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Original Research

The MUSES∗: a prognostic study on 1360 patients with sinonasal cancer undergoing endoscopic surgery-based treatment

∗*MUlti-institutional collaborative Study on Endoscopically treated Sinonasal cancers*

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Abstract ***Background:*** Over the last 2 decades, transnasal endoscopic surgery (TES) has become the most frequently employed surgical technique to treat sinonasal malignancies. The rarity and heterogeneity of sinonasal cancers have hampered large non-population-based analyses.

Methodology: All patients receiving TES-including treatment between 1995 and 2021 in 5 referral hospitals were included. A prognostic study was performed, and multivariable models were transformed into nomograms. Training and validation sets were based on results from 3 European and 2 non-European centres, respectively.

Results: The training and validation set included 940 and 420 patients, respectively. The mean age at surgery, primary-versus-recurrent presentation, histology distribution, type of surgery, T category and type of adjuvant treatment were differently distributed in the training and validation set. In the training set, 5-year overall survival and recurrence-free survival with a 95%-confidence interval were 72.7% (69.5–76.0%) and 66.4% (63.1–69.8%), respectively, significantly varying with histology. At multivariable analyses, age, gender, previous treatment, the extent of resection on the cranial, lateral and posterolateral axes, grade/subtype, T category, nodal status, margin status and adjuvant treatment were all associated with different prognostic outcomes, displaying a heterogeneous significance and effect size according to histology. The internal and external validation of nomograms was satisfactory (optimism-corrected C-index >0.7 and cumulative area under curve >0.7) for all histologies but mucosal melanoma.

Conclusions: Outcomes of TES-based treatment of sinonasal cancers vary substantially with histology. This large, non-population-based study provides benchmark data on the prognosis of sinonasal cancers that are deemed suitable for treatment including TES.

1. Introduction

Since it was first reported as a method for sinonasal cancer removal in the early 2000s [1–6], transnasal endoscopic surgery has rapidly evolved and is now the most frequently employed surgical technique to treat malignancies of the nasal cavity and paranasal sinuses [7]. With the exception of sinonasal cancers that still require an open maxillectomy and/or craniofacial resection (CFR), endoscopic surgery has progressively replaced open surgery by virtue of its lower morbidity, shorter hospital stay and at least equal ability to achieve uninvolved margins [8–19]. This technical evolution of sinonasal oncologic surgery occurred simultaneously

with the observation that the behaviour of a sinonasal cancer is profoundly relative to its histology, thus leading to a more analytical, 'histology-driven' management of such malignancies [20,21]. However, in view of the rarity and unparalleled histological heterogeneity of sinonasal cancers, most scientific publications are based on small numbers and multi-histology retrospective series, with only 1% of registered trials on skull base tumours assessing sinonasal cancers [22]. In addition, to overcome the limited numbers ensuing from the rarity of sinonasal cancers, the scientific strategy most frequently employed has been to perform population-based studies from national cancer databases, thereby increasing the number of patients studied but losing in data quality and uniformity of management. As a consequence, the authors of this paper initiated the 'multi-institutional collaborative study on endoscopically treated sinonasal cancers' (MUSES). This multi-institutional and international effort was inspired by the International Collaborative Study on anterior CFR [23], which in the early 2000s provided the scientific community with a number of seminal papers that have guided research and clinical practice in the field of sinonasal oncology. MUSES is composed of the largest non-population-based database on endoscopically treated sinonasal cancers, thereby enabling a relatively large number of cases to be analysed almost 2 decades after the first application of transnasal endoscopic oncological surgery.

The aim of the present paper is to provide the clinical community with a benchmark to understand the prognostic factors of different sinonasal cancers that are eligible for endoscopic surgery. It is the authors' opinion that this evidence, although based on retrospective analysis, will help clinicians in the management of a spectrum of rare and challenging tumours, while also offering a background to researchers who are interested in performing translational studies and prospective trials on sinonasal malignancies.

2. Materials and methods

2.1. Dataset preparation

The following criteria were applied to select patients to be included into the main dataset:

- Patients were affected by primary or recurrent resectable sinonasal cancer.
- Surgery included an endoscopic transnasal approach performed as part of curative treatment at one of the three European centres of the MUSES (*i.e.* 'ASST Spedali Civili di Brescia' – University of Brescia [Brescia, Italy], 'Ospedale di Circolo e Fondazione Macchi' – University of Insubria [Varese, Italy], 'Hôpital Lariboisière' – University of Paris [Paris, France]).
- Period of inclusion: 1995–2018.
- Treatment was performed within a multidisciplinary framework (*i.e.* at least a head and neck surgeon with expertise in endoscopic skull base surgery, a radiation oncologist, a medical oncologist and a radiologist were involved)

The following exclusion criteria were used:

- Patients affected by systemic lymphoproliferative disorders with sinonasal localisation.
- Distant metastasis at presentation.
- Patients receiving any of the following surgical procedures: open maxillectomy, open CFR, rhinectomy, Riedel's operation, osteoplastic frontal approach, midfacial degloving approach, lateral rhinotomy approach and orbital exenteration/clearance.

The same inclusion and exclusion criteria were applied to patients treated at the University Health Network (Toronto, Ontario, Canada) between 2001 and 2018, and at Tata Memorial Hospital (Mumbai, India) between 2005 and 2021 to create a secondary dataset for external validation purposes. Informed consent was obtained from all participants included in the study, which was conducted in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by local institutional review boards ('ASST Spedali Civili di Brescia' – University of Brescia: protocol NP3616; 'Ospedale di Circolo e Fondazione Macchi' – University of Insubria: Insubria Board of Ethics, approval number 0033025/2015; 'Hôpital Lariboisière' – University of Paris: REFCOR database approval CNIL #91204 and CCTIR #11.337; University Health Network: REB approval 19-5875; Tata Memorial Hospital: IRB Project No. 900540).

2.2. Principles of multidisciplinary management of sinonasal cancers adopted in the European centres of MUSES

The three European centres of MUSES have shared the same principles of treatment of sinonasal cancers throughout the study period, thus ensuring a reasonable degree of uniformity in terms of treatment policy.

2.2.1. Neoadjuvant chemotherapy

Neoadjuvant (NA) chemotherapy (ChT) was considered for the following histologies: poorly differentiated squamous cell carcinoma (SCC), Hyams grade III/IV olfactory neuroblastoma (ONB), sinonasal undifferentiated carcinoma (SNUC), poorly/non-differentiated sinonasal carcinomas not otherwise specified (SNCNOS), neuroendocrine carcinomas (NECs) and selected soft tissue sarcomas. Indications for NA-ChT were not uniform over the entire study period: roughly, during the first decade, NA-ChT was indicated only for locally advanced cases (cT4a and cT4b), whereas

thereafter it was indicated for the majority of Hyams grade III/IV ONB, SNUC, SNCNOS, NECs, poorly differentiated SCC regardless of the disease stage, selected advanced-stage soft tissues sarcomas and selected locally advanced well/moderately differentiated SCC (Table 1). The number of cycles ranged according to response and toxicity. Restaging through contrast-enhanced locoregional imaging (*i.e.* either computed tomography [CT] or magnetic resonance) was performed according to 2 different strategies: (1) after the 2nd cycle and after the 4th or 5th cycle, if NA-ChT continued beyond the 2nd cycle, in patients who were treated at 'ASST Spedali Civili di Brescia' – University of Brescia (Brescia, Italy) or 'Hôpital Lariboisière' – University of Paris (Paris, France); (2) after the 1st, 3rd and 5th cycle in patients treated at 'Ospedale di Circolo e Fondazione Macchi' – University of Insubria (Varese, Italy).

Of note, cancers demonstrating partial/complete response to NA-ChT (according to response evaluation criteria in solid tumours [RECIST] version 1.1) [24] were preferably treated through definitive radiotherapy (RT) with concomitant ChT and were therefore excluded from the MUSES dataset unless they showed incomplete response to definitive treatment and were therefore salvaged with surgery. For a subset of patients (*i.e.* those included in the SINTART study – Clinicaltrials.gov identifier: NCT02099175), the threshold to send patients for definitive (ChT)-RT was based on 80%-or-greater reduction of initial tumour volume instead of RECIST criteria.

2.2.2. Classification and indications of endoscopic procedures

The following operations were considered as 'purely endoscopic procedures' for sinonasal cancer: (1) 'endoscopic resection' (ER), which was defined as the resection of the tumour through the nostrils under videoendoscopic guidance, with no surgical transgression of the skull base; (2) 'ER with transnasal

Table 1
Summary of chemotherapeutical schemes most frequently employed.

Scheme	Drug (dosage)	Histology
TPF*	- Docetaxel (75 mg/m^2, administered on day 1) - Cisplatin (75 mg/m^2, administered on day 1) - 5-fluorouracil (750 mg/m^2/day, administered from day 1 to day 4)	- SCC - SNUC - SNCNOS not displaying neuroendocrine features
PF*	- Cisplatin (75 mg/m^2, administered the day 1 of each cycle) - 5-fluorouracil (750 mg/m^2/day, administered from day 1 to day 4 of each cycle)	- SCC - SNUC - SNCNOS not displaying neuroendocrine features
PE*	- Cisplatin (33–75 mg/m^2/day, administered from day 1 to day 3) - Etoposide (100–150 mg/m^2/day, administered from day 1 to day 3)	- ONB - NECs - SNCNOS displaying neuroendocrine features
PE-AI*	Odd cycles [*i.e.*, 1st, 3rd, 5th] - Cisplatin (33 mg/m^2/day, administered from day 1 to day 3) - Etoposide (150 mg/m^2/day, administered from day 1 to day 3) Even cycles [*i.e.*, 2nd, 4th] - Adriamycin (20 mg/m^2/day, administered from day 1 to day 3) - Ifosfamide (3000 mg/m^2/day, administered from day 1 to day 3)	- ONB - NECs - SNCNOS displaying neuroendocrine features
VAC	- Vincristine (1.5 mg/m^2/day, administered on day 1) - Actinomycin-D (1.5 mg/m^2/day, administered on day 1) - Cyclophosphamide (1.2 mg/m^2/day, administered on day 1)	- RMS
IVA	- Vincristine (1.5 mg/m^2/day, administered on day 1) - Actinomycin-D (1.5 mg/m^2/day, administered on day 1) - Ifosfamide (3000 mg/m^2/day, administered from day 1 to day 2)	- RMS
VIr	- Vincristine (1.5 mg/m^2/day, administered on day 1) - Irinotecan (20–50 mg/m^2/day, administered from day 1 to day 5)	- RMS
EI	- Epirubicin (60 mg/m^2/day, administered from day 1 to day 2) - Ifosfamide (1800–3000 mg/m^2/day, administered from day 1 to day 2–5)	- Non-RMS soft tissue sarcomas
DI	- Doxorubicin (20–30 mg/m^2/day, administered from day 1 to day 2–3) - Ifosfamide (2500–3750 mg/m^2/day, administered from day 1 to day 2–3)	- Non-RMS soft tissue sarcomas

NECs, neuroendocrine carcinomas; ONB, olfactory neuroblastoma; RMS, rhabdomyosarcoma; SCC, squamous cell carcinoma; SNCNOS, sinonasal carcinoma not otherwise specified; SNUC, sinonasal undifferentiated carcinoma.

