# Sinonasal Undifferentiated Carcinoma

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**Purpose:** The purpose of this paper is to discuss the treatment and outcomes for patients with sinonasal undifferentiated carcinoma.
**Methods:** Review of the pertinent literature.
**Results:** Most series contain a limited number of patients treated with various combinations of surgery, radiotherapy (RT), and chemotherapy. Follow-up periods for disease-free patients are sometimes relatively short. The majority of patients present with locally advanced tumors; 10% to 30% have clinically positive regional nodes. The risk of local–regional recurrence after treatment is probably 20% to 30% or higher, depending on the extent of disease. The likelihood of distant dissemination is approximately 25% to 30% and the cure rate varies from roughly 20% to 50%. Better outcomes are observed in patients treated with craniofacial resection combined with pre- or postoperative RT alone or with adjuvant chemotherapy. This is probably due, in part, to selection bias. Patients with incompletely resectable tumors are best treated with definitive RT and adjuvant chemotherapy.
**Conclusion:** The optimal treatment is craniofacial resection combined with adjuvant RT alone or with chemotherapy. The risk of relapse is relatively high and the probability of cure is modest. Patients with incompletely resectable tumors may sometimes be cured with definitive chemoradiation.

**Key Words:** outcomes, treatment, craniofacial resection, chemoradiation, radiotherapy

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Sinonasal undifferentiated carcinoma is a rare, aggressive malignancy first described by Frierson et al in 1986.[1–3] The etiology is unknown. Sinonasal undifferentiated carcinoma is thought to be a part of the spectrum of neuroendocrine carcinomas that includes esthesioneuroblastoma, neuroendocrine carcinoma, and small cell carcinoma.[4] The prognosis for patients with sinonasal undifferentiated carcinomas is worse than for those with esthesioneuroblastomas, similar to that observed in patients with neuroendocrine carcinomas, and better than the outcomes for patients with small cell carcinomas.[4] Patients are likely to be male; the median age is approximately 50 years with a wide range (Table 1).[4–8] The tumor usually arises in the nasal cavity and is locally advanced when diagnosed.[9] Musy et al[10] reported on 15 patients treated at the University of Virginia (Charlottesville) between 1991 and 2000. Eight patients (53%) had intracranial extension with dural involvement, 6 patients (40%) had periorbital invasion, 5 patients (33%) had orbital invasion, and 5 patients (33%) had extension to the cavernous sinus. Presenting symptoms depend on the primary site and often include epistaxis, bloody rhinorrhea, visual changes, nasal obstruction, headaches, and facial pain.[10] The interval between onset of symptoms and diagnosis is approximately 4 months.[8,10]

Approximately 10% to 30% of patients present with clinically positive cervical lymph nodes.[2,6–8,11] Hematogenous dissemination at diagnosis is unusual. Distant metastases commonly involve the lungs and bone. The tumor may rarely seed the cerebrospinal fluid and "drop metastases" may develop.[3]

## DIAGNOSTIC EVALUATION

A history is obtained and a thorough head and neck examination, including fiberoptic nasopharyngoscopy, is performed. Magnetic resonance imaging (MRI) and computed tomography (CT) are used to assess the extent of the primary tumor; the latter is also used to detect metastases in the cervical lymph nodes. A chest radiograph is obtained to detect pulmonary metastases. Additional studies, such as chest CT or positron emission tomography (PET), may be considered for the patient who presents with advanced regional disease. Patients who present with bone pain should be considered for a bone scan.

## HISTOLOGY

Sinonasal undifferentiated carcinomas are composed of nests, sheets, and trabeculae of small to median sized cells with large, ovoid nuclei.[1,9] The nuclear to cytoplasm ratio is generally high and the tumor cells contain small amounts of eosinophilic cytoplasm.[1,9] The malignancies have a high mitotic rate and exhibit prominent vascular permeation and areas of tumor necrosis.[1]

Immunohistochemical stains are useful to distinguish sinonasal undifferentiated carcinomas from other types of sinonasal neoplasms. Cerilli et al[9] analyzed the immunohistochemical profile in 22 patients with sinonasal undifferenti-

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**TABLE 1.** Patient Characteristics

| Parameter | Series | | | |
|---|---|---|---|---|
| | MDAH[4] | PMCC[6] | U. Cincinnati[7] | U. Florence[8] |
| No. patients | 16 | 10 | 14 | 13 |
| Age (years) | — | Median, 50 | Mean, 54 | — |
| | — | Range, 36–84 | Range, 22–83 | Range, 20–82 |
| M:F ratio | 1:1 | 4:1 | 13:1 | 1.2:1 |
| AJCC T stage | | | | |
| T1 | 0% | 10% | — | — |
| T2 | 12% | 0% | — | — |
| T3 | 19% | 0% | — | — |
| T4 | 69% | 90% | — | — |
| Positive regional nodes | 0% | 30% | 14% | 15% |

