U	Y	4
97	NUT carcinoma presenting in the palate - a case report	1	Y	N	N	N	U	U	U	U	U	U	Y	4
98	Nuclear protein in testis carcinoma of the mediastinum: a case report	1	Y	N	N	N	U	U	U	U	U	U	Y	4
99	Clinicopathological characteristics of primary lung nuclear protein in testis carcinoma: a single-institute experience of 10 cases	10	Y	N	Y	Y	U	U	U	U	U	U	Y	4
100	NUT midline carcinoma presenting with bilateral ovarian metastases: a case report	1	Y	N	N	N	U	U	U	U	U	U	Y	4
101	A 47-year-old woman with nuclear protein in testis midline carcinoma masquerading as a sinus infection: a case report and review of the literature	1	Y	N	N	N	U	U	U	U	U	U	Y	4
102	NUT midline carcinoma masquerading as a thymic carcinoma	2	Y	N	N	N	U	U	U	U	U	U	N	4
103	NUT midline carcinoma in the mediastinum in a 10-year-old boy	1	Y	N	N	N	N	U	U	U	U	U	Y	4
104	NUT midline carcinoma: a case report with a novel translocation and review of the literature	1	Y	N	N	N	U	U	U	U	U	U	Y	4
105	Diagnosis of NUT carcinoma of lung origin by next-generation sequencing: case report and review of the literature	1	Y	N	N	N	U	U	U	U	U	U	Y	4
106	NUT midline carcinoma in a newborn with multiorgan disseminated tumor and a 2-year old with a pancreatic/hepatic primary.	2	Y	N	N	N	N	U	U	U	U	U	Y	4
107	Successful treatment of a case with NUT midline carcinoma in the larynx and review of the literature	1	Y	N	N	N	N	U	U	U	U	U	Y	4
108	Clinicopathological analysis of five cases of NUT midline carcinoma, including one with the gingiva	5	Y	N	N	U	N	U	N	N	U	N	Y	4
109	Rediagnosis of lung cancer as NUT midline carcinoma based on clues from tumor genomic profiling	1	Y	N	N	U	N	U	N	N	U	N	U	4
110	NUT midline carcinoma of the lung, a rare form of lung cancer	1	Y	N	N	N	N	N	N	N	N	N	N	4
111	NUT midline carcinoma as a primary lung tumor: a case report	1	Y	N	N	N	N	N	N	N	N	N	Y	4

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Table S3. ***(Continued)***

ID	Literatures	Sample	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Evidence level
112	Challenging diagnosis in NUT carcinoma	2	Y	N	N	N	N	N	N	N	N	N	N	4
113	Long-term survival of a patient with squamous cell carcinoma harboring NUT gene rearrangement	1	Y	N	N	N	N	N	N	N	N	N	N	4
114	NUT carcinoma: a clinical, morphological, and immunohistochemical mimicker – the role of RNA sequencing in the diagnostic procedure	1	Y	N	N	N	N	N	N	N	N	N	Y	4
115	Nut midline lung cancer: a rare case report with literature review	1	Y	N	N	N	N	U	N	N	N	U	Y	5
116	NUT midline carcinoma of the lung in a 6-year-old child	1	Y	N	N	N	N	U	N	N	N	N	Y	4
117	Lung cancer with prominent mediastinal lymphadenopathy – who thinks of NUT carcinoma?	1												
118	Cytological features of a variant NUT midline carcinoma of the lung harboring the NSD3-NUT fusion gene: a case report and literature review	1	Y	N	N	N	N	U	N	N	N	N	Y	4
119	Abrupt dyskeratotic and squamoid cells in poorly differentiated carcinoma: case study of two thoracic NUT midline carcinomas with cytohistologic correlation	2	Y	N	N	N	N	N	N	N	N	N	N	4
120	NUT carcinoma: a rare and devastating neoplasm	1	Y	N	N	N	N	N	N	N	N	N	N	4
121	The primary pulmonary NUT carcinomas and some uncommon somatic mutations identified by next-generation sequencing: a case report	1	Y	N	N	N	N	U	N	N	N	U	Y	4
122	Immunohistochemical neuroendocrine marker expression in primary pulmonary NUT carcinoma: a diagnostic pitfall	1	Y	N	N	N	N	U	N	N	N	U	Y	4
123	Cytologic findings of NUT midline carcinoma in the hilum of the lung	1	Y	N	N	N	N	N	N	N	N	N	Y	4
124	Nuclear protein in testis midline carcinoma with unusual elevation of α-fetoprotein and synaptophysin positivity: a case report and review of the literature	1	Y	N	N	U	U	U	U	N	N	N	Y	4
125	Genomic profiling of solid tumors harboring BRD4-NUT and response to immune checkpoint inhibitors	2	Y	N	N	U	U	U	U	N	N	N	U	4
126	NUT (nuclear protein in testis) carcinoma: a report of two cases with different histopathologic features	2	Y	N	N	U	U	U	U	N	N	N	Y	4
127	NUT midline carcinoma: report of 2 cases suggestive of pulmonary origin	2	Y	N	N	U	U	U	U	N	N	N	Y	4
128	Case Report and Literature Review: primary Pulmonary NUT-Midline Carcinoma	1	Y	N	N	N	N	N	N	N	N	N	Y	4
129	Clinical pathological observations of three cases of pulmonary NUT carcinoma	3	Y	N	N	N	N	N	N	N	N	N	Y	4
130	A Case Report of Primary Pulmonary NUT Carcinoma and Literature Review	1	Y	N	N	U	U	U	U	N	N	N	U	5
131	Thoracic nuclear protein in testis (NUT) carcinoma: expanded pathological spectrum with expression of thyroid transcription factor-1 and neuroendocrine markers	6	Y	U	Y	Y	N	N	N	N	N	N	U	4
132	Clinical features, treatment, and survival outcome of primary pulmonary NUT midline carcinoma	7	Y	U	Y	Y	N	N	N	N	N	N	U	4