* Carboplatin (area under curve [AUC] 5, administered the day 1 of each cycle) was given instead of cisplatin in the patient developing or bearing a high risk to develop a renal, neural or otovestibular toxicity.

craniectomy' (ERTC), which was defined as an ER including the anterior skull base and, if needed, the overlying dura mater and part of the frontal lobe of the brain as part of the resection. The term 'cranioendoscopic resection' (CER) was defined as ER combined with a coronal incision, frontal craniotomy and subfrontal approach. The term 'endoscopic-assisted craniofacial resection' (EACFR) was used to describe any procedure partially performed under endoscopic guidance and not attributable to ER, ERTC or CER (*e.g.* a combination of transorbital and/or transoral routes). CER and EACFR were considered 'endoscopic-assisted procedures'.

All surgical procedures were planned with the aim of achieving a gross total resection of the lesion, possibly with uninvolved margins all along tumour surfaces. Margin evaluation was made possible by the 'multiblock' technique [25], which consists of removing additional, anatomically oriented structures to be used as margins after completing the resection of the main surgical specimen(s). This technique enabled a 3-dimensional reconstruction of margin status. Patients affected by borderline-extended cancers possibly requiring transnasal craniectomy or a transcranial approach were consented to for possible intraoperative switch from ER to ERTC or from ERTC to CER, respectively. Similarly, patients possibly requiring orbital ablation or other open surgical procedures were preoperatively counselled and consented accordingly.

Nasoethmoidal cancers were considered eligible for ER/ERTC when the local extension was limited within the following structures (schematised according to 6 spatial vectors of growth; the 'medial' vector was excluded as tumours exceeding the midline were treated according to spatial criteria described for the 'lateral' vector applied to the contralateral side) at preoperative imaging and intraoperative evaluation:

- Anterior: mucoperiosteum of the nasal bones and frontal process of the maxillary bone.
- Posterior: lateral and posterior sphenoidal bony wall; lateral, superior and posterior nasopharyngeal wall and underlying bony/cartilaginous structures.
- Lateral: extraconal fat (minimal invasion confirmed intraoperatively was considered suitable for ER/ERTC; gross invasion detected at preoperative imaging was considered a contraindication to orbit-sparing surgery) [26] and medial wall of the lacrimal sac.
- Posterolateral: pterygopalatine fossa, infratemporal fossa, upper parapharyngeal space (non-massive invasion was considered as suitable to ER when unaltered tissue surrounding the gross tumour could be reached and resected as clear margins) [27].
- Inferior: mucoperiosteum of the nasal floor, nasopharyngeal side of soft palate mucosa, mucoperiosteum of the maxillary sinus floor [28].
- Superior: brain invasion limited to the gyrus rectus and medial orbital gyrus; invasion of the falx cerebri limited inferiorly to the apex of the crista galli. CER was indicated when superior and superolateral (*i.e.* above the orbital cavities) extension of the tumour exceeded the aforesaid structures [29].

Cancers of the maxillary sinus were considered eligible for ER when the local extension was limited to the medial, superior and posterior maxillary walls, pterygopalatine fossa, infratemporal fossa and upper parapharyngeal space. Invasion of the bony lateral, anterior and/or inferior maxillary walls mandated open surgery, whereas involvement limited to the overlying mucosa was managed through either ER or open surgery on a case-by-case basis.

Cancers arising into the frontal or sphenoidal sinus were considered eligible for ER/ERTC only in the rare cases of endoluminal exophytic tumours with no-to-minimal extension to the targetable bony boundaries of the sinus (*i.e.* all bony boundaries for the sphenoid sinus, only the floor and posterior wall for the frontal sinus).

The ability of the surgical teams to operate on sinonasal cancers progressively evolved over the study period, thus expanding the gamut of anatomical extensions that were considered as suitable for ER/ERTC. This implies that some tumours considered eligible for ER/ERTC in the more recent part of the inclusion period were treated differently than during the early phases.

Comprehensive neck dissection was performed during the same surgical procedure in cases presenting with nodal involvement.

2.2.3. Adjuvant (chemo)radiation

Adjuvant RT was indicated in any of the following circumstances: locally advanced cancers at definitive pathological examination (*i.e.* pT3, pT4a and pT4b categories); tumours designated as 'high-grade' based on the available World Health Organization Classification of Head and Neck Tumours (of note, tumours such as mucosal melanoma [MM], SNUC, SNCNOS and NECs were considered as high-grade by definition); margin involvement; nodal metastases; perineural invasion. Postoperative target volume definition was usually defined according to the principles of 'compartment-related volume', as described by Claus *et al.* [30] Briefly, three target volumes were usually defined according to pathological features: (1) high-risk (HR) clinical target volume (CTV) included the original insertional site, the microscopically affected margins and nodal levels with extranodal extension (ENE); (2) intermediate-risk (IR) CTV included anatomical areas at the risk of bearing subclinical disease based on gross tumour extension and histological features (*i.e.* it included nerve course and respective foramina in the base of the skull in case of perineural invasion). Nodal level(s) bearing a nodal metastasis without ENE and those located adjacently

were included in IR-CTV; (3) low-risk (LR) CTV included areas at a low risk of microscopic tumour spread from initial macroscopic tumour extension and clinically uninvolved nodal levels I-III and retropharyngeal nodes (elective nodal irradiation [ENI]) when indicated. ENI was indicated for selected cases of histologies with a relevant risk of subclinical nodal involvement (*e.g.* ONB [particularly if Kadish C/D], NECs, SNUC, SNCNOS, SCC [particularly if locally advanced and involving the maxillary sinus]). Irradiation was unilateral in well-lateralised tumours (*i.e.* those not invading a midline structure) and bilateral otherwise. Planning target volumes were delineated by 0–5 mm isometric expansion of CTVs. In terms of radiation dose, 66–70 Gy (in case of multiple positive margins), 60 Gy and 50–54 Gy were delivered to HR-, IR- and LR-planning target volumes, respectively. As regards the RT technique, 2-dimensional conventional (for a minority of patients), 3-dimensional conformal and intensity-modulated RT were employed throughout the study period. A conventional or moderately accelerated fractionation schedule was employed, with the dose per fraction ranging from 1.8 to 2.2 Gy.

Concurrent cisplatin ChT was given in case of margin involvement, nodal metastasis with ENE and/or in selected cases of aggressive histologies (*e.g.* Hyams grade III/IV and/or Kadish C/D ONB, SNUC, SNCNOS, NECs). The dose regimen was either 100 mg/m^2 every 3 weeks or 30–50 mg/m^2 in weekly administration. In case of neural, renal or acoustic toxicity, replacement with weekly carboplatin (weekly, area under the free carboplatin plasma concentration versus time curve [AUC] 2; or 3-weekly, AUC 6) has been considered.

The above-mentioned aspects (*e.g.* radiation dose, indication and dose of concurrent ChT, neck irradiation) could vary on a case-by-case basis.

2.3. Statistical analysis

The detailed description of the statistical analysis is reported as Supplementary data. A summary of the main steps of the analysis is reported herein.

2.3.1. Descriptive statistics and subseries creation

Statistical analysis was performed using RStudio (Version 1.2.5042).

Variables were described through distribution (categorical variables), median and interquartile range (continuous variables). The rate of missing data was calculated and variables with >30% of missing data were excluded. Training and validation cohorts were compared in terms of quantitative and qualitative variables.

Tumours were grouped in the following categories (hereby referred to as 'histological groups') according to histopathological diagnosis: intestinal-type adenocarcinoma (ITAC), SCC, ONB, MM, mesenchymal tumours (MeT), minor salivary gland carcinomas (MiSGC), 'aggressive carcinomas eligible to NA-ChT' (ACENC) (*i.e.* SNUC, NECs and SNCNOS), non-intestinal-type adenocarcinomas, sinonasal germinal tumours (SGTs), sinonasal localised hemolymphoproliferative disorders and sinonasal primitive neuroectodermal tumours (*i.e.* Ewing's sarcomas and peripheral primitive neuroectodermal tumours). Groups with less than 30 observations were excluded.

2.3.2. Survival analysis

The following outcomes were considered: overall survival (OS), cancer-specific survival (CSS), recurrence-free survival (RFS), local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS) and distant recurrence-free survival (DRFS). Time was calculated from the date of completion of treatment to the date of the event. The Kaplan–Meier method was used to evaluate each survival outcome.

Univariate survival analysis was performed with the log-rank test. The following variables were tested on the entire series and histological groups: gender, primary *versus* recurrent presentation, previous RT, previous ChT (excluding NA-ChT), NA-ChT, type of surgery, the cranial extent of the resection, the lateral extent of the resection, the posterolateral extent of the resection, histological grade/subtype, nasoethmoidal *versus* non-nasoethmoidal tumour epicentre, pathological T category, presence of nodal metastasis, margin status and adjuvant (ChT)-RT.

Age-effect was tested on each survival outcome with a univariate Cox proportional-hazards model (CPHM) analysis.

Multivariable analysis was performed with CPHM. The selection of variables to be included in the model was made *a priori* based on the clinical relevance of each factor according to the authors' personal experience. Moreover, variables not selected *a priori* and exhibiting a prognostic effect at univariate analysis were also considered to build the multivariable model. Redundancy of information was avoided by eliminating variables having a similar clinical significance. Assumptions of the CPHM were checked. Multi-collinearity of covariates was assessed. The time-dependent effect on OS of histology as a multivariable-adjusted covariate was assessed through Aalen's model. Covariates were described through hazard ratio with 95% confidence interval and p-value. Competing risk analysis was performed for CSS, LRFS, RRFS and DRFS to assess risk of informative censoring.

Nomograms were created based on multivariable models.

Internal validation of multivariable models at each timepoint selected for the respective nomogram was performed by calculating the C-index and Nagelkerke R^2. Optimism correction was applied to each index and models were classified as either excellent (optimism-corrected C-index >0.8), useful (0.8 ≥optimism-corrected C-index >0.7) or frail (optimism-corrected C-index ≤0.7).

