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SPECIAL ARTICLE

Sinonasal malignancy: ESMO—EURACAN Clinical Practice Guideline for diagnosis, treatment and follow-up☆

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INTRODUCTION

The term sinonasal malignancies (SMs) groups together many tumours of variable histology and biological behaviour.

This Clinical Practice Guideline (CPG) covers the histotypes included in the fifth edition of the World Health Organization classification of tumours of the nasal cavity, paranasal sinuses and skull base (see Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.104121) under 'carcinomas', 'adenocarcinomas' and 'olfactory neuroblastomas'. Additionally, this CPG covers neuroendocrine carcinomas rising in this area such as small-cell neuroendocrine carcinoma (SCNEC) and large-cell sinonasal neuroendocrine carcinoma (SNEC).

Salivary-type malignancies, mesenchymal tumours and mucosal melanoma of the sinonasal tract have been excluded, since dedicated guidelines already exist.

INCIDENCE AND EPIDEMIOLOGY

Malignancies of the nasal cavity and paranasal sinuses, including all histopathological subtypes, have an age-adjusted incidence of <10 per million (five to nine for males and two to five for females)[1,2] and correspond to <5% of total head and neck malignancies.[3] The nasal cavity is the most common site followed by the maxillary, ethmoid, sphenoid and frontal sinuses.[1] Epithelial subtypes [squamous-cell carcinoma (SCC), adenocarcinomas and epithelial neoplasms not otherwise specified] are the most common (80%). SCCs are the most common regardless of site. Adenocarcinomas are the second most common histopathological subtype in the maxillary, ethmoid and sphenoid sinuses[1] but are more commonly found in the ethmoid and maxillary sinus. Incidence is higher in male patients at every site, with the age-standardised male-to-female incidence rate ratio varying from 1.3 in Norway to 2.5 in Italy and Finland. Most patients (both female and

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male) are ≥65 years of age worldwide, with a few exceptions, mainly in East Asian countries.[3] From 1970 to 2010, decreases in incidence were observed for both male and female patients in Hong Kong, Finland and England and male patients in Australia, the Netherlands, New Zealand and Norway.[2] In the Netherlands, a decrease in the incidence of sinonasal adenocarcinoma in male patients and an increase in the incidence of sinonasal SCCs (SNSCCs) in female patients has been observed.[4] The former may be the result of preventive measures combined with fewer workers in high-risk occupations.[4] The latter is most likely due to changing smoking habits. Relative survival (RS) represents cancer survival in the absence of other causes of death. SNSCC RS was 50% at 5 years (diagnosis years 2000-2007).[3] Sinonasal adenocarcinoma RS was 63.1%, 47.8% and 36.6% at 5, 10 and 15 years, respectively (diagnosis years 1973-2009).[5] Female patients had a slightly better, but not statistically significant, survival than male patients.[3,5] In Europe, 5-year RS of sinonasal cancers was the lowest in eastern European countries.[3] RS has been improving, especially since 2010.[6,7]

Risk factors

Few risk factors are known for sinonasal cancers. Most of these are exposures to inhaled substances in the workplace (wood, textile, leather, flour, nickel and chromium dusts), especially in sinonasal adenocarcinoma. The remaining are similar to those for other cancers in the head and neck area, such as smoking, and are more commonly associated with SCC.

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

Sinonasal cancers are rare malignancies with heterogeneous clinical, histological and genetic characteristics, which pose challenges in diagnosis and treatment.

Clinical diagnosis

Most patients are asymptomatic or have vague symptoms that can be associated with other benign diseases and, therefore, are often overlooked by patients and clinicians.[8] The most common symptoms include unilateral nasal obstruction and discharge, facial or dental pain and epistaxis. Persistence of such symptoms after a short course of medical therapy (maximum of 3 weeks) should prompt referral for specialist assessment. Presence of cranial neuropathy such as limitation of extraocular movements, trigeminal hypoesthesia and vision loss are signs of advanced disease.[8] Diagnosis begins with a thorough history and physical examination. An endoscopic examination is necessary to identify the tumour site, obtain a biopsy for tissue diagnosis and assess the local extent of the disease. Biopsy of the tumour is ideally carried out after radiological imaging (see 'Staging and Risk Assessment' for radiological evaluation). It can be carried out in the office or as day surgery depending on the risk of bleeding and the need to assess critical extensions (e.g. orbital invasion). Maxillary, ethmoid and frontal sinus lesions should be biopsied transnasally under endoscopic guidance unless the tumour has extended externally (e.g. maxillary sinus tumour growing into the oral cavity).[8] Cervical lymph node metastases are uncommon at presentation when the disease is confined to the sinuses, while the retropharyngeal lymph nodes are the first ones to be affected in more extensive disease.[9] Distant metastases are uncommon at presentation. Lung, liver and bone are most frequently involved when distant metastases occur.

Pathology and molecular biology

Given the rarity of SM, misdiagnoses are not uncommon. It is highly recommended to seek a second opinion from experienced pathologists at a high-volume institution. This might lead to changes in treatment and potentially improve survival.[10]

A variety of histologically distinct carcinomas originate from the nasal cavity, paranasal sinuses and skull base (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.104121). Distinct tumour subgroups can now be identified based on specific molecular alterations, including protein expression, chromosomal translocations, infection by oncogenic viruses or specific gene mutations.

SCC accounts for 50%-75% of sinonasal tumours.[11,12] It can be further distinguished into keratinising (KSCC) and non-keratinising (NKSCC) variants. NKSCC harbours transcriptionally active high-risk human papillomavirus (HPV; 35%-50%) more frequently than KSCC.[13] An emerging subtype of NKSCC is defined by recurrent *DEK*::*AFF2* fusions, but current data are too limited to determine the clinical significance of this variant.[14] SNSCC can be synchronous or metachronous to sinonasal papilloma, most frequently of the inverted subtype.[15] HPV-related multiphenotypic sinonasal carcinoma is recognised as a separate entity defined by the presence of multiple lines of differentiation, including squamous, ductal and myoepithelial, and by its association with high-risk HPV, usually of the rare type 33.[16] Despite the frequent aggressive histological appearance, this tumour has a favourable clinical course.

Excluding salivary-type tumours that replicate the histopathological features of tumours of minor salivary glands, adenocarcinomas can be categorised into intestinal-type (ITAC) and non-ITAC. The histological and immunophenotypic profile of ITAC is similar to that of primary ITAC,[17] while non-ITAC is a heterogeneous category, which includes low-grade and high-grade gland-forming malignancies that do not present an intestinal phenotype. They, therefore, represent a diagnosis of exclusion.[18]

A number of sinonasal carcinomas presenting with an undifferentiated or poorly differentiated morphology can be classified into separate diagnostic categories based on the identification of driver molecular changes.