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Table S3. ***(Continued)***

ID	Literatures	Sample	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Evidence level
133	Differentiated papillary NUT carcinoma: an unexpected, deceptively bland presentation of a sinonasal carcinoma	1	Y	N	N	N	N	N	N	N	N	N	Y	4
134	Clinical response of carcinomas harboring the BRD4–NUT oncoprotein to the targeted bromodomain inhibitor OTX015/MK-8628	4	Y	N	Y	Y	U	U	U	U	U	U	Y	4
135	Images. Thoracic NUT carcinoma: an exceptionally rare entity with a challenging approach	1	Y	N	N	N	N	N	N	N	N	N	N	4
136	Metastatic NUT Carcinoma in a child	1	Y	N	N	N	N	N	N	N	N	N	N	4
137	Histone deacetylase inhibitor for NUT midline carcinoma	1	Y	N	N	N	N	N	N	N	N	N	Y	4
138	Differentiation of NUT midline carcinoma by epigenomic reprogramming	1	Y	N	N	N	N	N	N	N	N	N	Y	4
139	Impressive response to dose-dense chemotherapy in a patient with nut midline carcinoma	1	Y	U	N	N	N	N	N	N	N	N	U	4
140	NUT carcinoma – an aggressive thoracic tumor	1	Y	N	N	N	N	U	N	N	N	U	Y	5
141	Upper respiratory tract carcinoma with chromosomal translocation 15;19: evidence for a distinct disease entity of young patients with a rapidly fatal course	2	Y	N	N	N	N	U	N	N	N	U	Y	4
142	Translocation (11;15;19): a highly specific chromosome rearrangement associated with poorly differentiated thymic carcinoma in young patients	1	Y	N	N	N	N	U	N	N	N	U	Y	4
143	Midline carcinoma of children and young adults with NUT rearrangement	7	Y	U	U	Y	N	Y	N	U	U	U	Y	4
144	A case of NUT midline carcinoma with complete response to gemcitabine following cisplatin and docetaxel	1	Y	N	N	N	U	U	N	N	N	U	Y	4
145	Nuclear protein in testis midline carcinoma misdiagnosed as adamantinoma	1	Y	N	N	N	U	U	N	N	N	U	Y	4
146	Primary pulmonary NUT midline carcinoma-clinical radiographic and pathologic characterization	8	Y	N	Y	N	U	U	N	N	N	U	Y	4
147	Primary pulmonary NUT midline carcinoma: clinical, radiographic, and pathologic characterizations	1	Y	U	Y	U	U	U	N	N	N	N	Y	4
148	Endobronchial NUT midline carcinoma with intraluminal growth	1	Y	U	N	U	U	U	N	N	N	N	Y	4
149	Nuclear protein in testis (NUT) midline carcinoma with a novel three-way translocation (4;15;19) (q13;q14;p13.1)	1	Y	N	N	N	N	U	N	N	N	N	Y	4
150	Midline carcinoma expressing NUT in malignant effusion cytology	2	Y	N	N	U	N	N	N	N	N	N	Y	4
151	NUTM1-rearranged carcinoma of the thyroid: a distinct subset of nut carcinoma characterized by frequent NSD3 - NUTM1 fusions.	14	Y	N	Y	Y	N	U	U	N	N	N	N	4
152	NUT carcinoma in the pelvic cavity with unusual pathologic features	1	Y	N	N	N	N	N	N	N	N	N	N	4
153	NUT carcinoma of the lung:A case report and literature analysis	1	Y	N	N	U	N	N	N	N	N	N	Y	4

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Table S3. ***(Continued)***

ID	Literatures	Sample	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Evidence level
154	NUT midline carcinoma of the sublingual gland: clinical presentation and review	1	Y	N	N	U	N	N	N	N	N	N	Y	4
155	Nuclear protein in testis midline carcinoma of larynx: an underdiagnosed entity	1	Y	N	N	N	N	N	N	N	N	N	N	4
156	NUT midline carcinoma of the nasal cavity	1	Y	N	N	N	N	N	N	N	N	N	Y	4
157	A tough NUT to crack: a 47-year old with diplopia from a rare malignancy	1	Y	N	N	N	N	N	N	N	N	N	Y	4
158	NUT carcinoma in a nutshell: a diagnosis to be considered more frequently	1	Y	N	N	N	N	N	N	N	N	N	Y	4
159	YAP1-NUTM1 gene fusion in porocarcinoma of the external auditory canal	2	Y	N	N	N	U	U	U	U	U	U	Y	4
160	Analysis of DNA methylation and microRNA expression in NUT (nuclear protein in testis) midline carcinoma of the sinonasal tract: a clinicopathological, immunohistochemical and molecular genetic study	3	Y	N	Y	Y	U	U	U	U	U	U	Y	4
161	Prevalence of NUT carcinoma in head and neck: analysis of 362 cases with literature review	4	Y	N	Y	Y	U	N	U	U	N	U	Y	5
162	Pediatric NUT carcinoma is a rare and challenging tumor: single-center experience of five children	5	Y	N	Y	Y	U	U	U	U	U	U	Y	4
163	NUT carcinoma of the submandibular gland: a case report	1	Y	N	N	N	N	N	N	N	N	N	Y	4
164	The whole treatment process and thinking of a patient with NUT carcinoma of the parotid gland: a case report	1	Y	N	N	N	N	N	N	N	N	N	Y	4
165	NUT carcinoma of the thorax in a 7-year-old child	1	Y	N	N	N	N	N	N	N	N	N	N	4
166	Novel t(15;19)(q15;p13) chromosome abnormality in a thymic carcinoma	1	Y	N	Y	N	N	N	N	N	N	N	Y	4
167	Renal NUT carcinoma: a case report	1	Y	N	N	N	N	N	N	N	N	N	Y	4
168	Renal BRD4-NUT fusion gene carcinoma	1	Y	N	N	N	N	N	N	N	N	N	N	4
169	Primary thyroid NUT carcinoma with high PD-L1 expression and novel massive IGKV gene fusions: a case report with treatment implications and literature review	1	Y	N	N	N	N	N	N	N	N	N	N	4
170	Sinonasal NUT carcinoma: a retrospective case series from a single institution	1	Y	N	Y	N	N	N	N	N	N	N	Y	4
171	NSD3-NUT-expressing midline carcinoma of the lung: first characterization of primary cancer tissue	1	Y	N	N	N	N	N	N	N	N	N	Y	4
172	A MXI1-NUTM1 fusion protein with MYC-like activity suggests a novel oncogenic mechanism in a subset of NUTM1-rearranged tumors	1	Y	N	N	N	N	N	N	N	N	N	Y	4
173	Case report of a pan-cytokeratin negative NUT midline carcinoma of pulmonary origin, a BRD3-NUT variant: challenges in cytomorphologic presentation	1	Y	N	N	N	N	N	N	N	N	N	Y	4
174	BRD–NUT oncoproteins: a family of closely related nuclear proteins that block epithelial differentiation and maintain the growth of carcinoma cells	2	Y	N	N	N	N	N	N	N	N	N	Y	4