External validation of multivariable models was performed through calibration slope and Chambless and Diao cumulative area under curve (cAUC). Calibration slope was used to establish whether discrimination on the validation set was significantly different compared with that on the training set. Chambless and Diao cAUC was used as an estimate of discrimination, which was classified as excellent (cAUC > 0.8), useful (0.8 ≥ cAUC > 0.7), or frail (cAUC ≤ 0.7).

3. Results

The present study included 1360 patients affected by sinonasal cancer and treated with an endoscopic surgery-including protocol. Characteristics of the European and non-European series were substantially different, as detailed further (Table 2). The histology of cancers was exceedingly variable, with 13 histological groups, some of which included different entities. Histology was intimately associated with prognosis. In fact, not only did it fundamentally affect outcomes but also

Table 2
Characteristics of the European and validation series.

Variable	European series	Validation series	p-value
Number of patients	940	420	N.A.
Mean age (years)	61.2 (median: 64; IQR: 52-73)	49.4 (median: 49; IQR: 39-61)	p < 0.0001
Male-to-female ratio	2.1	2.0	p = 0.495
Presentation	Primary: 745 (79.3%)	Primary: 210 (50.0%)	p < 0.0001
	Recurrent: 195 (20.7%)	Recurrent: 210 (50.0%)	
Histology	ITAC: 332 (35.3%)	ITAC: 57 (13.6%)	ITAC (p < 0.0001)
	SCC: 140 (14.9%)	SCC: 82 (19.5%)	SCC (p = 0.039)
	ONB: 114 (12.1%)	ONB: 82 (19.5%)	ONB (p = 0.0004)
	MM: 90 (9.6%)	MM: 32 (7.6%)	MM (p = 0.303)
	MeTs: 84 (8.9%)	MeTs: 33 (7.9%)	MeTs (p = 0.532)
	MiSGCs: 80 (8.5%):	MiSGCs: 41 (9.8%)	
	ACC: 49 (5.2%)	ACC: 33 (7.9%)	ACC (p = 0.065)
	non-ACC: 31 (3.3%)	non-ACC: 8 (1.9%)	non-ACC (p = 0.165)
	ACENC: 58 (6.2%)	ACENC: 41 (9.8%)	
	SNUC: 21 (2.2%)	SNUC: 8 (1.9%)	SNUC (p = 1.000)
	NECs: 37 (3.9%)	NECs: 28 (6.7%)	NECs (p = 0.038)
	SNCNOS: 4 (0.4%)	SNCNOS: 5 (1.2%)	SNCNOS (p = 0.145)
	NITACs: 23 (2.4%)	NITACs: 13 (3.1%)	NITACs (p = 0.472)
	SGTs:* 7 (0.7%)	SGTs:* 34 (8.1%)	SGTs (p < 0.0001)
	SLHLDs: 6 (0.6%)	SLHLDs: 1 (0.2%)	SLHLDs (p = 0.447)
	SPNETs: 6 (0.6%)	SPNETs: 4 (1.0%)	SPNETs (p = 0.510)
Surgery	ER: 373 (39.7%)	ER: 283 (67.4%)	ER (p < 0.0001)
	ERTC: 464 (49.4%)	ERTC: 95 (22.6%)	ERTC (p < 0.0001)
	CER: 84 (8.9%)	CER: 41 (9.8%)	CER (p = 0.687)
	EACFR: 19 (2.0%)	EACFR: 1 (0.2%)	EACFR (p = 0.030)
Margin status	R0: 723 (76.9%)	R0: 326 (77.6%)	p = 0.457
	R1: 217 (23.1%)	R1: 94 (22.4%)	
Pathological T category	T1: 150 (16.0%)	T1: 54 (12.9%)	T1 (p = 0.278)
	T2: 199 (21.2%)	T2: 82 (19.5%)	T2 (p = 0.469)
	T3: 186 (19.8%)	T3: 148 (35.2%)	T3 (p < 0.0001)
	T4a: 158 (16.8%)	T4a: 62 (14.8%)	T4a (p = 0.340)
	T4b: 246 (26.2%)	T4b: 74 (17.6%)	T4b (p = 0.0004)
Nodal status	N0: 920 (97.9%)	N0: 407 (96.9%)	p = 0.288
	N+: 20 (2.1%)	N+: 13 (3.1%)	
Adjuvant treatment	None: 375 (39.9%)	None: 132 (31.4%)	None (p = 0.002)
	RT: 527 (56.1%)	RT: 288 (50.5%)	RT (p = 0.059)
	ChT-RT: 37 (3.9%)	ChT-RT: 76 (18.1%)	ChT-RT (p < 0.0001)

ACENC, aggressive carcinomas eligible to neoadjuvant chemotherapy; ACC, adenoid cystic carcinoma; CER, cranioendoscopic resection; ChT, chemotherapy; EACFR, endoscopic-assisted craniofacial resection; ER, endoscopic resection; ERTC, endoscopic resection with transnasal craniectomy; IQR, interquartile range; ITAC, intestinal-type adenocarcinoma; MeTs, mesenchymal tumours; MM, mucosal melanoma; N.A., not assessable; N0, no nodal metastasis; N+, nodal metastasis; NECs, neuroendocrine carcinomas; NITACs, non-intestinal-type adenocarcinomas; ONB, olfactory neuroblastoma; R0, clear margins; R1, microscopically involved margins; RT, radiation therapy; SCC, squamous cell carcinoma; SGT, sinonasal germinal tumours; SLHLD, sinonasal localized hemolymphoproliferative disorders; SNCNOS, sinonasal carcinomas not otherwise specified; SNUC, sinonasal undifferentiated carcinoma; SPNET, sinonasal primitive neuroectodermal tumours.

* All teratocarcinosarcomas.

influenced the timing of events such as death or recurrence and the effect size of other prognosticators. High T category, presence of nodal metastases, and margin involvement were independently associated with worse prognosis in the majority of histologies. For most histologies, adjuvant (ChT)-RT had an independent positive effect on prognosis.

The main differences between the training and validation series are hereby reported alongside the most relevant results of the survival analysis. Detailed results are thoroughly reported in Tables 2–4, Tables S1–23, Fig. 1 and Figures S1–S45.

3.1. Characteristics of the European series and validation series

The European series and validation series of MUSES included 940 and 420 patients, respectively. The mean age at surgery, male-to-female ratio, primary *versus* recurrent presentation, histology, type of surgery, margin status, pathological T category, nodal involvement and type of adjuvant treatment are summarised in Table 2. The European and validation series were significantly different in terms of age at diagnosis ($p < 0.0001$) and presentation ($p < 0.0001$). Moreover, while ITAC was more frequent in the European series ($p < 0.0001$), SCC, ONB, NECs and SGTs were significantly more represented in the validation series ($p = 0.039$, $p = 0.0004$, $p = 0.038$ and $p < 0.0001$, respectively). Non-intestinal-type adenocarcinomas, SGTs, sinonasal localised hemolymphoproliferative disorders and sinonasal primitive neuroectodermal tumours were excluded from survival analysis owing to the paucity of cases. ER was more frequently employed in the validation series ($p < 0.0001$), whereas ERTC and EACFR in the European series ($p < 0.0001$ and $p = 0.030$, respectively). The European series showed a higher rate of pT4b tumours ($p = 0.0004$), whereas pT3 tumours were more represented in the validation series ($p < 0.0001$). Unimodal surgical treatment was more frequent in the European series ($p = 0.002$), whereas adjuvant ChT-RT was more often employed in the validation series ($p < 0.0001$).

3.2. Survival analysis

OS, CSS, RFS, LRFS, RRFS and DRFS estimates of MUSES European series were, respectively, 80.4%, 83.6%, 71.2%, 80.8%, 95.8% and 87.7% at 3 years, 72.7%, 78.2%, 66.4%, 76.1%, 95.2% and 85.1% at 5 years, and 59.5%, 70.8%, 61.1%, 71.3%, 94.3% and 82.8% at 10 years (Fig. 1, Table 3). Histology-specific outcomes are summarised in Table 3.

Results of the survival analysis are thoroughly detailed in Tables S1-S16 (as sorted by histology) and Tables S17-S22 (as sorted by outcome).

Table 4 summarises the impact of covariates on different histologies, alongside the result of internal and external validation. Age and gender had an effect on survival in specific histologies such as ITAC, ONB, MeTs and MiSGCs. Previous treatment mostly affected the LRFS of certain histologies such as SCC, MeTs, and ACENC. The extent of resection of the cranial, lateral and posterolateral vector was associated with different outcomes for all histologies but ONB. Main tumor characteristics, namely grade/subtype, pathological T category, and nodal status, were the main factors affecting prognosis, with the majority of outcomes being independently associated with at least 2 thereof. Margin status and adjuvant therapy had also an impact on the prognosis of the majority of histologies. Competing risk analysis did not identify covariates losing significance with respect to CPHM, thus excluding a relevant informative censoring-related bias for outcomes associated with competing events (*e.g.* CSS, LRFS, DRFS).

Prognostic nomograms are illustrated in Figures S1–S45. All histologies but MM showed useful-to-excellent models (Table 4). Unmet assumptions are reported in Table S23.

4. Discussion

The prognosis of patients included in the European series of MUSES was closely related to histology: 5-year OS was 72.7%, ranging from 35.7% to 38.9% for MM and NECs, respectively, to 94.0% and 96.7% for ONB and non-ACC MiSGCs, respectively (Fig. 2). Local control was also related to histology, with 5-year estimates varying from 40.4% for MM to 91.0% for ONB. Overall, regional control was optimal, with >80% at 5 years irrespective of histology. The incidence of distant metastasis was a remarkable modality of relapse for certain histologies including MM, NECs and ACC. These results, thoroughly reported in Table 3, express the oncologic outcomes achievable through endoscopic surgery-including treatment in patients affected by sinonasal cancer, according to a 2-decade experience in referral centres.

The main finding of the present study is that the prognostic impact of previous treatment history, patient-specific, tumour-related and treatment-related factors varies considerably from one sinonasal cancer to another (Table 4). This heterogeneity translated into a violation of the proportional hazard assumption of CPHM for several outcomes when merging histologies in a single series (Fig. 2; Table S23), thus mandating a single-histology or similar-histologies analysis. This result was obtained from an unprecedently large non-population-based dataset of patients affected by sinonasal cancers eligible for endoscopic surgery. The fact that the MUSES dataset was based on a direct chart review ensures higher information reliability and

Table 3
Oncologic outcomes of the European series of 940 patients treated at 'ASST Spedali Civili di Brescia' − University of Brescia [Brescia, Italy], 'Ospedale di Circolo e Fondazione Macchi' − University of Insubria [Varese, Italy], 'Hôpital Lariboisière' − University of Paris [Paris, France]).