NUT carcinoma is defined by a rearrangement of the *NUTM1* gene most frequently with *BRD4* and less frequently with *BRD3*, *NSD3*, *ZNF532*, *ZNF592* or other

unidentified genes. Immunohistochemical nuclear staining for NUT, usually with a characteristic speckled pattern, is considered sensitive and specific enough to support diagnosis.[19]

SWItch/Sucrose Non-Fermentable (SWI/SNF) complex-deficient sinonasal carcinomas are a group of rare and highly aggressive undifferentiated tumours that include *SMARCB1*- and *SMARCA4*-deficient carcinomas.[20] By definition, neoplastic cells present loss of nuclear expression of *SMARCB1* (alternatively *INI1*) or *SMARCA4* (alternatively *BRG1*).

Sinonasal undifferentiated carcinoma (SNUC) is a rare high-grade epithelial neoplasm without any identifiable line of differentiation (squamous, glandular or neuroendocrine) and it is, therefore, a diagnosis of exclusion.[21] *IDH2* mutations have been identified in SNUC; however, they also occur in other high-grade SMs, including adenocarcinomas, neuroendocrine carcinomas and SCCs. Irrespective of the histological subtype, *IDH2*-mutated sinonasal carcinomas may represent a distinct tumour entity with less aggressive clinical behaviour.[20]

Lymphoepithelial carcinoma, which is strongly associated with the Epstein—Barr virus similar to nasopharyngeal carcinoma, and neuroendocrine carcinoma, which may present in small-cell and large-cell variants, are other high-grade undifferentiated sinonasal carcinomas.

Teratocarcinosarcoma is a rare and aggressive epithelial tumour that is unique to the sinonasal tract. It presents multiple lines of differentiation, including epithelial, mesenchymal and primitive neuroepithelial elements.

Other molecular alterations

Several recurrent genetic abnormalities have been reported in sinonasal cancers, in addition to those that can guide diagnosis. These include *EGFR* exon 20 mutations in inverted sinonasal papilloma-related SNSCC,[22] *DEK*::*AFF2* fusions in NKSCC[14] and *IDH2* codon 172 mutations in SNUC.[20] Subsets of low-grade non-ITACs can carry *CTNNB1* and *BRAF* mutations and gene fusions such as *ETV6*::*NTRK3* and *ETV6*::*RET*.[23] Up to 82% of teratocarcinosarcomas can carry *SMARCA4* inactivation mutations; *CTNNB1* mutations have also been reported.[24] Recent studies have revealed less frequent recurrent mutations in *TP53* and *CDKN2A* in SNSCC and ITAC, as well as *APC*, *CTNNB1*, *PIK3CA* and *NF1* mutations in ITAC.[25,26]

HPV appears to play a role in several sinonasal tumour subtypes, with HPV type 33 being frequent in HPV-related multiphenotypic sinonasal carcinoma and types 16 and 18 in NKSCC. Other tumour subtypes associated with HPV include basaloid SCC, papillary SCC and adenosquamous carcinoma.[13]

Recommendations

- Patients with sinonasal symptoms lasting $\geq$3 weeks should promptly undergo a complete ear, nose and throat examination, including nasal endoscopy [V, A].
- Diagnosis should be confirmed by radiological imaging and histopathology with the addition of immunohistochemistry and molecular studies [V, A].
- Pathological diagnosis should be carried out by a trained pathologist at a high-volume institution, especially for poorly differentiated and high-grade tumours [IV, A].
- Molecular genetic analyses should be carried out to define a histological subtype [IV, A].

STAGING AND RISK ASSESSMENT

Fibreoptic examination is the first step in the work-up of sinonasal tumours, followed by cross-sectional imaging to accurately identify and map the extent of the lesion in areas that are critical for staging and treatment planning, particularly with respect to the orbit, skull base, infratemporal fossa invasion and perineural spread along named nerves.[27-29] See Supplementary Material Section 1, Tables S2 and S3, available at https://doi.org/10.1016/j.esmoop.2024.104121, for details on disease extension, clinical classification and staging according to the Union for International Cancer Control (UICC) TNM (tumour—node—metastasis) eighth edition, respectively.

Imaging

In most cases, patients are initially examined with multidetector computed tomography (CT), with an excellent demonstration of the thin bony laminae at the interface with the orbit or the skull base. Magnetic resonance imaging (MRI), however, is superior in showing the periosteum that invades the inner orbit and the skull base floor. This layer is the most effective barrier to tumour spread, appearing as a homogeneous hypointense layer regardless of bone mineralisation.[30] On MRI, the dura frequently responds to an invading lesion with marked enhancement and thickening (nodular).[31,32]

Key imaging findings for local extent assessment

MRI is superior to CT in predicting the absence of orbital invasion, with a high negative predictive value (NPV; $>$93%).[32-34] A recent study analysed the diagnostic performance of MRI in assessing the involvement of single orbital structures; diagnostic accuracy was satisfactory ($\geq$80%) for the bony layer, extraconal fat and muscle layer, but suboptimal ($<$80%) for the periorbital and intraconal compartment.[35] Therefore, MRI for contact/displacement of the orbital bone walls is more valuable in ruling out invasion of the orbital contents (T4a) than the invasion of the orbital walls (T3).

When used to assess the involvement of the anterior bony skull base (T3), CT was shown to have a lower positive predictive value (PPV) than MRI (77.8% versus 88.9%).[32] In the same study, dural invasion (T4b) was predicted by MRI with a PPV of $>$85%. A similar PPV (88.2%) was obtained in another study.[31] The former study, however, reported a

significant underestimation of dural invasion on 'normal' MRI studies, with an NPV of 82%.

On MRI, brain invasion (T4b) is suspected in case of transdural invasion with an enhancing tumour extending within the adjacent frontal lobe. Even though brain oedema may be present, it may be secondary to mass effect and not actually be a parenchymal invasion.[27]

Posterior spread into the pterygoid plates (T4a), pterygopalatine fossa or infratemporal fossa (T4a in maxillary sinus tumours) is a key factor in treatment planning.

MRI is the imaging modality of choice to detect perineural distant spread. Findings suggestive of perineural spread are nerve enhancement and enlargement. Sensitivity has been reported to be ≤95%, but mapping is only 60% complete.[36,37]

Lymph nodal and distant metastasis

The incidence of nodal metastases varies according to tumour histology. In SNSCC, it has been reported to be 14% (4%-27%, depending on the site and local extent).[38] The two main routes of lymphatic drainage from the sinonasal complex lead to the submandibular nodes (level I) and the ipsilateral jugulodigastric nodes (level II), the latter via the retropharyngeal nodes. The examination of neck lymph nodes can be obtained directly with MRI or contrast-enhanced CT. Ultrasound is another technique that can be used. Although the NPV of fluorodeoxyglucose (FDG)—positron emission tomography (PET) hybrid imaging is high (>90%), the rate of false-positive lymph nodes is notable.[39] The most important information provided by FDG—PET is the detection of distant metastases, seldom present at the time of their initial presentation, and second primary tumours.[40]

Recommendations

- Locoregional extension should be evaluated with MRI [IV, A] or CT [IV, B].
- The following critical extensions should be assessed during imaging [IV, A]:
  - Orbital walls and extraconal fat
  - Orbital apex
  - Anterior skull base, dura and brain
  - Sphenoid sinus (internal carotid artery, cavernous sinus)
  - Frontal sinus
  - Lacrimal pathway
  - Nasal bones
  - Premaxillary soft tissues
  - Infratemporal fossa (masticatory space)
  - Perineural and subperiosteal spread
  - Retropharyngeal node
- In the imaging report, a differentiation should be made between inflammatory changes and the tumour [IV, A].
- Distant spread should be evaluated, particularly with an FDG—PET examination in high-grade tumours [IV, A].