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Table S3. ***(Continued)***

ID	Literatures	Sample	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Evidence level
175	Pathologic characteristics of NUT midline carcinoma arising in the mediastinum	4	Y	N	Y	N	N	N	N	N	N	N	N	4
176	Cutaneous primary nut carcinoma with BRD3-NUTM1 fusion	1	Y	N	Y	N	N	N	N	N	N	N	N	4
177	Clinicopathological and preclinical findings of NUT carcinoma: a multicenter study	13	Y	N	Y	Y	U	U	U	U	U	U	Y	4
178	Exceptional response to bromodomain and extraterminal domain inhibitor therapy with BMS-986158 in BRD4-NUTM1 NUT carcinoma harboring a BRD4 splice site mutation	1	Y	U	Y	Y	N	N	N	U	U	Y	Y	4
179	Intra-, para-, and suprasellar nuclear protein of testis carcinoma with infiltration of cavernous sinus and clivus – a case report	1	Y	N	N	N	N	N	N	N	N	N	Y	4
180	NUT carcinoma: an uncommon, yet the overlooked entity	1	Y	N	Y	N	N	N	N	N	N	N	N	4
181	NUT midline carcinoma an aggressive intrathoracic neoplasm	1	Y	N	N	N	N	N	N	N	N	N	Y	4
182	Possible primary thyroid nuclear protein in testis carcinomas with NSD3::NUTM1 translocation revealed by RNA sequencing: a report of two cases	2	Y	N	N	N	U	N	N	N	N	U	Y	4
183	A Phase 1 study of RO6870810, a novel bromodomain and extra-terminal protein inhibitor, in patients with NUT carcinoma, other solid tumors, or diffuse large B-cell lymphoma	8	Y	U	Y	Y	U	U	Y	U	Y	Y	Y	4
184	Phase 1 study of molibresib (GSK525762), a bromodomain and extra-terminal domain protein inhibitor, in NUT carcinoma and other solid tumors	19	Y	U	Y	Y	N	N	Y	N	Y	Y	Y	3
185	Epithelioid hyalinizing sarcoma with MGA-NUTM1 fusion	1	Y	N	Y	N	N	N	N	N	N	N	Y	4
186	Primary spindle cell sarcoma of the lung with MGA::NUTM1 fusion: an extremely rare case of a potentially emerging entity and review of the literature	1	Y	N	Y	N	N	N	N	N	N	N	Y	4
187	Detecting disease-defining gene fusions in unclassified round cell sarcomas using anchored multiplex PCR/targeted RNA next-generation sequencing-molecular and clinicopathological characterization of 16 cases	1	Y	N	Y	U	N	N	N	N	N	N	Y	4
188	Sarcoma with MGA::NUTM1 fusion: a report of three cases and literature review	3	Y	N	Y	U	N	N	N	N	N	N	Y	4
189	Clinicopathological and preclinical findings of NUT carcinoma: a multicenter study.	1	Y	N	Y	U	N	N	N	N	N	N	Y	4
190	Molecular analysis of NUT-positive poromas and porocarcinomas identifies novel break points of YAP1::NUTM1 fusions	13	Y	N	N	N	U	N	N	N	N	U	U	4
191	Poroid adnexal skin tumors with YAP1 fusions exhibit similar histopathologic features: a series of six YAP1-rearranged adnexal skin tumors	8	Y	N	N	N	U	N	N	N	N	U	U	4
192	Experience in the diagnosis of mediastinal NUT carcinoma by Ebus-TBNA combined with pleural effusion cell block	1	Y	N	N	N	U	N	N	N	N	U	U	4

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Table S3. ***(Continued)***

ID	Literatures	Sample	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Evidence level
193	Clinical pathological analysis of 10 cases of NUT carcinoma	10	Y	N	N	N	U	N	N	N	N	U	Y	4
194	Cytological diagnosis of lung NUT carcinoma in pleural fluid: a case report	1	Y	N	N	N	U	N	N	N	N	U	Y	4
195	A case of nasopharyngeal NUT midline carcinoma	1	Y	N	N	N	U	N	N	N	N	U	Y	4
196	A case report of salivary NUT midline carcinoma	1	Y	N	N	N	U	N	N	N	N	U	U	4
197	Two cases of pulmonary NUT midline carcinoma and literature review	2	Y	N	Y	N	N	N	N	N	N	U	U	4
198	CT manifestations of pulmonary NUT carcinoma	7	Y	N	N	N	U	N	N	N	N	U	N	4
199	Clinical pathological analysis of 2 cases of NUT carcinoma and literature review	2	Y	N	N	N	U	N	N	N	N	U	N	4

Notes: Y = Yes, N = No, and U = Uncertain.
Q1: Is the source of the data clear (survey, literature review)?
Q2: Are the inclusion and exclusion criteria or references to previous publications for the exposed and non-exposed groups (cases and controls) listed?
Q3: Are the time stages of patient identification given?
Q4: If not from a population source, are the study subjects consecutive?
Q5: Does evaluator subjectivity obscure other aspects of the study subjects?
Q6: Are any assessments made to ensure quality (e.g., detection/re-detection of primary outcome measures) described?
Q7: Are reasons for excluding any patients from analysis explained?
Q8: Are measures taken to assess and/or control for confounding factors described?
Q9: If possible, is how missing data were handled in the analysis explained?
Q10: Is the response rate of patients and the completeness of data collection summarized?
Q11: If there is follow-up, is the percentage of expected patients with incomplete data or the follow-up results clarified?
Evidence level:
Level 1: Systematic review of multiple randomized controlled trials or N-of-1 trials.
Level 2: Randomized controlled trials or large observational studies with statistically significant differences in effect size between treatment and control groups.
Level 3: Non-randomized controlled trials/cohort studies, as well as systematic reviews without randomized controlled trials or N-of-1 trials.
Level 4: Case series, case–control studies, or historical control studies, including single-arm studies.
Level 5: Narrative literature reviews and expert commentaries.
Abbreviations: BRD: Bromodomain-containing protein; CIC: Capicua; COVID-19: Coronavirus disease 19; CT: Computed tomography; DNA: Deoxyribonucleic acid; Ebus-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration; FDG: Fluorodeoxyglucose; HDAC: Histone deacetylase; IGKV: Immunoglobulin kappa variable cluster; MGA: MAX gene-associated protein; MXI1: MAX interactor 1; NSD3: Nuclear receptor binding SET domain protein 3; NUT: Nuclear protein of the testis; NUTM1: Nuclear protein of the testis midline carcinoma family member 1; PCR: Polymerase chain reaction; PD-L1: Programmed cell death ligand 1; PET: Positron emission tomography; RNA: Ribonucleic acid; TTF-1: Thyroid transcription factor-1; YAP1: Yes1 associated transcriptional regulator; ZNF532: Zinc finger protein 532.