Group	OS (95%-CI)	CSS (95%-CI)	RFS (95%-CI)	LRFS (95%-CI)	RRFS (95%-CI)	DRFS (95%-CI)
Entire series	3-y: 80.4% (77.7−83.2%)	3-y: 83.6% (81.1−86.2%)	3-y: 71.2% (68.2−74.4%)	3-y: 80.8% (78.2−83.6%)	3-y: 95.8% (94.4−97.2%)	3-y: 87.7% (85.4−90.0%)
	5-y: 72.7% (69.5−76.0%)	5-y: 78.2% (75.2−81.3%)	5-y: 66.4% (63.1−69.8%)	5-y: 76.1% (73.0−79.2%)	5-y: 95.2% (93.6−96.8%)	5-y: 85.1% (82.6−87.8%)
	10-y: 59.5% (55.2−64.1%)	10-y: 70.8% (67.0−74.8%)	10-y: 61.1% (57.4−65.2%)	10-y: 71.3% (67.8−75.1%)	10-y: 94.3% (92.4−96.2%)	10-y: 82.8% (79.6−86.1%)
ITAC	3-y: 80.4% (75.9−85.2%)	3-y: 84.7% (80.5−89.1%)	3-y: 75.7% (71.0−80.8%)	3-y: 82.6% (78.4−87.1%)	3-y: 97.2% (95.2−99.3%)	3-y: 89.5% (86.0−93.2%)
	5-y: 72.7% (67.3−78.5%)	5-y: 80.0% (75.1−85.2%)	5-y: 73.2% (68.1−78.6%)	5-y: 79.9% (75.2−84.9%)	5-y: 97.2% (95.2−99.3%)	5-y: 88.0% (84.1−92.0%)
	10-y: 58.0% (51.0−66.0%)	10-y: 73.7% (67.8−80.1%)	10-y: 68.4% (62.4−75.0%)	10-y: 76.3% (70.9−82.1%)	10-y: 97.2% (95.2−99.3%)	10-y: 86.3% (81.5−91.5%)
SCC	3-y: 74.8% (67.4−83.1%)	3-y: 77.6% (70.3−85.7%)	3-y: 62.3% (54.2−71.6%)	3-y: 74.9% (67.5−83.0%)	3-y: 94.3% (90.3−98.5%)	3-y: 85.5% (79.1−92.5%)
	5-y: 66.2% (57.9−75.8%)	5-y: 69.8% (61.5−79.2%)	5-y: 54.5% (46.0−64.7%)	5-y: 68.9% (60.7−78.2%)	5-y: 94.3% (90.3−98.5%)	5-y: 80.0% (72.3−88.6%)
	10-y: 57.6% (47.8−69.4%)	10-y: 63.6% (53.8−75.2%)	10-y: 54.5% (46.0−64.7%)	10-y: 67.2% (58.6−77.0%)	10-y: 92.2% (86.5−98.1%)	10-y: 80.0% (72.3−88.6%)
ONB	3-y: 96.9% (93.5−100.0%)	3-y: 99.9% (96.9−100.0%)	3-y: 86.4% (79.8−93.6%)	3-y: 95.9% (92.1−100.0%)	3-y: 94.6% (90.1−99.3%)	3-y: 95.7% (91.5−99.9%)
	5-y: 94.0% (88.9−99.3%)	5-y: 96.0% (91.5−100.0%)	5-y: 81.9% (74.1−90.6%)	5-y: 91.0% (84.7−97.9%)	5-y: 94.6% (90.1−99.3%)	5-y: 92.5% (86.8−98.6%)
	10-y: 89.0% (80.9−97.8%)	10-y: 90.8% (83.0−99.4%)	10-y: 69.9% (58.7−83.3%)	10-y: 86.2% (77.7−95.7%)	10-y: 92.2% (86.0−98.9%)	10-y: 88.5% (79.4−98.6%)
MM	3-y: 51.4% (41.4−63.8%)	3-y: 52.7% (42.5−65.2%)	3-y: 33.6% (24.4−46.4%)	3-y: 56.6% (46.1−69.5%)	3-y: 90.3% (82.9−98.4%)	3-y: 57.5% (46.5−71.0%)
	5-y: 35.7% (26.0−48.9%)	5-y: 39.2% (29.1−52.8%)	5-y: 21.3% (13.2−34.1%)	5-y: 40.4% (29.1−56.1%)	5-y: 84.5% (74.5−95.9%)	5-y: 48.4% (37.0−63.5%)
	10-y: 19.9% (8.2−48.2%)	10-y: 21.8% (9.1−52.5%)	10-y: 21.3% (13.2−34.1%)	10-y: 26.9% (11.3−63.9%)	10-y: 84.5% (74.5−95.9%)	10-y: 48.4% (37.0−63.5%)
MeTs	3-y: 92.0% (86.0−98.4%)	3-y: 95.8% (91.1−100.0%)	3-y: 88.2% (81.2−95.9%)	3-y: 89.8% (83.3−96.8%)	3-y: 100.0% (100.0−100.0%)	3-y: 98.3% (95.1−100.0%)
	5-y: 83.8% (74.9−93.9%)	5-y: 93.6% (87.5−100.0%)	5-y: 86.3% (78.7−94.8%)	5-y: 87.9% (80.7−95.8%)	5-y: 100.0% (100.0−100.0%)	5-y: 98.3% (95.1−100.0%)
	10-y: 62.7% (48.0−82.0%)	10-y: 89.8% (80.9−99.7%)	10-y: 83.6% (74.6−93.6%)	10-y: 85.1% (76.4−94.7%)	10-y: 100.0% (100.0−100.0%)	10-y: 94.4% (86.6−100.0%)
ACC	3-y: 93.6% (86.8−100.0%)	3-y: 95.5% (89.6−100.0%)	3-y: 61.1% (48.4−77.0%)	3-y: 64.6% (51.9−80.4%)	3-y: 97.8% (93.7−100.0%)	3-y: 88.6% (79.6−98.6%)
	5-y: 87.7% (78.0−98.6%)	5-y: 92.5% (84.7−100.0%)	5-y: 61.1% (48.4−77.0%)	5-y: 64.6% (51.9−80.4%)	5-y: 97.8% (93.7−100.0%)	5-y: 88.6% (79.6−98.6%)
	10-y: 64.0% (46.7−87.6%)	10-y: 67.5% (49.8−91.5%)	10-y: 45.3% (30.9−66.5%)	10-y: 52.9% (38.5−72.8%)	10-y: 97.8% (93.7−100.0%)	10-y: 77.4% (62.4−96.1%)
Non-ACC MiSGCs	3-y: 96.7% (90.5−100.0%)	3-y: 100.0% (100.0−100.0%)	3-y: 93.4% (85.0−100.0%)	3-y: 93.4% (85.0−100.0%)	3-y: 100.0% (100.0−100.0%)	3-y: 96.7% (90.5−100.0%)
	5-y: 96.7% (90.5−100.0%)	5-y: 100.0% (100.0−100.0%)	5-y: 85.1% (72.4−99.9%)	5-y: 85.1% (72.4−99.9%)	5-y: 100.0% (100.0−100.0%)	5-y: 96.7% (90.5−100.0%)
	10-y: 80.1% (63.8−100.0%)	10-y: 95.0% (85.9−100.0%)	10-y: 79.4% (64.3−98.0%)	10-y: 79.4% (64.3−98.0%)	10-y: 100.0% (100.0−100.0%)	10-y: 96.7% (90.5−100.0%)
NECs	3-y: 42.4% (28.6−63.0%)	3-y: 48.8% (33.7−70.6%)	3-y: 40.5% (26.7−61.5%)	3-y: 66.6% (50.1−88.4%)	3-y: 91.4% (82.6−100.0%)	3-y: 70.5% (55.7−89.1%)
	5-y: 38.9% (25.3−59.8%)	5-y: 44.8% (29.8−67.2%)	5-y: 30.9% (17.5−54.3%)	5-y: 50.7% (31.5−81.6%)	5-y: 81.3% (63.1−100.0%)	5-y: 64.6% (48.3−86.4%)
	10-y: 34.0% (20.5−56.3%)	10-y: 39.2% (24.1−63.5%)	10-y: 30.9% (17.5−54.3%)	10-y: 50.7% (31.5−81.6%)	10-y: 81.3% (63.1−100.0%)	10-y: 64.6% (48.3−86.4%)
SNUC and SNCNOS	3-y: 82.2% (65.5−100.0%)	3-y: 82.2% (65.5−100.0%)	3-y: 69.5% (51.7−93.4%)	3-y: 80.1% (64.4−99.7%)	3-y: 89.3% (76.2−100.0%)	3-y: 94.1% (83.6−100.0%)
	5-y: 82.2% (65.5−100.0%)	5-y: 82.2% (65.5−100.0%)	5-y: 69.5% (51.7−93.4%)	5-y: 80.1% (64.4−99.7%)	5-y: 89.3% (76.2−100.0%)	5-y: 94.1% (83.6−100.0%)
	10-y: 82.2% (65.5−100.0%)	10-y: 82.2% (65.5−100.0%)	10-y: 60.8% (41.0−90.3%)	10-y: 70.1% (49.8−98.6%)	10-y: 89.3% (76.2−100.0%)	10-y: 94.1% (83.6−100.0%)

ACC, adenoid cystic carcinoma; CSS, cancer-specific survival; DRFS, distant recurrence-free survival; ITAC, intestinal-type adenocarcinoma; LRFS, local recurrence-free survival; MeTs, mesenchymal tumors; MiSGCs, minor salivary gland carcinomas; MM, mucosal melanoma; NEC, neuroendocrine carcinoma; ONB, olfactory neuroblastoma; OS, overall survival; RFS, recurrence-free survival; RRFS, regional recurrence-free survival; SCC, squamous cell carcinoma; SNCNOS, sinonasal carcinoma not otherwise specified; SNUC, sinonasal undifferentiated carcinoma.

Table 4
Summary of prognostic effect of each variable. Red cell = significant ($p < 0.05$) at multivariable model analysis; orange cell = close-to-significant ($0.10 > p \geq 0.05$) at multivariable model analysis; dark green cell = excellent model (optimism-corrected C-index/cumulative area under curve [cAUC]≥0.8) at validation; light green cell = useful model (0.8≥optimism-corrected C-index/cAUC>0.7) at validation; yellow cell = frail model (optimism-corrected C-index/cAUC≤0.7). ACENC, aggressive carcinomas eligible to neoadjuvant chemotherapy; CSS, cancer-specific survival; DRFS, distant recurrence-free survival; ITAC, intestinal-type adenocarcinoma; LRFS, local recurrence-free survival; MeTs, mesenchymal tumors; MiSGCs, minor salivary gland carcinomas; MM, mucosal melanoma; ONB, olfactory neuroblastoma; OS, overall survival; RFS, recurrence-free survival; RRFS, regional recurrence-free survival; SCC, squamous cell carcinoma.