MANAGEMENT OF LOCAL AND LOCOREGIONAL DISEASE

Multimodal approaches and organ preservation strategies

Treatment options for SM include surgery, radiotherapy (RT) and systemic therapies. These treatments can be combined to optimise the oncological outcome and/or limit the overall morbidity of the treatment ('organ preservation' concept). Given the rarity of SMs, they should preferably be managed by an expert multidisciplinary team (MDT; ear, nose and throat surgeon, medical and radiation oncologist, radiologist and pathologist) in a high-volume centre, taking into account the histological type, grade and possibly the molecular profile (analysed by an expert pathologist).[41]

Neoadjuvant chemotherapy (NACT) may be indicated in high-grade and poorly differentiated tumours. It may be discussed in locally advanced tumours that are not amenable to surgery or RT at the outset with the aim of achieving tumour shrinkage, thus facilitating surgery or RT/chemoradiotherapy (CRT).[42] Some authors advocate its use in orbit preservation strategies.[43,44] Whether surgery may be avoided to preserve the orbit after response to NACT is debated. Some teams advocate surgery in poor-prognosis tumours, while others highlight that definitive CRT after response to NACT results in improved survival compared with those who undergo definitive surgery followed by RT.[45,46] This could depend on histology, as a better prognosis with NACT response-adapted treatment has been reported in SNUC and potentially in SCC, while weaker evidence is available for other histologies.

When NACT is not suitable (e.g. low- or intermediate-grade tumours, well-differentiated tumours), surgery with resection in negative margins is indicated as first-line therapy.

Post-operative RT may be indicated when locally advanced tumours (pT3-T4), positive margins, perineural invasion, lymph node invasion or high-grade and/or poorly differentiated tumours are present. In pT2 tumours, avoiding RT might be discussed if all poor prognosis factors are absent. Older series, in which only location and stage were taken into account in therapeutic strategy decisions, reported survival rates inferior or equivalent to 'histology-driven' strategy.[47,48] Encouraging results have been obtained in monocentre studies for several histological types and confirmed in a large multicentre study with prolonged follow-up.[49] Several studies have used this strategy and have reported different outcomes. These have been summarised in Supplementary Material Section 2, available at https://doi.org/10.1016/j.esmoop.2024.104121.

Surgery

Treatment of the primary. The first question to be answered when discussing surgery in SMs is whether the tumour can be resected with free margins. Contrary to other anatomic sites in the head and neck, there are no recommendations on how wide the margins should be or

whether they should be assessed on the resected specimen or the surgical bed. The frequent proximity of the lesion to critical anatomic structures, like the orbit, optic nerve, internal carotid artery, cavernous sinus, skull base, dura and brain, explains the difficulty in carrying out oncologically and clinically appropriate tumour resection with negative margins.[50,51] Surgery is only indicated when a complete resection appears feasible; partial and subtotal resections have not demonstrated a benefit.[49,52-54] *En-bloc* resection—always having been regarded as the dogma for external surgical techniques—has been challenged by the introduction of transnasal endoscopic surgery (TES), which frequently utilises a multi-bloc resection,[50,51] also called 'tumour disassembling'.[55] Although prospective comparative data are lacking, several studies suggest that regardless of the resection technique (multi bloc versus *en bloc*), achieving clear margins remains the main prognostic factor.[52,56] Therefore, sending tissue samples taken at the periphery of the resection for frozen sections is strongly recommended to trace tumour spread along the nerves and the periosteum.

After tumour ablation, appropriate primary reconstruction should be planned with the intent to close oronasal communication, seal dural defects, restore the contour of the maxillofacial skeleton, protect exposed vessels (i.e. internal carotid artery), provide dental rehabilitation and minimise complications of post-operative RT. Tissue selection among grafts, local or regional vascularised flaps and revascularised microsurgical flaps should take into account the size and site of the defect, communication with oral cavity and/or intracranial space, entity of bony/soft-tissue defect and patient age and comorbidities.

At the end of any endoscopic or external procedure, the surgical cavity may be packed with one of the materials available to prevent bleeding, which is left in place for at least 48 h.

Treatment of the neck. The risk of nodal involvement at diagnosis or during follow-up is relatively low compared with other head and neck malignancies, but varies from 3% to 33%[57] in relation to tumour histology, location and stage.[49,58] Currently, for clinically node-positive patients, the role of surgical treatment with or without adjuvant treatment is well established, while elective treatment for clinically node-negative patients remains controversial. A higher risk is observed with specific histologies [SNUC, high-grade olfactory neuroblastoma (ONB), SCC],[57,59,60] locally advanced stages and tumours extending to the dura, infratemporal fossa, orbit, oral cavity and nasopharynx.[57,61] In these settings, RT is the most frequently adopted treatment, while surgery has a very limited role especially when retropharyngeal occult metastasis may be expected.[62]

Definition of resectable disease. Although the definition of cancer 'resectability' is still widely used, it is necessary to differentiate between when a lesion is technically not completely resectable ('true unresectability'), when removal can be achieved with a loss of function (i.e. orbital exenteration) or when the tumour is unsuitable for primary surgery due to its extent and aggressiveness (i.e. SNUC). If the tumour extent includes one of the following five critical locations, it is considered unresectable: involvement of the orbital apex, cavernous sinus or optical chiasm, encasement of the internal carotid artery, massive brain invasion with perilesional oedema or involvement of major vessels (i.e. anterior cerebral artery).

Selection of surgical approaches. Surgical techniques for removal of sinonasal tumours can be divided in two broad groups, TES and external approaches. Both approaches can address tumours with or without involvement of the skull base. Their combination can be used to optimise the overall exposure of the lesion.[49,54] Over the past 20 years, the indications for TES have progressively expanded, and TES has become established as the treatment of choice for most nasoethmoidal malignancies. In contrast, only a minority of maxillary cancers are amenable to TES. TES overall survival (OS) and disease-specific survival are equal or even superior to those of external techniques,[63] especially with respect to length of hospitalisation, morbidity[64] and quality of life (QoL).[65,66]

See Supplementary Material Section 2, available at https://doi.org/10.1016/j.esmoop.2024.104121, for more information on the criteria for the selection of surgical approaches and on surgical complications and their management.