Table S4. Oxford Centre for Evidence-Based Medicine (OCEBM) levels of evidence and their definitions

Evidence level	Definition
Level 1	Systematic review of multiple randomized trials or N-of-1 trials
Level 2	Randomized trials or observational studies with large effect size (statistically significant differences between treatment and control groups)
Level 3	Non-randomized controlled cohort/follow-up studies, and systematic review without randomized trials or N-of-1 trials
Level 4	Case series, case–control studies, or historical control studies, including single-arm studies
Level 5	Descriptive literature reviews and expert commentaries

Table S5. Descriptive statistics of the 526 cases analyzed in this study

Demographic/ clinical feature/ treatment	Literature dataset† (*N*=526)		
	Total*	Thoracic	Head and neck
Sex			
Male	54.33%, 276/508	60.25%,144/239	49.39%, 81/164
Female	45.67%, 232/508	39.75%, 95/239	50.61%, 83/164
Unknown	3.42%, 18/526	1.52%, 8/526	1.33%, 7/526
Area			
America	51.52%, 271/526	19.77%,104/526	16.54%, 87/526
Asian	34.6%, 182/526	20.91%,110/526	10.27%, 54/526
European	11.98%, 63/526	5.32%, 28/526	5.51%, 29/526
Oceania	1.71%, 9/526	0.95%, 5/526	0.19%, 1/526
Age			
Average (year)	37.94	40.02	33.82
Median (year)	36	37	34
Smoking history			
Known	23.57%, 124/526	43.10%, 103/239	6.10%, 10/164
Smoking	39.52%, 49/124	15.90%, 38/239	3.66%, 6/164
Stage			
Known	20.91%, 110/526	27.62%,66/239	23.17%,38/164
I	3.64%, 4/110	4.55%, 3/66	2.63%, 1/38
II	11.82%, 13/110	6.06%, 4/66	23.68%, 9/38
III	33.64%, 37/110	36.36%, 24/66	26.32%, 10/38
IV	50.91%, 56/110	53.03%, 35/66	47.37%, 18/38
Unknown	79.09%, 416/526	34.41%, 181/526	25.29%, 133/526
Symptoms at first diagnosis			
Known	58.56%, 308/526	51.88%, 124/239	50.61%, 83/164
Pain	31.49%, 97/308	40.32%, 50/124	37.35%, 31/83
Cough	27.60%, 85/308	56.45%, 70/124	6.02%, 5/83
Compression symptoms	20.13%, 62/308	4.84%, 6/124	53.01%, 44/83
Dyspnea	15.91%, 49/308	30.65%, 38/124	6.02%, 5/83
Hemorrhage	7.79%, 24/308	9.68%, 12/124	13.25%, 11/83
Fever	5.19%, 16/308	9.68%, 12/124	1.20%, 1/83
Nasal congestion	4.22%, 13/308	0.00%, 0/124	14.46%, 12/83
Weight loss	4.22%, 13/308	7.26%, 9/124	2.41%, 2/83
Hemoptysis	3.25%, 10/308	6.45%, 8/124	1.20%, 1/83
Night sweats	2.27%, 7/308	3.23%, 4/124	0.00%, 0/83
Fatigue	1.30%, 4/308	2.42%, 3/124	0.00%, 0/83
Nausea and vomiting	1.30%, 4/308	0.81%, 1/124	1.20%, 1/83
Loss of vision	0.97%, 3/308	0.00%, 0/124	3.61%, 3/83
Numbness	0.97%, 3/308	0.00%, 0/124	2.41%, 2/83
Superior vena cava syndrome	0.97%, 3/308	1.61%, 2/124	0.00%, 0/83
Dizzy	0.65%, 2/308	0.81%, 1/124	1.20%, 1/83
Double vision	0.65%, 2/308	0.00%, 0/124	2.41%, 2/83
Hoarseness	0.65%, 2/308	0.81%, 1/124	1.20%, 1/83
Shed tears	0.65%, 2/308	0.00%, 0/124	2.41%, 2/83
Stomach pain	0.65%, 2/308	0.81%, 1/124	0.00%, 0/83
Loss of smell	0.32%, 1/308	0.81%, 1/124	0.00%, 0/83
Pneumonia	0.32%, 1/308	0.81%, 1/124	0.00%, 0/83
Protrusion of the eyeballs	0.32%, 1/308	0.00%, 0/124	1.2%, 1/83
Dysphagia	0.00%, 0/308	0.00%, 0/124	0.00%, 0/83
Diameter			
Average (cm)	6.04	6.86	4.08
Median (cm)	5.2	6.35	4
Fusion partner			
Known	56.27%, 296/526	23.57%, 124/526	19.96%, 105/526
BRD4::NUTM1	56.42%, 167/296	61.29%, 76/124	56.19%, 59/105
BRD3::NUTM1	6.76%, 20/296	11.29%, 14/124	14.29%, 15/105
NSD3::NUTM1	9.80%, 29/296	10.48%, 13/124	14.29%, 15/105
Other::NUTM1	27.03%, 80/296	16.94%, 21/124	15.24%, 16/105
Metastasis			
Total	52.28%, 275/526	60.25%, 144/239	40.85%, 67/164
Bone	37.09%, 102/275	48.61%, 70/144	35.82%, 24/67
Liver	13.45%, 37/275	18.06%, 26/144	4.48%, 3/67
Lung	12.73%, 35/275	9.72%, 14/144	5.97%, 4/67
Pleural	5.82%, 16/275	8.33%, 12/144	1.49%, 1/67
Brain	5.45%, 15/275	5.56%, 8/144	7.46%, 5/67
Mediastinum	4.73%, 13/275	7.64%, 11/144	0.00%, 0/67
Sinusoidal area	4.73%, 13/275	0.00%, 0/144	17.91%, 12/67
Adrenal gland	4.36%, 12/275	6.94%, 10/144	1.49%, 1/67
Peritoneum	3.64%, 10/275	3.47%, 5/144	2.99%, 2/67
Under the skin	3.27%, 9/275	3.47%, 5/144	2.99%, 2/67
Muscle and soft tissue	3.27%, 9/275	2.08%, 3/144	2.99%, 2/67
Spine	2.55%, 7/275	2.78%, 4/144	1.49%, 1/67
Kidney	2.18%, 6/275	2.78%, 4/144	0.00%, 0/67
Nasal area	1.82%, 5/275	0.00%, 0/144	5.97%, 4/67
Pancreas	1.45%, 4/275	0.69%, 1/144	1.49%, 1/67
Widespread transfer	1.45%, 4/275	1.39%, 2/144	1.49%, 1/67
Glandular	1.09%, 3/275	0.00%, 0/144	4.48%, 3/67
Pelvic	1.09%, 3/275	0.69%, 1/144	1.49%, 1/67
Eye	1.09%, 3/275	0.00%, 0/144	4.48%, 3/67
Oral cavity	0.73%, 2/275	0.00%, 0/144	2.99%, 2/67
Throat	0.73%, 2/275	0.00%, 0/144	2.99%, 2/67
Ovarian attachments	0.73%, 2/275	1.39%, 2/144	0.00%, 0/67
Nerves	0.73%, 2/275	0.69%, 1/144	1.49%, 1/67
Mammary gland	0.73%, 2/275	1.39%, 2/144	0.00%, 0/67
Heart and pericardium	0.73%, 2/275	1.39%, 2/144	0.00%, 0/67
Spleen	0.36%, 1/275	0.69%, 1/144	0.00%, 0/67
Cervix	0.36%, 1/275	0.69%, 1/144	0.00%, 0/67
Esophagus	0.36%, 1/275	0.69%, 1/144	0.00%, 0/67