Covariate	Entire series	ITAC	SCC	ONB	MM	MeTs	MiSGCs	ACENC
Histology	OS, CSS, RFS, LRFS, RRFS, DRFS							
Age	OS	OS		OS, CSS, RFS, LRFS, DRFS		OS		
Gender	OS / CSS			RRFS			OS	RRFS
Previous treatment	LRFS / CSS		RFS / LRFS			LRFS		LRFS
Cranial extent of the resection	LRFS, DRFS	OS, CSS, LRFS, DRFS	OS / CSS		RFS, LRFS		DRFS	
Lateral extent of the resection	OS, CSS, RFS, LRFS	RFS, LRFS / OS, RRFS	CSS, LRFS			OS	CSS	RFS, LRFS
Posterolateral resection		OS				OS, LRFS		LRFS
Grade/subtype	RFS, RRFS, DRFS / LRFS	CSS, RRFS, DRFS	OS, RFS, DRFS / CSS, RRFS	OS, CSS		OS, CSS	OS, CSS, RFS, DRFS	OS, CSS / RFS, DRFS
Pathological T category	OS, CSS, RFS, LRFS, RRFS, DRFS	OS, CSS, RFS, LRFS, RRFS / DRFS	OS, CSS, RFS, LRFS, RRFS, DRFS	RFS, LRFS / DRFS	OS, CSS, DRFS / RFS, LRFS	LRFS	OS	LRFS
Nodal status	OS, CSS, RFS, LRFS, RRFS, DRFS	OS, CSS, RFS, RRFS, DRFS	OS, CSS, RFS, RRFS, DRFS	OS, CSS, RFS, DRFS / RRFS	OS, CSS, LRFS / RRFS		LRFS	LRFS, RRFS
Margin status	OS, CSS, RFS, LRFS, DRFS / RRFS	OS, CSS, RFS, LRFS, RRFS, DRFS	OS, CSS, RFS, LRFS	RFS, LRFS / CSS		CSS	CSS / RFS	CSS, RFS, LRFS / OS
Adjuvant treatment	OS, RFS, LRFS	RFS, LRFS		LRFS / RFS	OS, CSS	OS / CSS	CSS / OS	
Internal validation	CSS, DRFS / OS, RFS, LRFS, RRFS	RFS, RRFS, DRFS / OS, CSS, LRFS	RRFS / OS, CSS, RFS, LRFS / DRFS	OS, CSS, RFS, LRFS, RRFS, DRFS	OS, CSS, RFS, LRFS, RRFS, DRFS	OS / CSS, LRFS / RFS	CSS / OS, RFS, LRFS, DRFS	OS, CSS, LRFS / RFS, RRFS, DRFS
External validation	CSS, RRFS, DRFS / OS, RFS, LRFS,	DRFS / OS, CSS / RFS, LRFS	CSS / OS, RFS, LRFS, RRFS, DRFS	OS, RFS, LRFS, RRFS, DRFS / CSS	RFS, LRFS, NRFS, DRFS / OS, CSS	OS, RFS, LRFS / CSS	OS, CSS, DRFS / RFS, LRFS	OS, CSS / RFS, LRFS, DRFS

treatment uniformity compared to national cancer database studies, as researchers could directly access the primary source of data (*e.g.* imaging, pathology, surgical report/video). The European 940-patient dataset involved subjects treated in 3 European academic institutions within a uniform treatment strategy, which has been ensured and periodically checked through long-standing collaboration over the last 2 decades. Moreover, every prognostic factor was tested through formal statistical analysis including a multivariable model with competing risk assessment, check for assumptions of the model, internal validation with optimism-correction and external validation. External validation was achieved on a dataset of 420 patients treated in world-renowned referral centres in North America and South Asia. These centres adopt similar but not identical principles in the treatment of sinonasal cancers and several differences in terms of histology distribution, pT category and therapeutic strategy were found between training and validation cohorts. This explains why most models had a significantly reduced fit (*i.e.* calibration slope significantly lower than 1). However, the majority of models maintained useful-to-excellent discrimination when applied to the validation set. This sound methodology highlighted both the prognostic factors to be relied on and those deserving further research. For instance, MM showed model frailty at internal and external validation. A possible explanation of this finding is that clinical variables may be insufficient to predict the prognosis for this histology. MMs could indeed bear a biological diversity that drives prognosis, but which is hidden behind similar clinical characteristics at presentation. The logical conclusion is that MM and other histologies with poorly predictable prognosis should be prioritised in translational studies assessing tumour biology and its impact on the prognosis of rare cancers.

Age was found to independently affect the prognosis of ITAC, ONB and MeTs (Fig. 3). Not surprisingly, the most affected outcome was OS, as already highlighted by other authors [31–33]. Other histologies did not show an independent effect of age on survival, probably because tumour aggressiveness prevailed over age-related, cancer-unrelated causes of death. Of note, age independently affected CSS, RFS, LRFS and DRFS of ONB, with elderly patients being affected by more aggressive tumours. Other authors described conflicting results when analysing smaller series [34,35]. Yin *et al.* recently demonstrated an independent association between age and CSS in a population-based study on 876

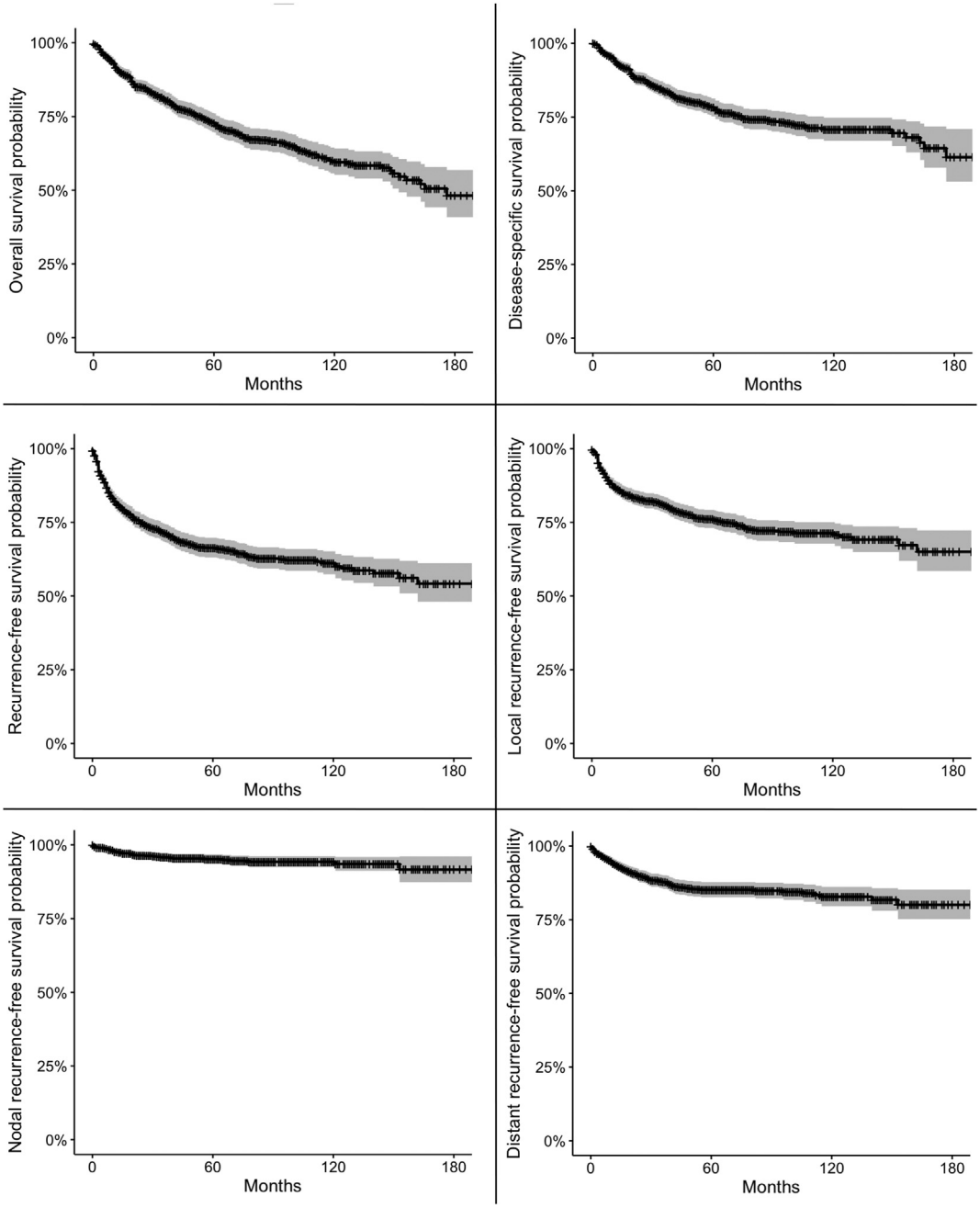

Fig. 1. Kaplan–Meier plots depicting overall, disease-specific (*i.e.* cancer-specific), recurrence-free, local recurrence-free, regional recurrence-free and distant recurrence-free survival of patients included in the MUSES training series.

ONBs. These findings suggest that tumour-host interaction could be age-dependent in ONB [36].

Gender affected the prognosis of ONB, MiSGCs and ACENCs, as already described by other authors [37,38]. Specifically, men affected by ONB and MiSGC showed a higher risk of nodal recurrence and death, respectively, whereas women had a higher chance of nodal recurrence from an ACENC. Similarly, Unsal *et al.* reported that the male gender was associated with an unfavourable prognosis in a large population-based study on 12,541 sinonasal cancers registered at the European Cancer Registry and the United States National Cancer Institute's Surveillance, Epidemiology and End Results databases [39].