MDAH, M. D. Anderson Hospital; PMCC, Peter MacCallum Cancer Centre.

ated carcinomas and found the following positive staining patterns: Ki-67, 21 of 22 (95%); p53, 13 of 22 (59%); CD-99, 3 of 22 (14%); epithelial membrane antigen (EMA), 4 of 22 (18%); and neuron-specific enolase (NSE), 4 of 22 (18%). All 22 tumors stained negatively for chromogranin, synaptophysin, placental alkaline phosphatase (PLAP), carcinoembryonic antigen (CEA), and latent membrane protein-1 (LMP-1).[9]

Franchi et al[12] evaluated the cytokeratin (CK) staining patterns in 6 patients with sinonasal undifferentiated carcinoma, 10 patients with squamous cell carcinomas, 10 patients with nonkeratinizing squamous cell carcinoma, and 5 patients with nasopharyngeal-type undifferentiated carcinomas. Sinonasal undifferentiated carcinomas stained positively for CK8 (6 of 6), CK7 (3 of 6), and CK19 (3 of 6). In contrast, squamous cell carcinomas, nonkeratinizing squamous cell carcinomas, and nasopharyngeal-type undifferentiated carcinomas frequently stained positively for CK5/CK6, CK8, CK13, and CK19. The treatment of sinonasal undifferentiated carcinomas and nasopharyngeal-type undifferentiated carcinomas is significantly different so that it is crucial to make the distinction between the 2 entities.

Epstein-Barr virus (EBV) is often detected in biopsy specimens from patients with undifferentiated nasopharyngeal carcinomas, and it is usually absent in sinonasal undifferentiated carcinomas.[5,13,14]

Jeng et al[5] evaluated the EBV status on biopsy specimens from 36 patients with sinonasal undifferentiated carcinoma and 13 patients with sinonasal nasopharyngeal-type undifferentiated carcinomas via EBER in situ hybridization. None of the 36 patients with sinonasal undifferentiated carcinomas stained positively for EBV versus 13 of 13 (100%) of those with nasopharyngeal-type undifferentiated carcinomas.

## STAGING

Patients are staged according to the American Joint Committee on Cancer (AJCC)[15] staging system (Table 2). Alternatively, patients may be staged according to the Kadish[16] staging system that was originally described for patients with esthesioneuroblastomas (Table 3).

**TABLE 2.** AJCC Definition of TNM: Nasal Cavity and Ethmoid Sinus

| | | | |
|---|---|---|---|
| Primary Tumor (T) | | | |
| T1 | Tumor restricted to any 1 subsite, with or without bony invasion | | |
| T2 | Tumor invading 2 subsites in a single region or extending to involve adjacent region within the nasoethmoidal complex, with or without bony invasion | | |
| T3 | Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate | | |
| T4a | Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses | | |
| T4b | Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than ($V_2$), nasopharynx, or clivus | | |
| Regional lymph nodes (N) | | | |
| NX | Regional lymph nodes cannot be assessed | | |
| N0 | No regional lymph node metastasis | | |
| N1 | Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension | | |
| N2 | Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension | | |
| N2a | Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension | | |
| N2b | Metastasis in multiple ipsilateral lymph nodes, none more that 6 cm in greatest dimension | | |
| N2c | Metastasis in bilateral or contralateral lymph node, none more than 6 cm in greatest dimension | | |
| N3 | Metastasis in a lymph node, more than 6 cm in greatest dimension | | |
| Distant Metastasis (M) | | | |
| MX | Distant metastasis cannot be assessed | | |
| M0 | No distant metastasis | | |
| M1 | Distant metastasis | | |
| Stage Grouping | | | |
| Stage 0 | Tis | N0 | M0 |
| Stage I | T1 | N0 | M0 |
| Stage II | T2 | N0 | M0 |
| Stage III | T3 | N0 | M0 |
| | T1 | N1 | M0 |
| | T2 | N1 | M0 |
| | T3 | N1 | M0 |
| Stage IVA | T4a | N0 | M0 |
| | T4a | N1 | M0 |
| | T1 | N2 | M0 |
| | T2 | N2 | M0 |
| | T3 | N2 | M0 |
| | T4a | N2 | M0 |
| Stage IVB | T4b | Any N | M0 |
| | Any T | N3 | M0 |
| Stage IVC | Any T | Any N | M1 |

From the American Joint Committee on Cancer (2002).[15]