RT

For patients with contraindications to surgery, either due to preference or tumour unresectability, RT is the mainstay of treatment; it may consist of concurrent CRT. In the post-operative setting, adjuvant RT has a different magnitude of benefit across histologies.[67,68] Local recurrence is the main cause of death in patients with sinonasal tumours, but spread patterns and response rates to RT vary widely across histologies and presentations.[69] Local control is dose-dependent but technically challenging due to the close proximity of critical organs and accompanying toxicities. These toxicities are also dose-dependent, arising at doses close to or below those necessary to achieve tumour control. Post-operative RT is the standard of care for resected sinonasal neoplasms, except for pT1 tumours involving the infrastructure only and with negative margins, low grade and no other risk factors.[70] Definitive RT with or without systemic therapy is the mainstay treatment of unresectable tumours.

Selection of RT approaches. Intensity-modulated radiotherapy (IMRT) has become the standard for sinonasal carcinoma RT.[71,72] Charged-particle therapy, which includes definitive/post-operative proton therapy or definitive carbon ion therapy, is another recognised technique for the treatment of sinonasal neoplasms,[73] but facilities remain rare. Proton therapy may be an alternative to IMRT[74-78] in the definitive and post-operative settings or may be used as

an adjunct, with carbon ions reserved for unresectable tumours.[79] No guidelines, however, are currently available to help clinicians choose between IMRT and particle therapy or between the different types of particle therapy (see Supplementary Material Section 2, available at https://doi.org/10.1016/j.esmoop.2024.104121).

Expected outcomes. Using IMRT dose-gradient shaping capacities,[80-82] the 2- and 5-year local control rates are ∼80% and ∼50%-70%, respectively, for sinonasal tumours undergoing post-operative RT (±20%, depending on histology).[74,83,84] Most series are retrospective and consist of 50-200 patients. IMRT (including volumetric modulated arc therapy) has shown improved 3-year locoregional recurrence-free survival (RFS) and OS rates compared with three-dimensional (3D) conformal RT for carcinomas (RFS 89% versus 60%, $P = 0.035$ and OS 85% versus 65%, $P = 0.02$, respectively, in two different studies).[85,86] For inoperable T4 paranasal sinus and skull base tumours, the steep dose-gradient between tumour and normal tissue is even more advantageous, given the crucial need to maintain dose intensity at the tumour site.[87] Some series reported improved disease-free survival (DFS) with IMRT compared with 3D conformal RT (60% versus 72%, $P = 0.02$).[88]

Toxicities induced by IMRT and particle RT and their management are discussed in Supplementary Material Section 2, available at https://doi.org/10.1016/j.esmoop.2024.104121.

Systemic therapy

Although only low-level evidence is available due to disease rarity and heterogeneity, systemic chemotherapy (ChT) is often used in the management of high-grade, locally advanced SM. In the curative setting, ChT is considered as part of a multimodal therapy, mostly as NACT or concomitant with RT.[89]

A favourable response to NACT is often associated with improved survival and a reasonable chance of organ preservation. Nonetheless, evidence is scarce and mostly from retrospective series.[90,91] Higher-grade evidence has been reported by two large series, a mono-institutional study focused on single histology[45] and a multi-institutional study with data on multiple histotypes.[49]

Recently conducted and ongoing prospective trials may consolidate and clarify the role of NACT. Two studies evaluated the effect of multimodal therapy with NACT, surgery, IMRT or heavy-ion radiation in resectable[92] and unresectable SM.[93] Both showed a progression-free survival and OS benefit in patients with major partial volumetric response to NACT and demonstrated the feasibility and safety of an organ preservation strategy in these patients. A recently conducted single-arm trial at the M.D. Anderson Cancer Center reported promising results on NACT with docetaxel, cisplatin and 5-fluorouracil (5-FU) in locally advanced SCC or poorly differentiated carcinoma of the nasal cavity or paranasal sinuses.[46] An ongoing trial, led by the Eastern Cooperative Oncology Group and the American College of Radiology Imaging Network, is randomising patients with locally advanced, nasal and paranasal sinus SCC to NACT followed by surgery and post-operative RT or to surgery and post-operative RT (NCT03493425).

The most frequently used NACT agents are platinum-based compounds, usually in combination with 5-FU, taxane, ifosfamide, doxorubicin or etoposide. A histology-driven approach has been proposed, differentiating ChT regimens based on histotype sensitivity.[47] NACT regimens used in recent trials, including the corresponding histotype, are reported in Table 1.

The timing of the radiological evaluation to assess NACT effectiveness is of paramount importance. A balance should be struck between adequate dose intensity for optimal results and the timely discontinuation of NACT when ineffective. Radiomic analyses of T1- and T2-weighted images and apparent diffusion coefficient maps of MRI carried out after just one NACT cycle were able to predict response to NACT.[94] Another analysis of the value of early evaluation of volumetric response (preferred over bidimensional) showed that response to NACT after one cycle or at the time of best response are equivalent regarding outcome prediction and patient selection (unpublished data from the prospective SINTART trials). Concomitant CRT is not usually part of prospective trials as malignancies arising in sinonasal subsites are often excluded from head and neck SCC (HNSCC) studies. The use of platinum-derived compounds mostly stems from HNSCC experience or retrospective studies with selection bias.[95-97]

Figure 1 depicts the treatment algorithm for local and locoregional disease.

Recommendations

Multimodal approaches and organ preservation strategies.

- Patients should be managed by MDTs in high-volume centres [IV, A].
- NACT should be considered in high-grade and poorly differentiated tumours [III, A]:
  - SCC
  - Hyams grade III-IV ONB
  - SNUC
  - SNEC
  - SCNEC
  - Poorly or non-differentiated sinonasal carcinomas not otherwise specified
  - NUT carcinoma
  - SWI/SNF complex-deficient sinonasal carcinoma
- NACT may be considered in potentially chemosensitive (high-grade and poorly differentiated), locally advanced tumours, in which surgery or RT has a very high morbidity (significant orbital invasion, proximity to the chiasma) [III, C].
- In high-grade and poorly differentiated tumours, the locoregional treatment can be adapted to tumour response (definitive CRT in patients with partial or complete response and surgery or CRT, if surgery is not possible, in patients with stable or progressive disease) [III, B].