(Cont'd...)

Table S5. ***(Continued)***

(Cont'd...)

Table S5. ***(Continued)***

Demographic/ clinical feature/ treatment	Literature dataset† (*N*=526)		
	Total*	Thoracic	Head and neck
Immunohistochemistry			
Known	66.35%, 349/526	67.78%,162/239	65.24%,107/164
p63	43.84%, 153/349	45.68%,74/162	56.07%,60/107
AE1/AE3	26.65%, 93/349	22.22%, 36/162	31.78%, 34/107
p40	24.36%, 85/349	27.16%, 44/162	33.64%, 36/107
CK5/6	22.92%, 80/349	29.63%, 48/162	23.36%, 25/107
CD99	12.61%, 44/349	8.64%, 14/162	14.02%, 15/107
Keratins	11.17%, 39/349	9.88%, 16/162	14.95%, 16/107
CK7	10.60%, 37/349	12.96%, 21/162	11.21%, 12/107
CAM 5.2	8.88%, 31/349	6.17%, 10/162	12.15%, 13/107
TTF-1	8.88%, 31/349	8.64%, 14/162	13.08%, 14/107
p16	7.74%, 27/349	1.85%, 3/162	20.56%, 22/107
CD34	6.88%, 24/349	5.56%, 9/162	9.35%, 10/107
EMA	6.88%, 24/349	5.56%, 9/162	10.28%, 11/107
Pan-CK	6.30%, 22/349	3.09%, 5/162	9.35%, 10/107
CD56	6.02%, 21/349	9.88%, 16/162	2.80%, 3/107
p53	5.44%, 19/349	6.17%, 10/162	5.61%, 6/107
Vimentin	5.16%, 18/349	6.17%, 10/162	6.54%, 7/107
Syn	4.58%, 16/349	4.94%, 8/162	2.80%, 3/107
Syptophysin	4.58%, 16/349	4.94%, 8/162	5.61%, 6/107
INSM1	3.72%, 13/349	8.02%, 13/162	0.00%, 0/107
PAX8	3.15%, 11/349	1.23%, 2/162	7.48%, 8/107
PD-1/PD-L1	2.29%,8/349	3.70%,6/162	0.93%,1/107
AFP	2.01%,7/349	3.70%,6/162	0.00%,0/107
CK20	2.01%,7/349	3.09%,5/162	0.00%,0/107
CD138	1.72%,6/349	2.47%,4/162	1.87%,2/107
S-100	1.72%,6/349	1.23%,2/162	1.87%,2/107
BCL2	1.43%,5/349	1.85%,3/162	0.93%,1/107
CD45	1.43%,5/349	1.85%,3/162	0.93%,1/107
CgA	1.43%,5/349	3.09%,5/162	0.00%,0/107
Chromogranin	1.15%,4/349	1.23%,2/162	0.93%,1/107
SMARCB1	1.15%,4/349	0.00%,0/162	3.74%,4/107
SOX10	1.15%,4/349	0.00%,0/162	2.80%,3/107
CD43	0.57%,2/349	1.23%,2/162	0.00%,0/107
ALK	0.29%,1/349	0.62%,1/162	0.00%,0/107
NSE	0.29%,1/349	0.62%,1/162	0.00%,0/107
ROS1	0.29%,1/349	0.00%,0/162	0.00%,0/107
SMARCA4	0.29%,1/349	0.00%,0/162	0.93%,1/107
Ki-67 (%)	55.16	54.43	57.38
Treatment			
Known	64.45%, 339/526	65.27%, 156/239	76.83%, 126/164
Chemotherapy	17.11%, 58/339	26.28%, 41/156	5.56%, 7/126
Include BET	13.27%, 45/339	14.10%, 22/156	11.11%, 14/126
Chemotherapy radiotherapy	10.62%, 36/339	13.46%, 21/156	9.52%, 12/126
Chemotherapy radiotherapy surgery	9.14%, 31/339	0.00%, 0/156	19.05%, 24/126
Include surgery immunotherapy	8.85%, 30/339	5.77%, 9/156	15.87%, 20/126
Chemotherapy surgery	8.26%, 28/339	9.62%, 15/156	5.56%, 7/126
Radiotherapy surgery	7.96%, 27/339	1.28%, 2/156	18.25%, 23/126
Include HDAC	5.31%, 18/339	6.41%, 10/156	1.59%, 2/126
Include immunotherapy	4.42%, 15/339	7.69%, 12/156	0.00%, 0/126
Surgery	4.13%, 14/339	3.21%, 5/156	3.17%, 4/126
Include targeted therapies	3.24%, 11/339	4.49%, 7/156	2.38%, 3/126
Radiotherapy	2.65%, 9/339	2.56%, 4/156	3.97%, 5/126
Include surgery BET	2.36%, 8/339	2.56%, 4/156	3.17%, 4/126
No treatment received	1.77%, 6/339	0.64%, 1/156	0.79%, 1/126
Include immunotherapy BET	0.59%, 2/339	1.28%, 2/156	0.00%, 0/126
Other therapies	0.29%, 1/339	0.64%, 1/156	0.00%, 0/126
Include surgery immunotherapy BET	0.00%, 0/339	0.00%, 0/156	0.00%, 0/126
Treatment sequence 1			
Known	64.45%, 339/526	65.27%, 156/239	76.83%, 126/164
Chemotherapy	40.12%, 136/339	51.92%, 81/156	29.37%, 37/126
Radiotherapy	7.37%, 25/339	7.05%, 11/156	10.32%, 13/126
Targeted therapy	2.06%, 7/339	3.21%, 5/156	0.79%, 1/126
Immunotherapy	2.36%, 8/339	4.49%, 7/156	0.00%, 0/126
Surgery	25.37%, 86/339	12.18%, 19/156	41.27%, 52/126
BET	5.90%, 20/339	6.41%, 10/156	5.56%, 7/126
HDAC	1.47%, 5/339	1.92%, 3/156	0.79%, 1/126
Other therapy	0.00%, 0/339	0.00%, 0/156	0.00%, 0/126
Treatment sequence 2			
Chemotherapy	15.04%, 51/339	7.69%, 12/156	23.02%, 29/126
Radiotherapy	20.94%, 71/339	14.10%, 22/156	31.75%, 40/126
Targeted therapy	1.77%, 6/339	1.28%, 2/156	3.17%, 4/126
Immunotherapy	3.24%, 11/339	5.13%, 8/156	2.38%, 3/126
Surgery	5.90%, 20/339	3.21%, 5/156	9.52%, 12/126
BET	5.31%, 18/339	8.97%, 14/156	3.17%, 4/126
HDAC	1.18%, 4/339	1.28%, 2/156	0.79%, 1/126
Other therapy	0.29%, 1/339	0.00%, 0/156	0.00%, 0/126
Treatment sequence 3			
Chemotherapy	1.47%, 5/339	0.00%, 0/156	3.97%, 5/126
Radiotherapy	7.96%, 27/339	4.49%, 7/156	10.32%, 13/126
Targeted therapy	0.88%, 3/339	0.64%, 1/156	1.59%, 2/126
Immunotherapy	2.95%, 10/339	3.21%, 5/156	2.38%, 3/126
Surgery	1.77%, 6/339	0.64%, 1/156	3.17%, 4/126