Treatment received prior to surgery also independently affected some outcomes, particularly LRFS. While recurrent SCC after (ChT)-RT showed a 2.82-fold risk of further local recurrence [40], MeTs and ACENC were more likely to be locally controlled if previously treated with any treatment and (ChT)-RT, respectively. This result is countertrend and deserves cautious interpretation. According to the policy of treatment adopted

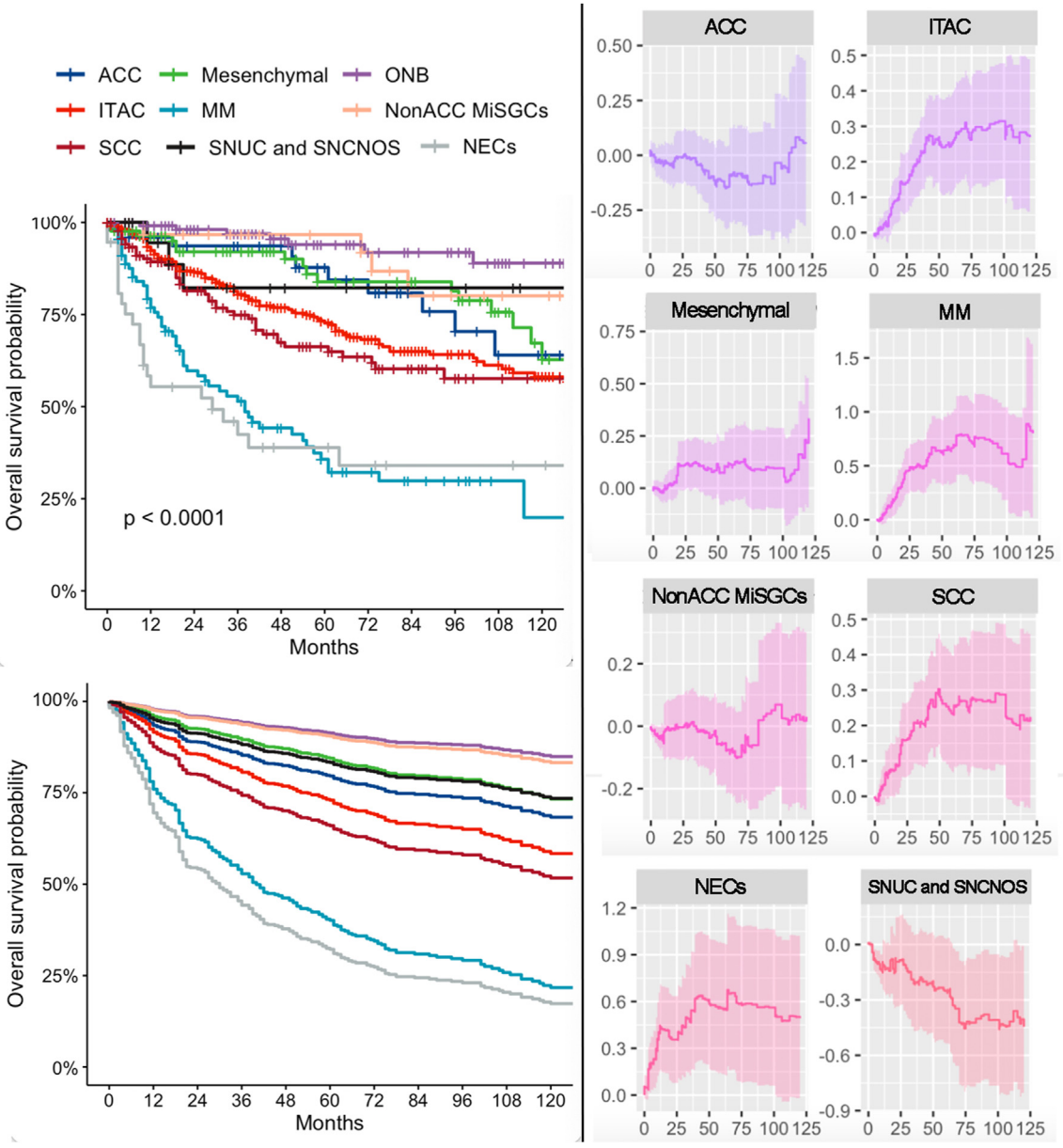

Fig. 2. Kaplan–Meier plot (left side, upper image) and multivariable model-adjusted survival curves (left side, lower image) depicting overall survival of patients included in MUSES training series according to histology. On the right side, the beta coefficient of risk of death (relative to olfactory neuroblastoma-subgroup) is depicted as a function of time according to Aalen's multivariable model for overall survival including histology, age, gender, previous treatment, the cranial extent of resection, the lateral extent of resection, posterolateral resection, grade/subtype, pathological T category, nodal status, margin status and adjuvant treatment. ACC, adenoid cystic carcinoma; ITAC, intestinal-type adenocarcinoma; MM, mucosal melanoma; NECs, neuroendocrine carcinomas; NonACC MiSGCs, non-adenoid cystic carcinoma minor salivary gland carcinomas; SCC, squamous cell carcinoma; SNCNOS, sinonasal carcinomas not otherwise specified; SNUC, sinonasal undifferentiated carcinoma.

by MUSES centres, ACENC (*i.e.* SNUC, SNEC and SNCNOS) are most frequently treated through NA-ChT, which allows chemoselection of definitive treatment. Thus, patients undergoing surgery after (ChT)-RT were mainly responders to NA-ChT, who have a notoriously better prognosis compared to non-responders [41]. This is consistent with the finding of Robin *et al.*, who found that NA ChT-RT increased the chance of achieving a complete resection by 2.64 times [42]. Similarly, in this series the subcategory of recurrent MeTs amenable for endoscopic surgery-including treatment gathered 2 types of lesions associated with relatively favourable prognosis as opposed to other MeTs: (1) low-to-intermediate grade [43,44] MeTs (*i.e.* glomangioperycitoma [45–47], chondrosarcoma [48] and fibrosarcoma) [49] treated with simple local excision [50] prior to referral and then undergoing clear margin-intended surgery for persistent disease in a

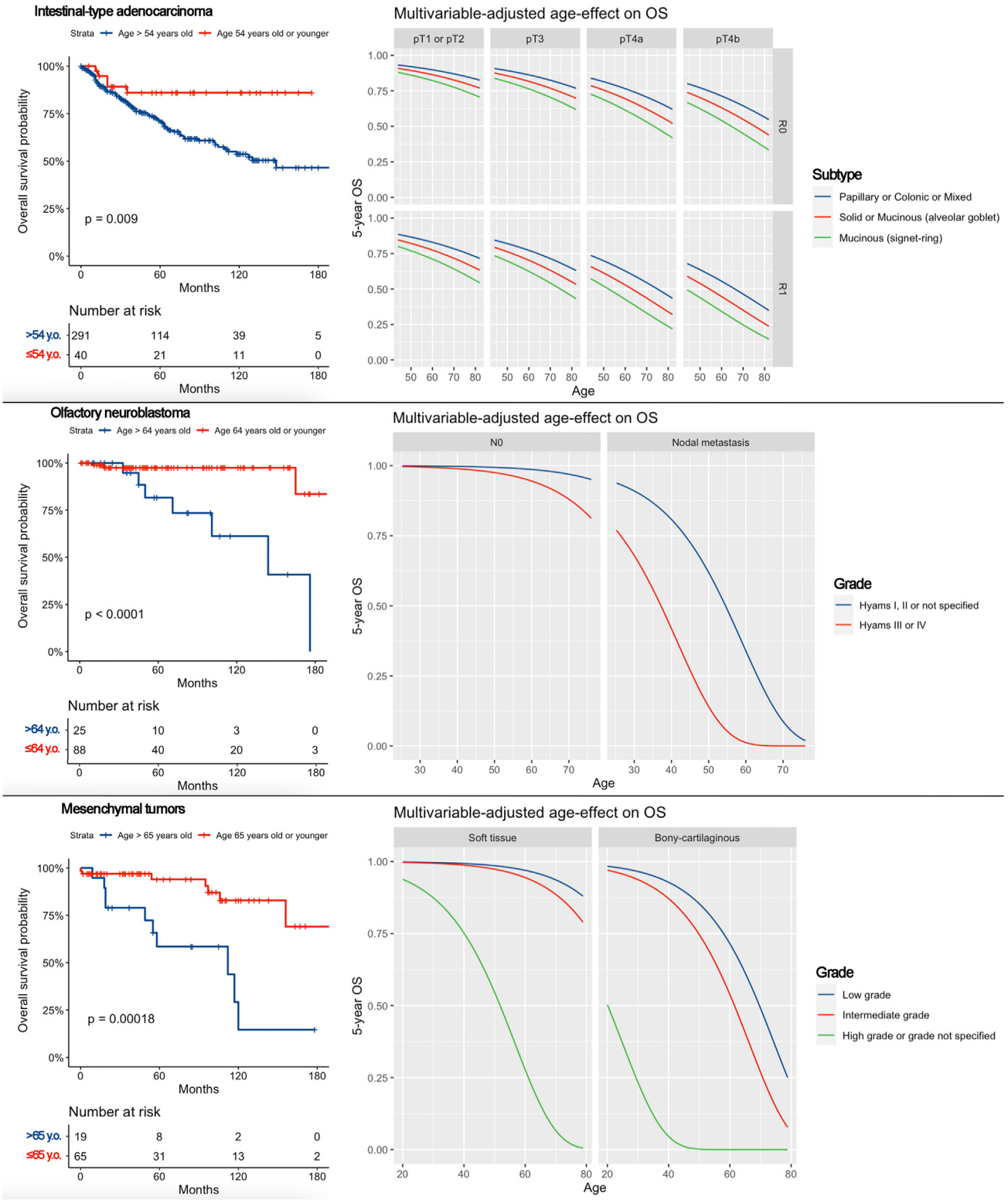

Fig. 3. Kaplan–Meier plots (left side) and multivariable model-adjusted regression plots (right side) showing age-effect on overall survival in intestinal-type adenocarcinoma, olfactory neuroblastoma and mesenchymal tumors, as observed in the MUSES training series. Age cut-offs were established with maxillary selected rank statistics. OS, overall survival.

MUSES centre and (2) microscopically-residual rhabdomyosarcomas after NA-ChT and definitive (ChT)-RT with radiological complete response [51–53].