Table 1. NACT regimens in recent clinical trials

Agents	Regimen	Histotype
TPF	Docetaxel 75 mg/m^2, day 1 Cisplatin 80 mg/m^2, day 1 5-FU 800 mg/m^2 per day, days 1-4 q21	SCC, SNUC
PFL	Cisplatin 100 mg/m^2 i.v. infusion, day 2 5-FU 800 mg/m^2/day i.v. infusion, days 2-5 Leucovorin 250 mg/m^2/day i.v. infusion, days 1-5	p53 wild-type ITAC
EI/AI	Cisplatin 33 mg/m^2/day i.v. infusion, days 1-3 Etoposide 150 mg/m^2/day i.v. infusion, days 1-3 Alternating with Doxorubicin 20 mg/m^2/day i.v. infusion, days 1-3 Ifosfamide 3000 mg/m^2/day i.v. infusion, days 1-3	SNEC, SCNEC, Hyams grade III-IV ONB

Doses according to SINTART trials.[92,93] Doses may differ according to centre-specific procedures.
5-FU, 5-fluorouracil; AI, doxorubicin—ifosfamide; EI, etoposide—cisplatin; ITAC, intestinal-type adenocarcinoma; i.v., intravenous; NACT, neoadjuvant chemotherapy; ONB, olfactory neuroblastoma; PFL, cisplatin—5-FU—leucovorin; SCC, squamous-cell carcinoma; SCNEC, small-cell carcinoma neuroendocrine carcinoma; SNEC, sinonasal neuroendocrine carcinoma; SNUC, sinonasal undifferentiated carcinoma; TPF, docetaxel—cisplatin—5-FU.

Surgery

- Surgery is recommended only when complete resection appears feasible, especially for early stage [III, A], but also for later-stage tumours [III, B].
- Sinonasal carcinoma should be considered unresectable when one of the following sites is involved: orbital apex, cavernous sinus or optical chiasm, encasement of the internal carotid artery, massive brain invasion with perilesional oedema or involvement of major vessels (i.e. anterior cerebral artery) [IV, A].
- Partial and subtotal resections should be avoided [IV, D].
- Intraoperative assessment of the surgical margins of frozen tissue sample sections from the periphery of the resection is strongly recommended [IV, A].
- In clinically node-negative patients, surgery cannot be widely recommended, especially when retropharyngeal occult metastasis may be expected such as in stage III-IV disease [IV, D].

RT

- Post-operative RT is recommended for resected locally advanced sinonasal tumours (pT3-T4), positive margins, perineural involvement, positive lymph nodes or high-grade and/or poorly differentiated tumours [IV, A].
- Post-operative RT is not recommended for low-grade pT1 tumours involving only the infrastructure and with negative margins and no other risk factors [IV, E].
- Post-operative RT may be indicated in pT2 tumours [V, C]. Adjuvant RT avoidance in pT2 tumours may be discussed [V, C].
- Definitive RT with or without systemic therapy can be recommended for unresectable tumours [IV, B].
- IMRT is highly recommended as the standard of care in both the definitive and post-operative settings [IV, A].
- Delineation (and dose constraints) of organs at risk (OARs) can be carried out based on recommendations in common head and neck sites and can also include neuro-ophthalmological OARs [IV, B].
- Intensity-modulated proton therapy (IMPT) can be proposed in the definitive or post-operative settings when dose distribution and toxicity probability are more advantageous compared with IMRT [II, B]. Carbon ions can be proposed for unresected radioresistant histologies [II, B].
- RT planning should consider changes in anatomy (adaptive RT) during treatment and specific dosimetric challenges in that anatomic area [IV, B].
- Due to the morbidity of RT in this anatomic area, efforts should be made to customise RT after TES with cautious multidisciplinary (RT, surgery, pathology) assessment of RT volumes and radiosensitive organs [IV, B].

Systemic therapy

- When considered for SCC, SNUC, SNEC, SCNEC and Hyams grade III-IV ONB (i.e. rapidly evolving tumours), evaluation of NACT response and restaging through contrast-enhanced locoregional imaging (i.e. CT or MRI) should be carried out at the latest after two cycles [IV, A].
- Post-operative CRT with platinum-based agents may be considered in high-grade and/or poorly differentiated tumours [IV, C].

MANAGEMENT OF LOCAL OR REGIONAL RECURRENCE

Due to the rarity of the disease, scant information exists on recurrent SM. Local or regional recurrence following surgery and adjuvant RT occurs in 40%-80% of patients,[45,84] with substantial variance according to histology, stage at primary diagnosis and other factors. Most tumours recur within 2-5 years after primary treatment,[98] but some specific histologies can relapse decades after the first presentation, e.g. ONB, with a relapse interval as long as 10-15 years.[99]

The treatment choice should factor in the global performance status, disease characteristics and tumour histology, and should be discussed in a multidisciplinary setting. Surgery is currently the mainstay for resectable tumours, when feasible. In a large, retrospective series, rpT class, margin status, perineural invasion and post-operative RT were used to stratify prognostic groups with different survival rates of 0%-84.4% at 5 years.[100]