(Cont'd...)

Table S5. ***(Continued)***

Demographic/ clinical feature/ treatment	Literature dataset[†](*N*=526)		
	Total*	Thoracic	Head and neck
BET	3.54%, 12/339	3.21%, 5/156	3.97%, 5/126
HDAC	1.77%, 6/339	1.92%, 3/156	0.00%, 0/126
Other therapy	0.00%, 0/339	0.00%, 0/156	0.00%, 0/126
Treatment sequence 4			
Chemotherapy	0.29%, 1/339	0.00%, 0/156	0.79%, 1/126
Radiotherapy	0.59%, 2/339	0.64%, 1/156	0.79%, 1/126
Targeted therapy	0.59%, 2/339	0.64%, 1/156	0.00%, 0/126
Immunotherapy	1.47%, 5/339	1.28%, 2/156	1.59%, 2/126
Surgery	0.88%, 3/339	1.28%, 2/156	0.00%, 0/126
BET	0.29%, 1/339	0.00%, 0/156	0.79%, 1/126
HDAC	0.00%, 0/339	0.00%, 0/156	0.00%, 0/126
Other therapy	0.59%, 2/339	0.00%, 0/156	0.79%, 1/126

Notes: †: All data are sourced from the literature and are not continuous. Table S5 presents the positive proportion and analysis of certain indicators (such as fusion partners, immunohistochemistry, etc.) within the 526 samples compiled from the literature. "Known" refers to the proportion of samples from which data are available, out of the 526 samples collected from the entire body of literature. It is important to note that due to the rarity of NUT carcinoma and the lack of large-scale cohort data, the vast majority of data in this study comes from case reports, making the data non-continuous with significant heterogeneity. These data results are for clinical reference only, and the results of analyses and statistics based on these data should be interpreted and treated with caution.

*: The tumor origins in the total dataset of collected literature include thoracic, head and neck, abdominal, bone, limbs, and other regions. However, due to limited data for tumors originating from the abdominal region, bones, limbs, and other sites, and the unclear primary tumor locations in these cases, we do not provide separate descriptions or analyses for these regions.

Abbreviations: AE1/AE3: Cytokeratin AE1/AE3; AFP: Alpha-fetoprotein; ALK: Anaplastic lymphoma kinase; BCL2: B-cell lymphoma 2; BET: Bromodomain and extra-terminal domain inhibitors; BRD: Bromodomain-containing protein; CAM 5.2: Anti-cytokeratin; CD: Cluster of differentiation; CgA: Chromogranin-A; CK: Cytokeratin; EMA: Epithelial membrane antigen; HDAC: Histone deacetylase inhibitors; INSM1: Insulinoma-associated protein 1; KI-67: Antigen Kile 67; NSD3: Nuclear receptor binding SET domain protein 3; NSE: Neuron-specific enolase; NUTM1: Nuclear protein of the testis midline carcinoma family member 1; Pan-CK: Pan cytokeratin; PAX8: Paired box 8; PD-1: Programmed cell death protein 1; PD-L1: Programmed cell death ligand 1; p16: Cyclin-dependent kinase inhibitor 2A; p40: Ribonucleic acid-binding protein p40; p63: Tumor protein p63; ROS1: ROS proto-oncogene 1; SMARCA4: Transcription activator BRG1; SMARCB1: SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1; SOX10: SRY-related HMG-box 10; Syn: Synuclein; S-100: Calcium-binding protein; TTF-1: Thyroid transcription factor-1.