The extent of endoscopic surgery had a variable impact on the prognosis of all histologies but ONB (Fig. 4), consistent with what was demonstrated by

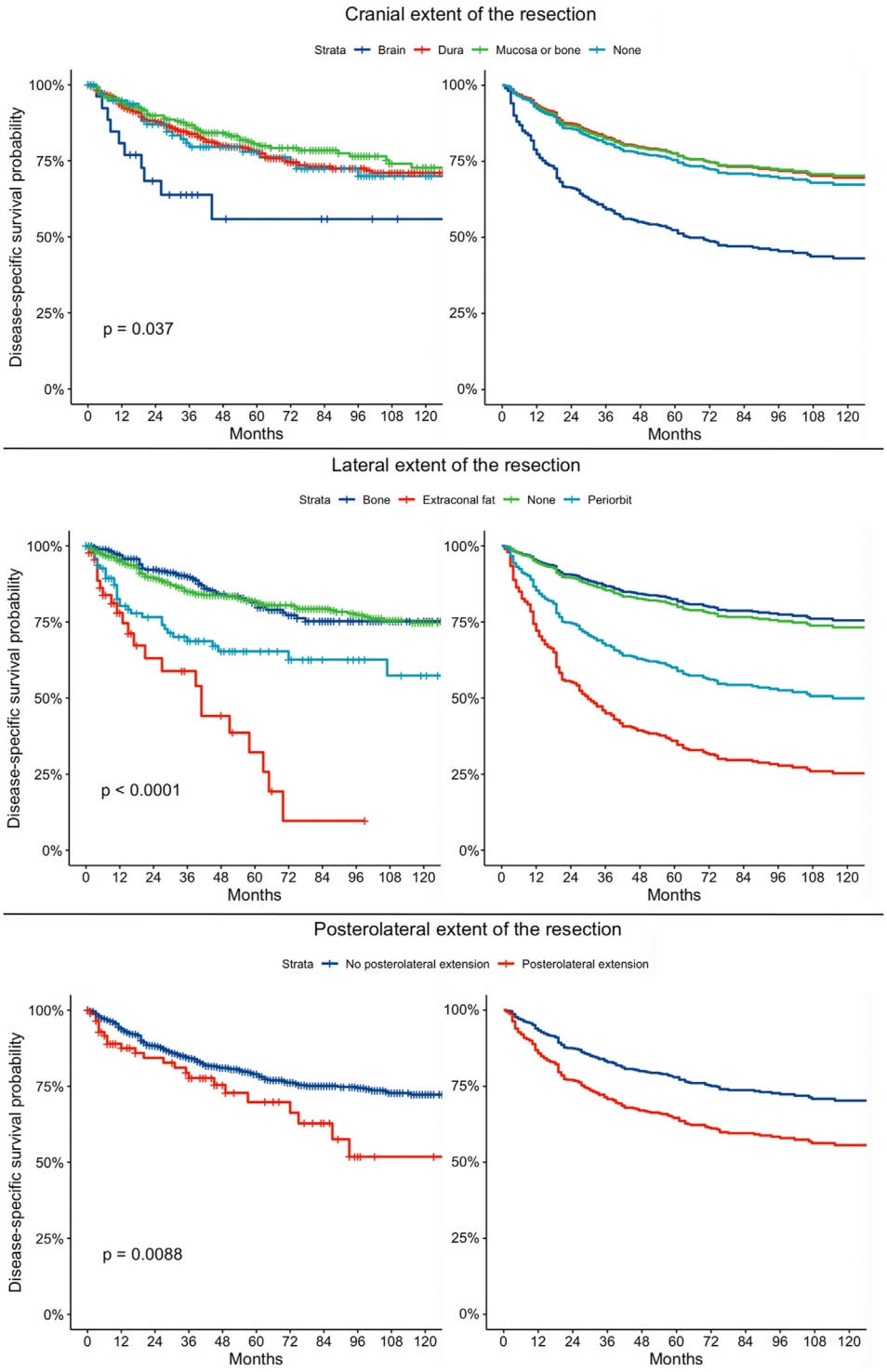

Fig. 4. Kaplan–Meier plots (left side) and multivariable model-adjusted survival curves (right side) showing the segregation of disease-specific (*i.e.* cancer-specific) survival according to reach of cranial, lateral and posterolateral resection, as observed in the MUSES training series.

Mays *et al.* for early-stage ONBs [54]. The extent of surgical ablation along the craniocaudal, mediolateral and posterolateral axes is a surrogate of tumour extension as clinically appreciable by imaging and intraoperative findings. Including this information in multivariable models was paramount as it provided a measure of the intensity of surgery to realistically weigh the prognostic effect of other covariates. The prognosis of some cancers such as MM was related only to the extent of resection on a caudal-to-cranial

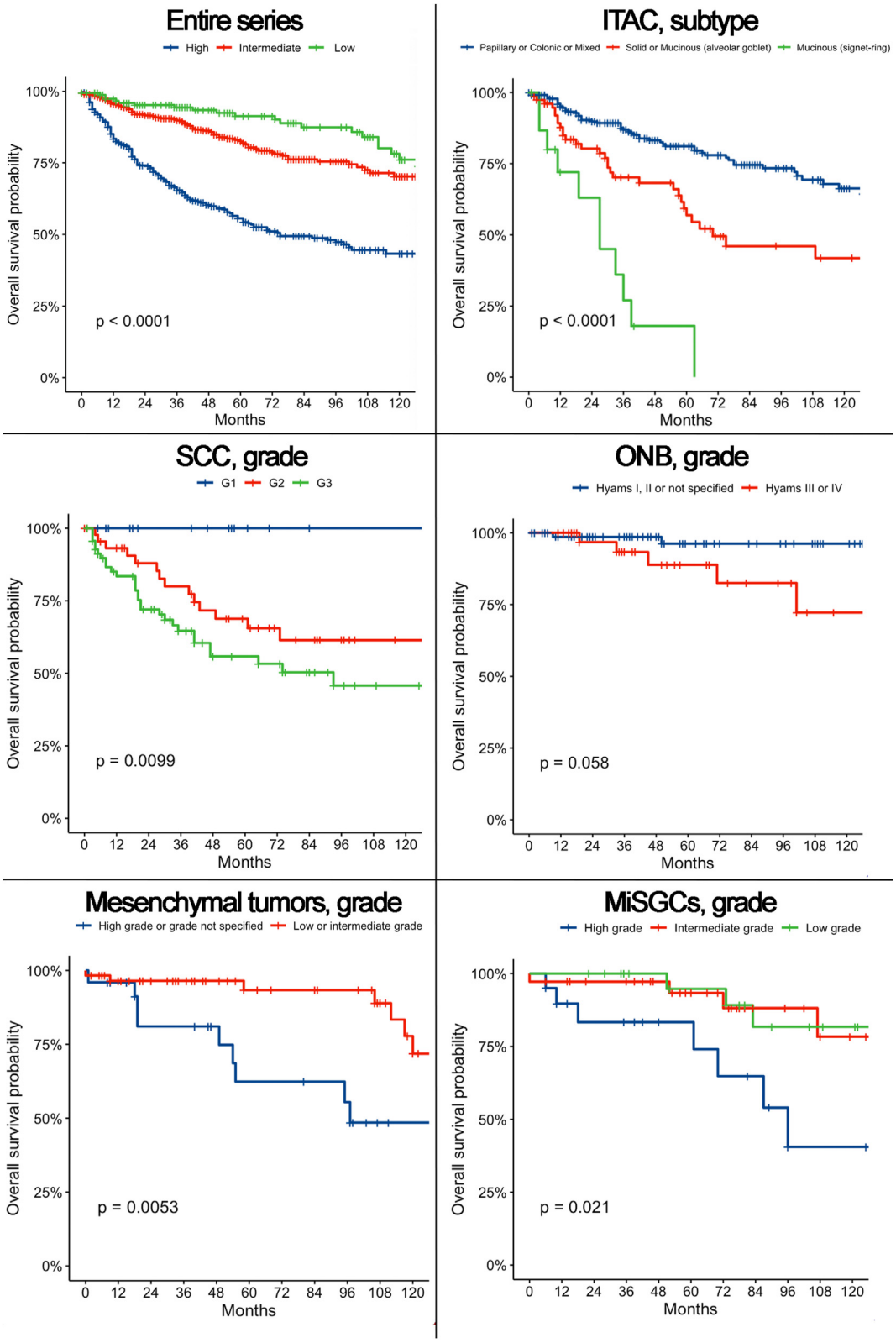

Fig. 5. Kaplan–Meier plots showing the prognostic relevance of tumour subtype/grade in terms of overall survival, as observed in the MUSES training series. ITAC, intestinal-type adenocarcinoma; MiSGCs, minor salivary gland carcinomas; ONB, olfactory neuroblastoma; SCC, squamous cell carcinoma; SNCNOS, sinonasal carcinomas not otherwise specified; SNUC, sinonasal undifferentiated carcinoma.

axis. Other histologies were associated with the extent of resection towards the orbit (*i.e.* MeTs and ACENC). The prognosis of the most common cancers (*i.e.* ITAC and SCC) and MiSGCs was associated with both vectors of resection. However, prognostic outcomes were not uniformly affected by the reach of cranial and lateral ablation (Table 4). The posterolateral extent of resection showed a less marked impact on prognosis. The diverse impact of ablation extent on outcomes is consistent with the fact that sinonasal cancers have a heterogeneous propensity to spread along different spatial vectors [55]. These findings emphasise the importance to accurately assess the extent of local disease together with histology-specific spreading pathways when planning for complete surgical resection. This should be especially taken into consideration when developing de-escalating surgeries, as already described for ONB and ITAC [56,57].

Tumour grade or subtype was invariably associated with prognostic outcomes, as already highlighted by other authors (Fig. 5) [26,31,43,44,58–77]. This finding suggests that the level of precision required to adequately manage sinonasal cancers should be set even beyond histological diagnosis. Clustering these cancers into subgroups based on histopathological characteristics is strongly correlated with prognosis and therefore enables the identification of patients who would benefit from the escalation of treatment intensity. However, most subclassifications are based on the qualitative evaluation of microscopic morphological features and are thus potentially flawed by a limited inter-rater agreement. Molecular classification of these rare cancers represents a promising step forward to increase the precision of sinonasal oncology [78–86] and will enable the development of tailored systemic treatment [87,88].