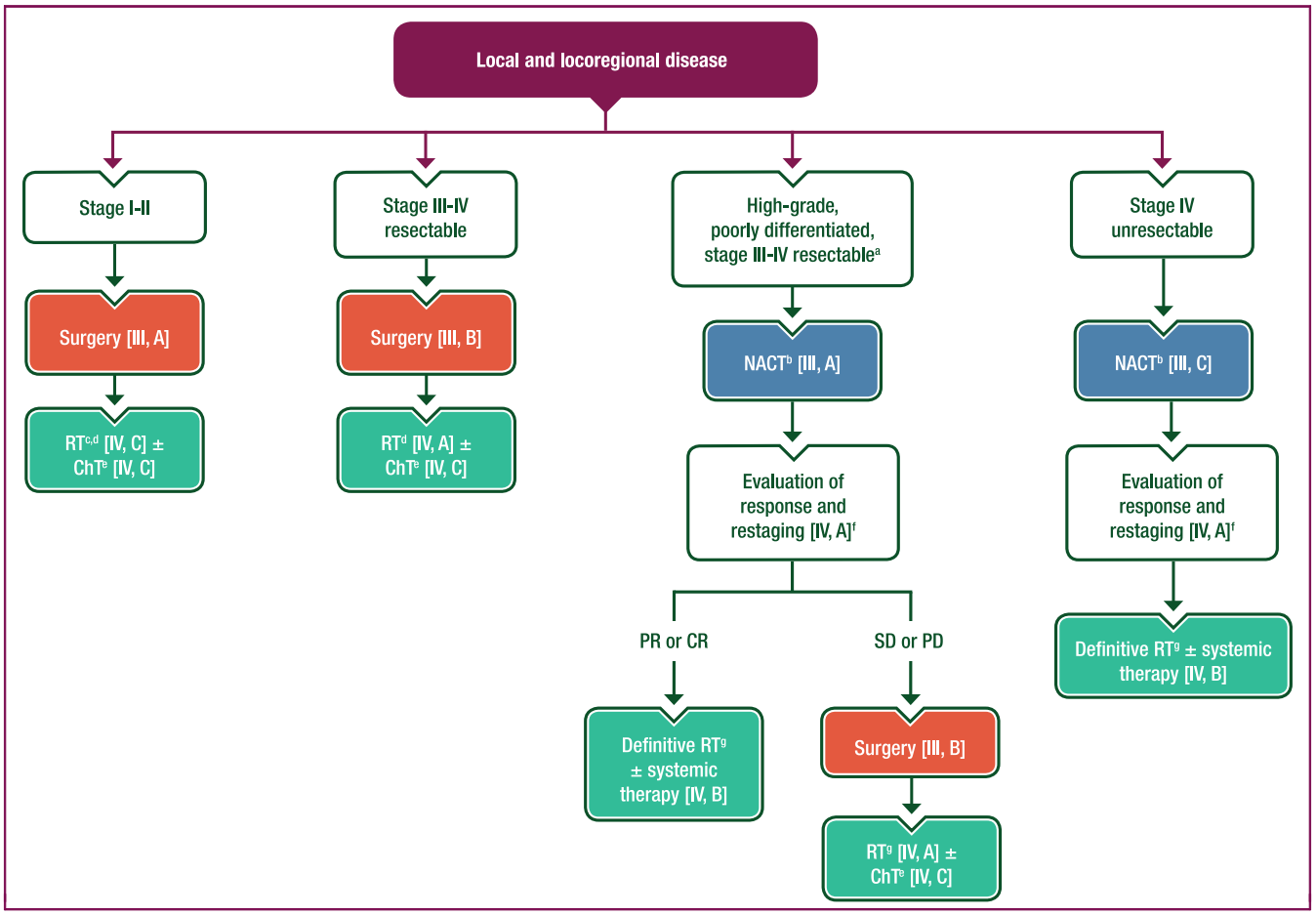

Figure 1. Management of local and locoregional disease.
Purple: algorithm title; orange: surgery; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects.
ChT, chemotherapy; CR, complete response; CRT, chemoradiotherapy; CT, computed tomography; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated radiotherapy; MRI, magnetic resonance imaging; NACT, neoadjuvant chemotherapy; ONB, olfactory neuroblastoma; PD, progressive disease; PR, partial response; RT, radiotherapy; SCC, squamous-cell carcinoma; SD, stable disease; SCNEC, small-cell neuroendocrine carcinoma; SNEC, sinonasal neuroendocrine carcinoma; SNUC, sinonasal undifferentiated carcinoma; SWI/SNF, SWItch/Sucrose Non-Fermentable.
[a]In SCC, Hyams grade III-IV ONB, SNUC, SNEC, SCNEC, poorly or non-differentiated sinonasal carcinomas not otherwise specified, NUT carcinoma and SWI/SNF complex-deficient sinonasal carcinoma.
[b]In potentially chemosensitive (high-grade and poorly differentiated), locally advanced tumours, in which surgery or RT has a very high morbidity (significant orbital invasion, proximity to the chiasma) [III, C].
[c]Not recommended for low-grade pT1 tumours involving only the infrastructure and with negative margins and no other risk factors [IV, E].
[d]IMRT [IV, A].
[e]Post-operative CRT with platinum-based agents may be considered in high-grade and/or poorly differentiated tumours [IV, C].
[f]Through contrast-enhanced locoregional imaging (i.e. CT or MRI) at the latest after two cycles.
[g]IMRT [IV, A] or IMPT [II, B].

Reirradiation (reRT) by IMRT or IMPT should be considered for local and/or regional recurrences not amenable to surgery and could be considered as adjuvant therapy after salvage surgery, especially when the interval is long and the volume is limited. ReRT survival benefit and locoregional control are unclear; it remains undefined whether it outweighs potential side-effects, some of which may be life-threatening. As part of the primary RT plan, and before recommending reRT, several disease- and patient-related factors need to be considered, e.g. dose distribution towards the target and critical structures.

At present, no evidence supports the use of ChT concomitant to reRT due to the expected additional toxicities.

See Supplementary Material Section 3, available at https://doi.org/10.1016/j.esmoop.2024.104121, for additional details. Figure 2 depicts the treatment algorithm for local or regional recurrence.

Recommendations

- For local and/or regional recurrences, surgery should be considered, especially when post-operative reRT is feasible [IV, A].
- ReRT could be considered for local or regional recurrences not amenable to surgery [IV, B].

MANAGEMENT OF METASTATIC DISEASE OR RECURRENCES NOT AMENABLE TO CURATIVE APPROACHES

In recurrent SMs that are not amenable to a curative approach, palliative options have to be considered.[101] The