**TABLE 3.** Kadish Staging System

| Stage | Definition |
|---|---|
| A | Tumor confined to the nasal cavity |
| B | Tumor extension beyond the nasal cavity to the paranasal sinuses |
| C | Tumor spread beyond the nasal cavity and paranasal sinuses |

Data from Kadish S, et al.[16]

## TREATMENT

There are 2 treatment alternatives: 1) surgery, which usually entails craniofacial resection and adjuvant RT, and 2) definitive RT. The advantage of surgery and adjuvant RT, which may either be administered pre- or postoperatively, is that local control may be better and the risk of late complications, particularly radiation-induced retinopathy and/or optic neuropathy, may be lower because a lower RT dose may be employed in the adjuvant setting.[17,18] Preoperative RT may render a marginally resectable tumor completely resectable and a lower dose (50–60 Gy) may be used compared with postoperative RT, thus reducing the risk of visual complications. The disadvantage of preoperative RT is that the risk of postoperative complications may be increased. The clinically negative neck should be electively irradiated because of the high risk of regional metastases. Patient with clinically positive lymph nodes at presentation should either undergo a neck dissection and postoperative RT or RT and evaluation for a planned dissection depending on the treatment plan for the primary tumor. Adjuvant chemotherapy should be considered because of the high risk of relapse after surgery, RT alone, or either combination. Based on data from other head and neck sites, it is likely that chemotherapy administered concomitantly with RT is more effective than either induction or maintenance chemotherapy. Chemotherapeutic agents that have been employed include doxorubicin, cyclophosphamide, vinblastine, etoposide, and cisplatin.[6,10,19,20] Some chemotherapeutic agents, such as doxorubicin, may be excessively toxic when administered concomitantly with RT.

## OUTCOMES

Treatment strategies can be broadly stratified into 2 categories: 1) surgery alone or combined with adjuvant RT, chemotherapy, or both; and 2) definitive RT alone or combined with adjuvant chemotherapy. In general, patients treated with definitive RT are more likely to have advanced incompletely resectable tumors and have a worse outcome.[8,19] Low to moderate dose RT and chemotherapy alone are reserved for palliative situations where the likelihood of cure is nil.[8,20] In contrast to patients with esthesioneuroblastomas who may sometimes develop recurrence more than 5 years after treatment, those with sinonasal undifferentiated carcinomas who recur almost always do so within 1 to 2 years.[4]

Treatment outcomes from 4 of the larger series reported in the literature are reported in Table 4.[4,6,7,10] A variable proportion of patients were treated surgically and, often, sites of recurrence were not specified. Rosenthal et al[4] reported on 16 patients treated at the M. D. Anderson Hospital (Houston, TX) between 1982 and 2002 with surgery alone or combined with RT and/or chemotherapy (7 patients), preoperative RT with or without chemotherapy (1 patient), and induction chemotherapy followed by surgery or RT with or without adjuvant chemotherapy (8 patients). The 5-year outcomes for the overall group of patients were as follows: local control, 79%; regional (neck) control, 84%; distant metastasis-free survival, 75%; and overall survival, 63% (Table 4). Kim et al[21] reported on 8 patients treated at University of California at Los Angeles between 1995 and 2002. Five patients were treated with surgery alone (1 patient), surgery and RT (2 patients), or surgery combined with chemoradiation (2 patients); local–regional control was obtained in 1 patient. Three of 8 patients were treated with RT and fluorouracil-cisplatin; local–regional control was obtained in 2 of 3 patients. Overall, 3 of 8 patients were local–regionally controlled after treatment, 4 patients developed distant metasta-

**TABLE 4.** Treatment Outcomes

| | Series | | | |
|---|---|---|---|---|
| **Outcome** | **MDAH[4]** | **U. Cincinnati[7]** | **U. Virginia[10]** | **PMCC[6]** |
| No. patients | 16 | 14 | 20 | 10 |
| Percent treated surgically | 63% | 64% | 55% | 20% |
| Local control | 79% (5 y)* | — | — | — |
| Regional control | 84% (5 y)* | — | — | — |
| Distant metastasis-free survival | 75% (5 y)* | — | — | — |
| Alive, disease-free | — | 36% (3–195 mo) | 20% (24–164 mo) | 50% (8–62 mo) |
| Alive with disease | — | 0% | 15% | 10% |
| Dead with disease | — | 50% | 65% | 40% |
| Dead, intercurrent disease | — | 14% (24–34 mo) | 0% | 0% |
| Overall survival | 63% (5 y)* | 36% | 20% | 50% |

*Outcomes are expressed as crude percentages unless otherwise indicated. Follow-up intervals are indicated in parentheses. Five-year outcomes are calculated by Kaplan-Meier product-limit method.[24]

MDAH, M. D. Anderson Hospital; mo, months; PMCC, Peter MacCallum Cancer Centre; y, years.

ses, 2 of 8 patients were alive and disease-free at 14 months and 15 months, and 6 of 8 patients were either alive with disease or dead with disease.