Table S6. Survival data for the 526 patients with nuclear protein of the testis midline carcinoma

Demographic/clinical feature/treatment	Literature dataset† (*N*=526)		
	Total	Thoracic	Head and neck
Overall	355, 10 (7.93,12)	164, 6 (5,7.9)	123, 15.6 (10.6,18)
Sex			
Female	170, 9 (7,12)	69, 8 (5, 12)	64,14.9 (8.4, 23)
Male	185, 10 (7,13)	95, 5 (4, 7)	59,15.6 (10.6, 23.6)
Area	Total	Thoracic*	Head and neck
America	160, 8 (6,12)	61, 5 (2.6,6)	57, 17 (10,NA)
Asian	132, 12 (9.3,16.5)	77, 11.4 (7,19)	38, 10 (23.6,6)
European	57, 7 (5.5,17)	24, 5 (4,9)	27, 14 (7,NA)
Age			
Ages 1–20	85, 12 (9,18)	27, 6 (4,17)	36, 18 (12.2,24)
Ages 21–40	129, 7 (6,11)	58, 5 (4,7)	49, 17 (14,28)
Ages 41–60	97, 10.6 (7,17)	53, 11.6 (5,25)	29, 8 (7,17)
Ages 61 and above	44, 8.2 (5,30)	26, 6 (2.3,19.5)	
Metastasis			
Bone	25, 6 (4,12)	13, 4 (3,NA)	
Lung	11, 6 (4,NA)		
Stage			
I – II	17, 54 (7,NA)		10, 24 (5.5,NA)
III	36, 14.9 (8,NA)	24, 12.9 (7,NA)	
IV	53, 6 (3.8,12)	32, 3 (2.3,8)	18, 10.6 (8.2,NA)
Diameter			
<5 cm	87, 12 (10,19)	30, 11.6 (6,19)	47, 14 (9,24)
≥5 cm, <7cm	47, 8 (5,19.5)	24, 4 (3,16)	16, 16.5 (10.6,NA)
≥7 cm	64, 5 (3.8,6)	48, 4 (3,5.2)	
Immunohistochemistry (Ki-67)			
40 – 60%	16, 8 (3.6,NA)		
70% and above	18, 8 (5.7,NA)		
Fusion partner			
BRD3-NUTM1	15, 3 (2,NA)	12, 2.2 (2,NA)	
BRD4-NUTM1	105, 7 (5.2,10)	49, 5 (4,11.4)	35, 10 (7,24.7)
NSD3-NUTM1	22, NA (5.7,NA)		13, NA (NA,NA)
Surgical versus non-surgical			
Non-surgical	125, 6 (5,7.93)	77, 5.5 (4.5,7.93)	35, 7.46 (5,12)
Surgical	114, 18.7 (12.2,29)	38, 12.9 (9.3,NA)	62, 16.5 (12,NA)
Immunotherapy versus non-immunotherapy			
Immunotherapy	43, 19.5 (12,NA)	18, 19.5 (8,NA)	20, 31.4 (6,NA)
Non-immunotherapy	204, 7.93 (6,10.6)	97, 6 (5.5,9)	77, 11 (7.46,16)
BET versus non-BET			
BET	17, 6 (5,28)		
Non-BET	230, 10 (7.8,12)		

(Cont'd...)

Table S6. ***(Continued)***

Demographic/clinical feature/treatment	Literature dataset† (*N*=526)		
	Total	Thoracic	Head and neck
Treatment			
Include surgery immunotherapy	30, 31.43 (10,NA)		20, 31.43 (6,NA)
Radiotherapy surgery	24, 24 (15,NA)		21, 24 (15,NA)
Chemotherapy radiotherapy surgery	29, 14 (8.2,29)		24, 14 (8.2,22)
Chemotherapy surgery	24, 12 (7,NA)	15, 19 (7,NA)	
Include immunotherapy	13, 12 (7,NA)	12, 12 (7,NA)	
Chemotherapy radiotherapy	32, 7.93 (6,12)	18, 6 (5,NA)	11, 7.46 (5.5,NA)
Surgery	11, 7 (6,NA)		
Include BET	17, 6 (5,28)		
Radiotherapy	8, 5.95 (3,NA)		
Include HDAC	15, 5.8 (3,NA)		
Chemotherapy	44, 4 (3,6)	35, 4 (3,5.6)	
Include immunotherapy BET			
Include surgery BET			
Treatment sequence 1-only‡			
Include BET			
Chemotherapy	72, 9 (6,13)	46, 6 (5,12)	19, 10.6 (9,NA)
Surgery	69, 15 (8,34)	14, 34 (34,NA)	44, 15 (8,NA)
Radiotherapy			
Treatment sequence 2-only‡			
Include BET			
Chemotherapy	27, 11 (7,NA)		13, 10 (5.5,NA)
Surgery	16, 16.5 (12,NA)		
Radiotherapy	48, 12 (8,34)		24, 22 (8.4,NA)
Immunotherapy			
Treatment sequence 1‡			
Include BET	13, 6 (5,NA)		
Chemotherapy	107, 8 (6,12)	67, 6(5,8)	31, 10 (8.4,28)
Surgery	70, 15 (8,34)	15, 34 (6,NA)	44, 15 (8,NA)
Radiotherapy	21, 7.46 (5.5,16)	10, 6.95 (3,NA)	11, 7.46 (5.5,NA)
Treatment sequence 2‡			
Include BET			
Chemotherapy	40, 11 (8,NA)	11, 54 (6,NA)	23, 10 (7,NA)
Surgery	17, 16.5 (10.6,NA)		
Radiotherapy	58, 10 (8,22)	18, 7 (5,NA)	34, 14 (8.2,NA)
Immunotherapy	11, 12 (6,NA)		
DDP/CBP versus IFO			
DDP/CBP	89, 8 (6,12)		
IFO	15, 8 (4.7,NA)		

(Cont'd...)

Table S6. ***(Continued)***

Demographic/clinical feature/treatment	Literature dataset† (*N*=526)		
	Total	Thoracic	Head and neck
Comparison of chemotherapy drugs			
ABX/DTX/PTX	62,8 (6,11)	35,6 (5.8,12)	20,10.6 (8,28)
ADM	26,7(4,22)	10,6.8 (4,NA)	
CTX	18,4.5(3.8,12)	10,5.3 (3.8,NA)	
DDP/CBP	106,8(6,10.6)	59,5.8 (5,10)	32,14 (10,NA)
IFO	32,9(6,15)	15,8 (5,NA)	7,10 (7,NA)
VP16	41,7(5,12)	23,5.6 (4.5,18)	8,10 (7,NA)
Comparison of chemotherapy regimens			
Include EP	21,7 (4,NA)	13,4.5 (3,NA)	
Include IE	13,8 (4.5,NA)		
Include IEP	10,10 (5.8,NA)		
Include TP	51,8.4 (6,16)	28,6 (5,NA)	