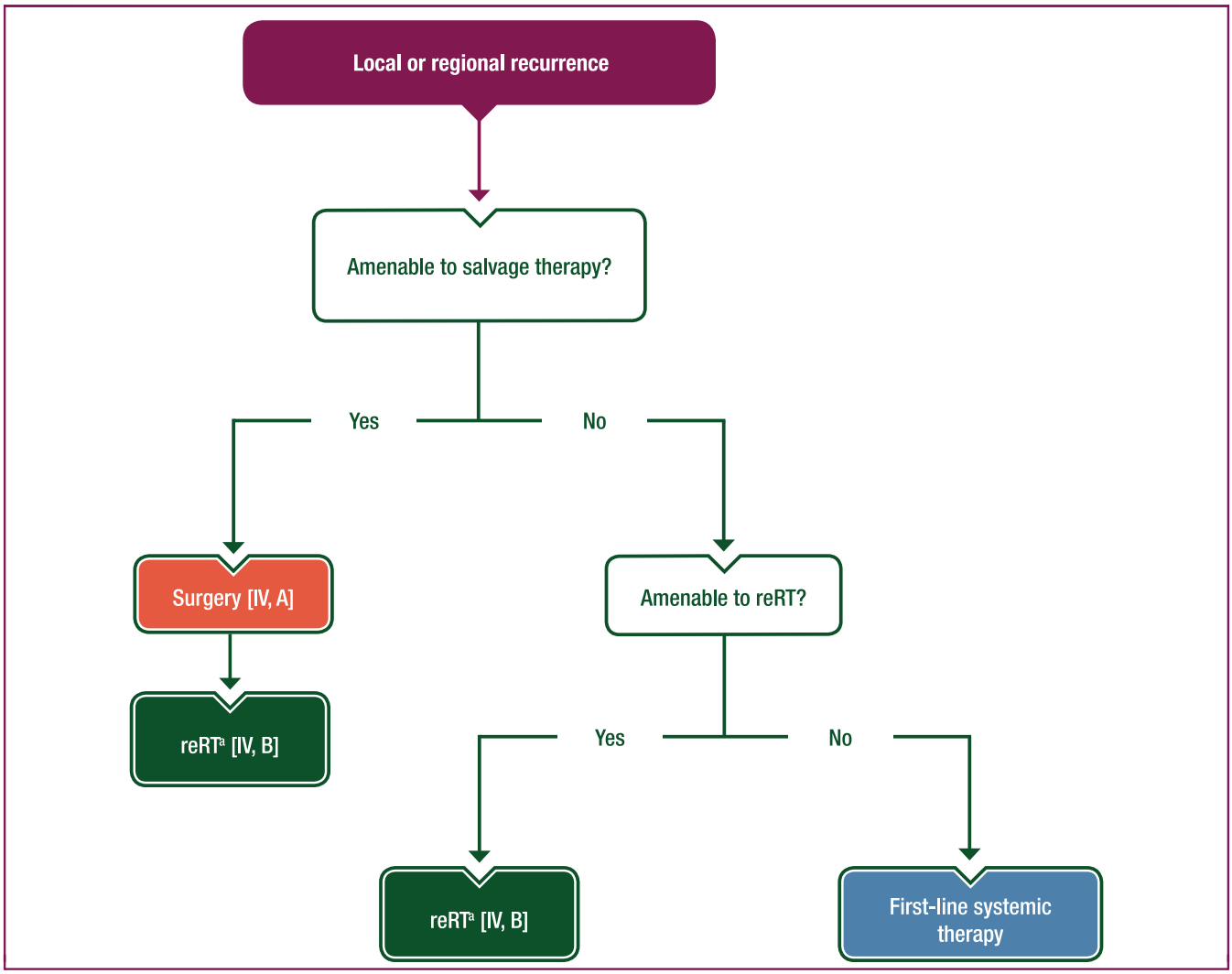

Figure 2. Management of local or regional recurrence.
Purple: algorithm title; orange: surgery; dark green: radiotherapy; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects.
IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated radiotherapy; reRT, reirradiation.
[a]ReRT with IMRT [IV, A] or IMPT [II, B].

management options and risks should be discussed within an MDT and transparently with the patient, and the option of not carrying out any active treatment beside best supportive care should be part of that discussion.

For isolated, inoperable, local recurrences, palliative surgery can be an option to reduce bleeding or nasal obstruction.[102] The approach should be minimally invasive, preferably endoscopic. When palliative surgery is feasible, it can lead to longer survival compared with palliative ChT.[103]

Palliative ChT options depend on histopathology. Very few studies have focused on nasal cavity and paranasal sinus cancer because of the rarity of the disease. Palliative ChT might lead to a response and increased survival, although prolonged responses are rare and toxicity can be significant. Most often, cisplatin-based ChT is used, sometimes combined with 5-FU, paclitaxel, docetaxel or cetuximab.[104-106] Using different combinations, responses in $<$60% of patients and a median OS $\leq$14.5 months have been achieved.[104-106] Agents with milder toxicity but less activity are carboplatin, methotrexate and capecitabine. In neuroendocrine tumours, etoposide can be added.[105,107]

In 2019, the Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved the programmed cell death protein 1 (PD-1) inhibitor pembrolizumab, alone or in combination with ChT, as first-line treatment for patients with metastatic or unresectable, recurrent HNSCC.[108,109] Patients with sinonasal cancers, however, were not included in the trial and, therefore, data on the use of immune checkpoint inhibitors in sinonasal cancers are unavailable.

Palliative targeted therapy, based on mutational analysis or gene expression profiles, is used in most solid cancers and can lead to responses in sinonasal cancer too.[110] Evidence in this setting, however, is limited to case reports or adopting treatments used in similar cancer types.

Figure 3 depicts the treatment algorithm for metastatic disease.

Recommendations

- The decision of whether a recurrence can be approached with curative intent would be best if made by experts in a multidisciplinary setting [V, C].
- Palliative ChT options can often include cisplatin-based ChT, which could be combined with 5-FU, paclitaxel, docetaxel or cetuximab [IV, B]. In neuroendocrine carcinomas, etoposide can be added [IV, B].
- In cases of *de novo* diagnosis of metastatic disease, local RT on T, N or M lesions following response to first-line therapy could be considered to maximise locoregional control [V, C].

PERSONALISED MEDICINE

All large head and neck cancer studies exclude this rare cancer. Few data are available on druggable targets and/or fusion genes that could support using targeted therapy in routine practice.[111] Determining the molecular profile of patients, however, could lead to their selection for a tumour-agnostic approach.

Histology-specific details are reported in Supplementary Material Section 4, available at https://doi.org/10.1016/j.esmoop.2024.104121.

Recommendations

- Testing for biomarkers or genomic alterations for which targeted therapies are available and approved (microsatellite instability-high/mismatch repair-deficient, tumour mutation burden-high, *NTRK1/2/3* fusions, *RET* fusions, *BRAF* V600E mutations, *FGFR1/2/3* fusions or mutations) may be recommended [IV, C; ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) score: I-C].
- Molecular profile analysis may be carried out to provide access to a tumour-agnostic approach [V, C].

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

Due to the low incidence of SM, an optimal surveillance strategy has not been clearly established. Decisions on monitoring options and frequency of planned examinations should be made by the clinician team and the patient. Follow-up consistent with other head and neck cancers is generally recommended: every 3 months in the first year, every 3-6 months in the second year, every 6-8 months in the third and fourth years and once a year thereafter.

Regular monitoring by an otorhinolaryngologist including endoscopy and imaging methods (preferably MRI) can theoretically improve outcomes of cancer survivors by early detection of recurrence. The combination of endoscopy and imaging, especially MRI, is the preferred modality for the assessment of local recurrence of tumours and can delineate soft tissue, intracranial and perineural spread.[112] Endoscopy identifies superficial lesions with better specificity, but its diagnostic potential is often impaired by abundant, adhesive secretions, which should be regularly removed and prevented with sinonasal washes. MRI provides a better evaluation of individual tissue relationships and has a superior PPV. Thus, MRI is considered an optimal imaging technique for the detection of local recurrence.[113] Baseline examination should be carried out 3-4 months after the completion of treatment.[114] For more advanced T2-T4 tumours, MRI is recommended at 6-month intervals during the first 3 years. PET—CT is not recommended for routine surveillance due to its high false-positivity rate and poor specificity, especially in the early post-treatment period. This modality should be reserved for malignancies with a higher likelihood of distant metastatic spread and in cases of inconsistent local findings.[115]

DFS interval strongly depends on tumour site, histology and perineural, carotid or clival invasion.[116]

In a large retrospective series with a training and validation cohort of 940 and 420 SM patients, respectively, 5-year OS and RFS were 72.7% and 66.4%, respectively, varying considerably with histology.[49]

Surveillance is based on a multidisciplinary approach that involves surgical specialists, both maxillofacial surgeons and otorhinolaryngologists, as well as medical and radiation oncologists. Approximately 75% of patients suffer post-treatment orbital function impairment or loss of vision that requires intervention by an ophthalmologist. The participation of an audiologist in the follow-up care is often necessary due to potential hearing impairments encountered in these patients.[117] The onset of neurological symptoms suggestive of meningitis in patients treated with surgery, including skull base resection and adjuvant RT, should alert clinicians to the possibility of dehiscence/necrosis of the duraplasty.