Gorelick et al[22] reported on 4 patients treated at the University of Michigan with craniofacial resection and postoperative RT combined with concomitant chemotherapy. Chemotherapeutic regimens included etoposide and cisplatin (2 patients), etoposide and carboplatin (1 patient), and cisplatin (1 patient). One patient developed a local recurrence, 1 patient relapsed with seeding of the cerebrospinal fluid, and 2 patients developed distant metastases. Overall, 1 patient was alive with disease at 27 months, and 3 patients died with disease from 5 months to 2 years after treatment. Smith et al[11] reported on 6 patients treated with surgery and postoperative RT at the Mount Sinai Medical Center (New York, NY); 2 patients remained disease-free at 6 months and 18 months, 3 patients were alive with disease from 6 months to 21 months, and 1 patient died with disease 10 months after treatment.

Musy et al[10] reported on 20 patients treated at the University of Virginia between 1986 and 2000; 1 patient was referred after failing treatment elsewhere and the remainder were initially treated at the authors' institution. Four patients had Kadish stage B tumors and 16 patients had Kadish stage C neoplasms. The preferred treatment was induction chemotherapy (cyclophosphamide, doxorubicin, and vincristine, or etoposide and cisplatin) followed by preoperative RT and craniofacial resection. Patients who were in poor health, had advanced disease, or both, were less likely to be treated surgically. Ten of the 19 patients treated initially at the University of Virginia underwent an operation and, in all cases, the surgical procedure was a craniofacial resection. The 2-year survival rate was 64% for the 10 patients who were treated surgically compared with 25% for the 9 patients who did not undergo resection ($P = 0.076$). Overall, 4 patients remained alive and disease-free at 24 months, 36 months, 49 months, and 164 months.

Rischin et al[6] reported on 10 patients treated between 1990 and 2002 at the Peter MacCallum Cancer Centre (Melbourne, Australia). One patient with a T1N0 tumor was treated with RT alone and was alive and disease-free at 62 months. Two patients with T4N0 cancers underwent surgery and postoperative RT; both developed a local–regional recurrence with distant metastases and died with disease. Seven patients (T4N0, 4 patients; T4N1, 1 patient; T4N2C, 2 patients) were treated with definitive RT and chemotherapy; local–regional control was achieved in 4 of 7 patients. Two of 7 patients died with disease, 1 patient was alive with disease, and 4 patients were alive and disease-free at 8 months, 10 months, 28 months, and 62 months after treatment. For the 7 patients treated with definitive RT and chemotherapy, the 2-year progression-free survival rate was 43% and the 2-year overall survival rate was 64%.

Kramer et al[23] reported on 4 patients treated at the University of British Columbia (Vancouver, Canada) between 1986 and 2001 with craniofacial resection and postoperative RT (1 patient) and definitive RT and chemotherapy (3 patients). One patient in the latter group failed in the neck at 19 months and was successfully salvaged. All 4 patients remained alive and disease-free at 27 months, 41 months, 66 months, and 70 months after treatment.

## CONCLUSION

Sinonasal undifferentiated carcinoma is a rare malignancy with a poor prognosis. The likelihood of local–regional, distant relapse, or both, after any treatment strategy is relatively high. The probability of cure after surgery and postoperative RT or definitive RT and chemotherapy is probably similar. Our preference is to treat patients with apparently resectable tumors with craniofacial resection and postoperative RT. The postoperative dose ranges from 64.8 to 74.4 Gy depending on the surgical margins, RT is administered 1.2 Gy per fraction twice daily to reduce the risk of visual complications. Alternatively, patients may be irradiated preoperatively (50–60 Gy) followed by surgery. Patients should be considered for adjuvant chemotherapy administered concomitantly with RT. Those with unresectable, potentially curable cancers are treated with definitive RT (74.4 Gy) and concomitant chemotherapy. Our current practice is to administer cisplatin 30 mg/m$^2$ per week during the RT course. The disadvantage of definitive RT is that the local control rate may not be as high, and there is a higher risk of late complications, particularly radiation-induced retinopathy and optic neuropathy, associated with higher doses of RT.[17,18] The clinically negative neck is electively irradiated in all patients. Heavy particle RT, using protons or carbon ions, may be used to reduce the dose to adjacent normal tissues and thus further reduce the risk of late complications.

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