Abbreviations: ABX: Abraxane; ADM: Doxorubicin; BET: Bromodomain and extra-terminal domain inhibitors; BRD: Bromodomain-containing protein; CBP: Carboplatin; CTX: Cyclophosphamide; DDP: Cisplatin; DTX: Docetaxel; HDAC: Histone deacetylase inhibitors; IFO: Ifosfamide; Ki-67: Antigen Kile 67; NA: Not available; NSD3: Nuclear receptor binding SET domain protein 3; NUTM1: Nuclear protein of the testis midline carcinoma family member 1; PTX: Paclitaxel; VP16: Etoposide.
Notes: EP: VP16+DDP/CBP;
IE: VP16+IFO;
IEP: VP16+IFO+DDP/CBP;
TP: ABX/PTX+DDP/CBP;
All data are expressed as the specific case number of the indicator/scheme, the median survival time of the indicator/scheme, and its 95% confidence interval (CI).
†The empty sections indicate insufficient data to perform an analysis for that part;
*A statistically significant difference ($p<0.05$) was observed.
‡"Treatment sequence 1/2-only" refers to the use of this treatment modality (e.g., chemotherapy) exclusively as either the initial or subsequent therapy. In contrast, treatments listed under "Treatment Sequence 1/2" may represent either sole use of this therapy or its inclusion in a combination treatment.

Table S7. Eight recommendations covering the entire process of diagnosing and treating nuclear protein of the testis carcinoma

No.	Recommendation
1	NUT carcinoma frequently presents as large masses, often accompanied by regional lymph node metastases and distant metastases. Due to its lack of specificity, its imaging features closely resemble those of advanced tumors in the corresponding anatomical regions. Bone metastases are commonly observed in NUT carcinoma, and clinicians should be particularly vigilant when patients present with extensive bone metastases at the time of initial diagnosis. Enhanced CT/MRI examinations of the relevant anatomical sites and bone scans or PET-CT (more recommended) are beneficial for staging and treatment evaluation (level of evidence: Grade 4; recommendation level: Strong recommendation).
2	Apart from surgical specimens, NUT carcinoma tissue samples can be obtained through endoscopy, aspiration, and core-needle biopsy. The histology of NUT carcinoma is often nonspecific, with some cases showing focal squamous differentiation accompanied by sudden keratinization and neutrophil infiltration. IHC staining for NUT typically reveals diffuse nuclear dot-like patterns. While NUT positivity is a key feature, other IHC markers in NUT carcinoma do not exhibit specificity (level of evidence: grade 4; recommendation level: strong recommendation). If the diagnosis remains inconclusive through these methods, supplementary diagnostic approaches, such as high-throughput sequencing via blood ctDNA, can be considered (level of evidence: grade 5; recommendation level: strong recommendation).
3	The clinical presentation, histopathology, and conventional IHC features of NUT carcinoma lack specificity, highlighting the importance of using specific NUT antibodies for IHC staining in its diagnosis. For patients with an initial diagnosis accompanied by rapid progression or distant metastasis, especially those with poorly differentiated carcinomas or small round cell tumors, it is strongly recommended to consider NUT IHC examination (evidence level: grade 4; recommendation level: strong recommendation). In addition, FISH or highthroughput sequencing should be considered to identify the type of NUTM1 fusion partner (such as BRD4, BRD3, and NSD3) (evidence level: grade 5; recommendation level: strong recommendation).
4	Patients with resectable NUT carcinoma should undergo curative surgery as the primary treatment as early as possible. Post-operative adjuvant therapy should be determined based on pre-operative and post-operative TNM staging and pathological conditions, surgical margins (R0, R1, and R2), and post-operative lymph node status (level of evidence: level 3;recommendation grade: stronglyrecommended). Pre-operative assessment by specialized physicians or an MDT can help determine the feasibility and approach of neoadjuvant therapy (level of evidence: level 4; recommendation grade: strongly recommended).
5	Patients with high-risk factors, such as lymph node positivity or non-R0 resection, especially those with inoperable NUT carcinoma, particularly in the head-andneck region, should undergo evaluation by specialized physicians or an MDT before treatment, aiming to select comprehensive therapy, primarily based on concurrent chemoradiotherapy. The radiotherapy protocol and dosage can be guided by delineating target areas and radiation doses for other corresponding malignant tumors (level of evidence: grade 3; recommendation level: strongly recommended).
6	Clinicians may consider selecting chemotherapy drugs primarily based on IFO or platinum-based agents or combining them with chemotherapy regimens used for other types of malignancies in corresponding anatomical sites of NUT carcinoma (level of evidence: level 4; recommendation grade: strongly recommended). High throughput sequencing can be considered to identify potentially sensitive personalized drug regimens (level of evidence: level 5; recommendation grade: recommended). For inoperable NUT carcinoma, a comprehensive treatment model combining induction chemotherapy with radiotherapy should be considered (level of evidence: level 4; recommendation grade: strongly recommended). Specific chemotherapy regimens should be evaluated based on the patient's condition after concurrent chemoradiotherapy (level of evidence: level 4; recommendation grade: strongly recommended).
7	For NUT carcinoma patients who are PD-L1/PD-1 positive, it is strongly recommended to consider combined immunotherapy as part of standard anti-tumor treatment. For patients who are PD-L1/PD-1 negative, the decision to use combined therapy should be made based on individual patient preference and circumstances (level of evidence: level 4; recommendation grade: strongly recommended).
8	For patients with post-operative recurrence or distant metastasis who are unsuitable for further surgery, apart from optimizing high-throughput sequencing to select sensitive drugs. It is recommended that patients either directly participate in clinical trials involving BET inhibitors, HDAC inhibitors, and other novel therapies, or on disease progression following conventional anti-tumor treatments, patients are encouraged to actively participate in clinical trials involving BET inhibitors, HDAC inhibitors, and other novel therapies (evidence level: grade 3; recommendation level: strongly recommended).In cases of treatment progression, high-throughput sequencing should be refined, suitable drugs should be selected based on the results, and participation in relevant clinical trials should be actively considered (evidence level: grade 5; recommendation level: strongly recommended).

Abbreviations: BRD: Bromodomain-containing protein; CT: Computed tomography; ctDNA: Circulating-tumor deoxyribonucleic acid; MDT: Multidisciplinary team; MRI: Magnetic resonance imaging; NSD3: Nuclear receptor binding SET domain protein 3; NUT: Nuclear protein of the testis; NUTM1: Nuclear protein of the testis midline carcinoma family member 1; PET: Positron emission tomography, PD-L1: Programmed cell death ligand 1; PD-1: Programmed cell death protein 1; TNM: TNM classification of malignant tumors.

Reference

1. Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.

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