Comprehensive surveillance should include supportive care provided by psychologists, nutritionists and speech therapists, when clinically indicated. Nutritional support and dietary counselling contribute to long-term benefits of multimodal treatment. Plastic surgeons and restorative dentists should be involved at the beginning of the primary surgical treatment to evaluate the best reconstruction option. Regular QoL assessment and screening for post-treatment side-effects and late toxicities that include depression, cognitive dysfunction, hearing loss, xerostomia, cranial nerve injury, lymphoedema and secondary tumours, should be an integral part of post-treatment clinical surveillance. Patient education on the symptoms indicative of recurrence may contribute to the early diagnosis of relapse. Primary prevention strategies should focus on smoking cessation, avoidance of alcohol consumption and exposure to carcinogenic substances (wood or leather dust, formaldehyde, welding fumes, arsenic, nickel or chromium compounds), as well as promotion of a healthy lifestyle and dietary habits. Patients should be directed to relevant patient organisations for support and information.

Recommendations

- It is suggested to initiate follow-up planning within 3 months after the end of treatment [V, C].
- It is advisable for the schedule of follow-up visits to be tumour-specific and correspond with the biological behaviour of the malignancy [V, C].

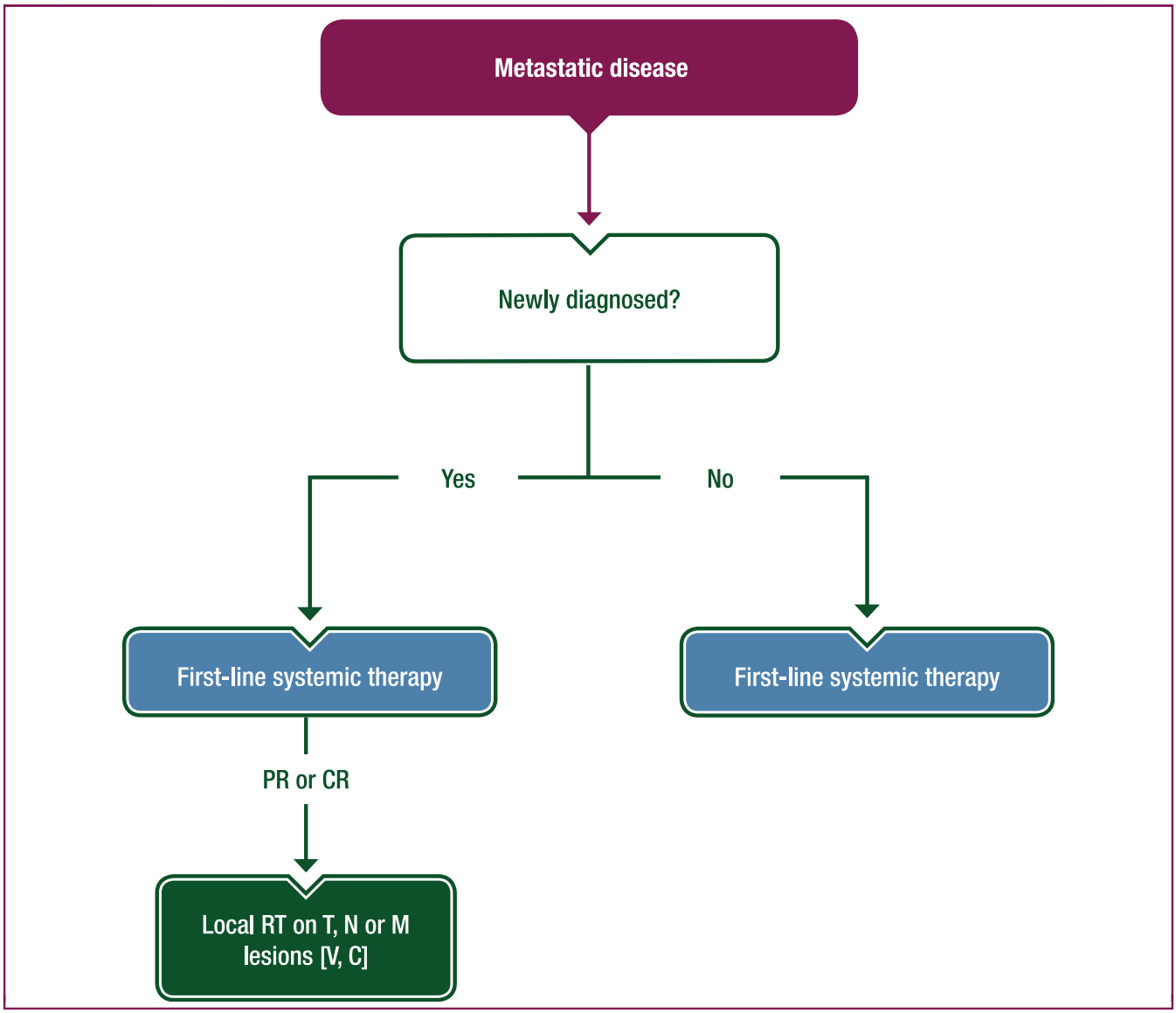

Figure 3. Management of metastatic disease.
Purple: algorithm title; dark green: radiotherapy; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects.
CR, complete response; PR, partial response; RT, radiotherapy.

- The combination of endoscopy and imaging, especially MRI, is the preferred modality for the assessment of local recurrence of tumours [IV, C].
- PET—CT would be best reserved for malignancies with a higher likelihood of distant metastatic spread and in cases of inconsistent local findings, rather than routine surveillance [IV, C].
- For more advanced T2-T4 tumours, MRI could be recommended at 6-month intervals during the first 3 years [V, B].
- A comprehensive monitoring of treatment-induced side-effects is advisable [V, B].
- Patient education on nasal hygiene procedures for preventing or removing nasal crusting is recommended together with periodic debridement of the endoscopic cavity under endoscopic guidance [V, A].
- Thyroid function could be tested once or twice a year using a blood test [V, B].
- Pituitary function monitoring might be considered for relevant clinical disorders and after exposure to RT [V, B].

METHODOLOGY

This CPG was developed in accordance with the ESMO standard operating procedures for CPGs development (https://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. A table of ESCAT scores is included in Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2024.104121. ESCAT scores have been defined and validated by the ESMO Translational Research and Precision Medicine Working Group (TRPM WG).[118,119] The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this CPG. Levels of evidence and grades of recommendation have been applied using the system shown in

Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2024.104121.[120] Statements without grading were considered justified standard clinical practice by the authors. For future updates to this CPG, including eUpdates and Living Guidelines, please see the ESMO Guidelines website: https://www.esmo.org/guidelines/guidelines-by-topic/head-and-neck-cancers.

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