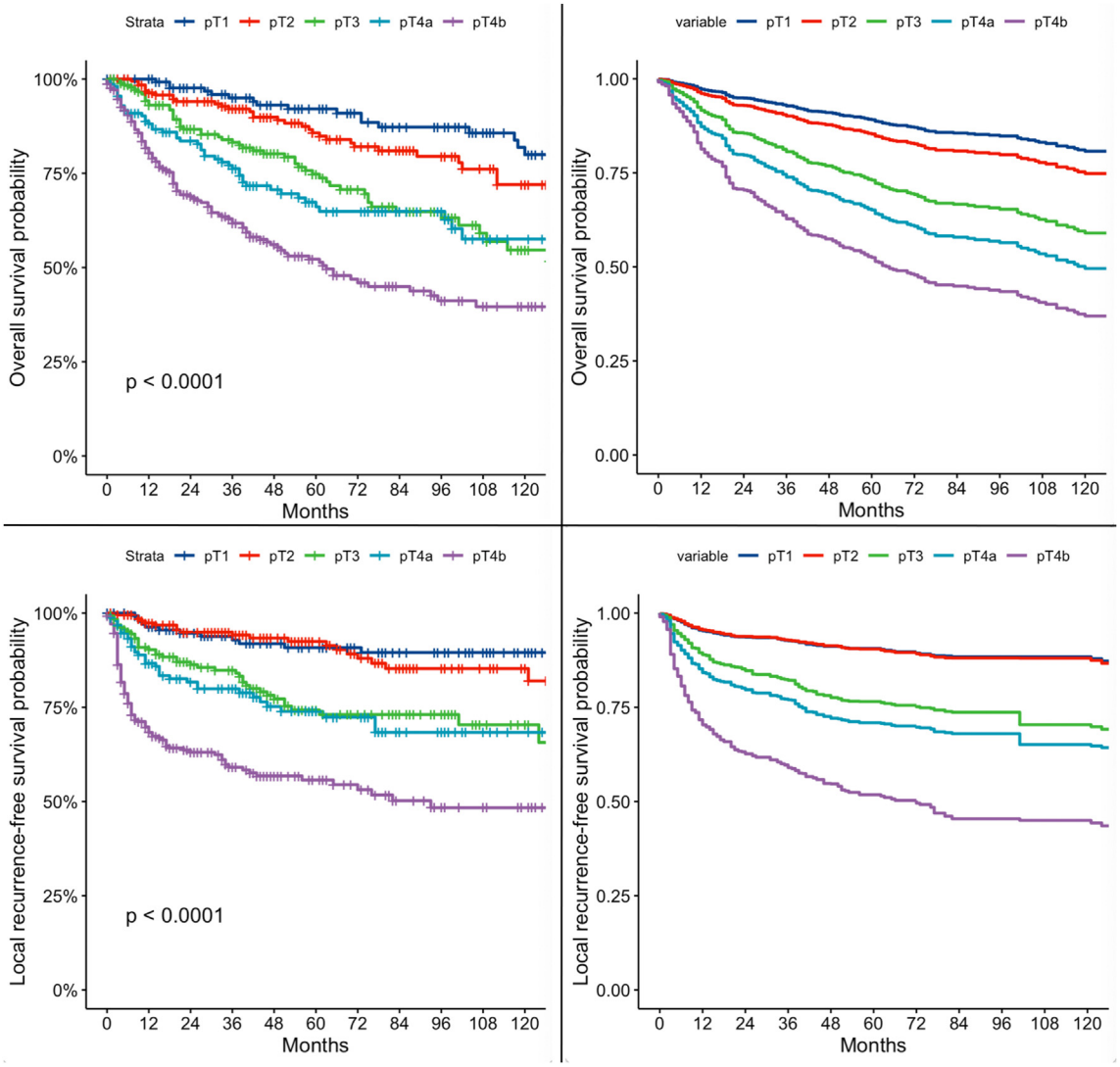

Fig. 6. Kaplan–Meier plots (left side) and multivariable model-adjusted survival curves (right side) showing the prognostic segregation in terms of overall and local recurrence-free survival based upon pathological T category, as observed in the MUSES training series.

The pathological T category is the only covariate that affected the prognosis of all histologies (Fig. 6). Not only was it almost invariably associated with LRFS but it also influenced several other prognostic outcomes, especially for some histologies such as ITAC, SCC and MM. This result aligns with previously published studies and has

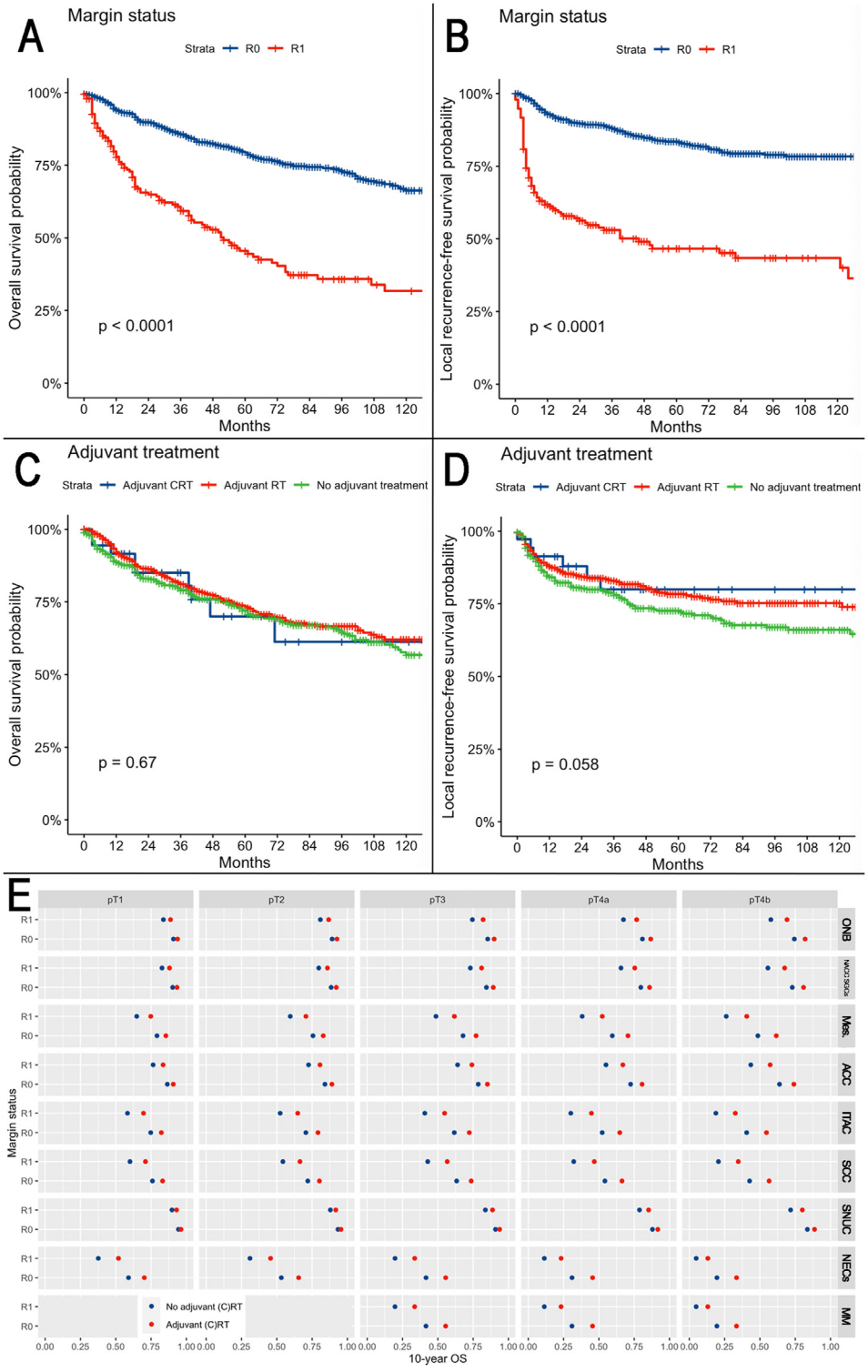

Fig. 7. Kaplan–Meier plots (A-D) and multivariable model-adjusted regression plot (E) depicting the prognostic effect of margin involvement and adjuvant treatment in terms of local recurrence-free survival, as observed in the MUSES training series. ACC, adenoid cystic carcinoma; CRT, chemoradiotherapy; ITAC, intestinal-type adenocarcinoma; Mes., Mesenchymal tumours; MM, mucosal melanoma; NECs, neuroendocrine carcinomas; NACC SGCs, non-adenoid cystic carcinoma minor salivary gland carcinomas; ONB, olfactory neuroblastoma; R0, uninvolved margins; R1, microscopically involved margins; RT, radiotherapy; SCC, squamous cell carcinoma; SNUC, sinonasal undifferentiated carcinoma and sinonasal carcinomas not otherwise specified.

several implications [9,14,25,31,36,38,52,66,67,80–84]. First, the current criteria (*i.e.* 8th TNM edition) to describe the local extension of sinonasal cancers resulted effective in stratifying the prognosis of a large cohort of patients treated through endoscopic surgery. Second, tailoring intensity of treatment (*e.g.* performing more extended surgery in advanced cancers) based on tumour extension is uncapable of compensating for the negative prognostic effect of locally advanced stage at diagnosis.

Nodal metastasis at presentation was rare (2.1%) and implied an unfavourable prognosis throughout all histologies except for MeTs, for which nodal metastases were observed neither at presentation nor at follow-up. This result is consistent with the published literature [31,36,63,68,80,82,85–90,97–99].

The involvement of margins had an independent negative effect on the prognosis of all sinonasal cancers but MM (Fig. 7). This result is consistent with several other studies [36,37,62,66,67,88,90–96,99–101,104]. This finding underlines the importance of adequately indicating and performing surgery, with the aim of achieving clear margins. In such an aggressive disease as MM, the propensity towards distant recurrence probably outweighed the negative prognostic effect of margin involvement.

Adjuvant (ChT)-RT had an independent positive effect on prognosis for all sinonasal cancers but SCC and ACENC (Fig. 7). Of note, these 2 histologies are frequently treated with NA-ChT, the response to which dictates whether subsequent locoregional treatment is surgery followed by adjuvant (ChT)-RT (non-responders) or definitive ChT-RT (responders). Thus, SCC and ACENC which were treated with adjuvant (ChT)-RT were mostly resistant to NA-ChT, which makes them more likely to be radioresistant. This could explain why adjuvant (ChT)-RT did not show an independent protective effect for this group of histologies as opposed to other sinonasal cancers. The role of adjuvant treatment has been already highlighted in other series [8,26,42,62,64,90–93,96,102,103,105–118].

The present study has some limitations that should not be neglected. First, the retrospective nature unavoidably limits the evidence ensued from the present analysis. This highlights the importance of coordinating referral centres for rare tumours in the joint effort of prospective, multi-institutional data collection. Second, despite the effort to comply with sound methodology, not all prognostic models developed herein fulfill assumption requirements nor did some models show an optimal performance (*e.g.* MM). Directing research towards the identification of molecular signatures is the logical step forward to improve the reliability of prediction in those cancers with poorly effective prognostic models. Third, the study was based on data gathered from only 5 centres, which is not fully representative of the wide heterogeneity of treatment of sinonasal cancer on a worldwide scale. Moreover, these are referral centres for sinonasal cancer, thus implying a 'referral centre bias', which means that data reported herein might partially depart from the respective figure in non-referral, non-academic centres.

5. Conclusion

Almost 2 decades after the first application of endoscopic surgery for sinonasal malignancies, MUSES has provided the head and neck oncology community with an unprecedently large non-population-based group of patients managed by endoscopic surgery-including treatment. An in-depth analysis confirmed that the impact of each prognostic factor significantly depends upon the histology of the sinonasal malignancy. This finding reinforces the belief that the management of sinonasal cancer should be histology-driven. Internally and externally validated prognostic models are herein presented as nomograms (Figure S1–S45), which represent a useful tool for clinicians who want to estimate the prognosis of their sinonasal cancer patients.

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.05.010.

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