Nasopharyngeal carcinoma: A medical oncology viewpoint. 
The Gustave Roussy experience

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Key words: chemotherapy, Epstein-Barr Virus, nasopharynx, radiotherapy, staging classification, undifferentiated carcinoma

Nasopharyngeal carcinoma (NPC) is a clinical entity different from other epidermoid carcinomas of the head and neck. It is distinguished by its particular histology, first described by Schmincke (1) and Regaud (2), its geographic distribution, its relationship to Epstein-Barr Virus (EBV), its natural history, and the absence of an alcohol or tobacco etiological relationship. NPC is one of the most aggressive tumors of the head and neck, with a very high rate of systemic dissemination. It is a very radiosensitive tumor, and radiotherapy provides excellent local control in approximately 90% of cases. The reported 5-year survival rates vary from 15% to 50%, with more than 65% of patients dying with or of metastatic spread. This tumor is also very chemo-sensitive and the relatively rapid appearance of metastases has led to a reappraisal of the use of chemotherapy in its management.

After examining the current knowledge about NPC, this review will present the recent experience of the Institute Gustave Roussy.

Epidemiology

NPC has a peculiar geographic distribution with a specific predilection for the southeastern provinces of China, the Philippines, Malaysia, Greenland, North Africa and the Mediterranean basin, although it has also been frequently described in the Caribbean, Black Africa and Saudi Arabia [5, 6, 12, 20, 48, 49]. South China has the highest incidence (30-80/100,000/year), followed by North Africa (8-12/100,000/year), where the undifferentiated type, strictly linked to the EBV, is predominant (90%). NPC is rare (1/100,000) in occidental countries except for areas with immigrants from endemic areas and the Mediterranean basin [20, 62]. NPC occurs most frequently in males, with a 2 to 4/1 sex ratio. This is in contrast to the 9/1 ratio for squamous head and neck cancer of all other sites. Undifferentiated carcinoma of the nasopharyngeal type (UCNT) is found in all age groups, with a bimodal age distribution in endemic areas, (15 to 25 years and 40 to 60 years), with 20% under 25 years [5, 6, 26, 61]. In Chinese series the predominant age is 40 to 60 years [5, 6, 61].

Etiological factors

Clinical and experimental data suggest EBV as an etiological agent for NPC. The main argument is the detection of the EBV genome in the epithelial tumor cells [20] and the characteristic EBV antibody pattern.

Many studies have looked for environmental factors in NPC etiology. Some studies have focused on the ingestion of salted foods (fish, vegetables), which are suggested as an important factor among Chinese, Eskimos and North Africans. The Chinese case control studies show a dose-response relationship between salted fish consumption and the incidence of NPC [14, 15, 16]. Experimental data show that large amounts of nitrates which are converted to carcinogenic nitrosamine in salted foods produce adenocarcinoma and undifferentiated carcinoma of the nasal and paranasal sinus cavities in rats [16].

Pathology

NPC is an epidermoid-cell-lineage carcinoma of the head and neck with a variety of morphological degrees of differentiation, which has led to controversy concerning its histological classification. The WHO [25] recognizes three types: well-differentiated, poorly-differentiated, and undifferentiated epidermoid carcinomas, depending on the quantitative presence of squamous differentiation. The Micheau classification [27] is based on two histological types: well-differentiated and undifferentiated or poorly-differentiated carcinoma. The undifferentiated type (UCNT) is the most frequent in the nasopharynx, especially in endemic areas,
where it represents more than 90% of the cases seen. These tumors are characterized by monomorphic cells [26], often with a syncytium-like aspect. Nuclei are clear with a large nucleolus and evident nuclear membrane. Cytoplasm is scanty, and the stroma is very rich in lymphocytes. According to the tumor cell’s aspect, Micheau recognizes three subtypes of UCNT: the Regaud-Reverchon type with syncytial-like aggregation, the Schmincke-lymphoepithelioma with prominent lymphoid stroma; and the spindle-cell carcinoma (Micheau), characterized by fusiform elongated cells with a sarcomatoid aspect [27].

Immunohistochemical studies have proven helpful in separating the very undifferentiated cases from non-Hodgkin’s lymphomas of the same area [28, 29].

The main controversy concerns the intermediate type (non-keratinizing) of the WHO classification, which is generally included in the Micheau classification for UCNT [25]. Non-keratinizing epidermoid carcinoma showing unusual differentiation on electronic microscopy falls within the NPC diagnosis. The neoplastic cells have fairly well defined cell margins with a paved aspect. There is no evidence of mucine production or glandular differentiation [25, 27, 28]. In contrast, typical keratinizing squamous cell carcinoma shows clear evidence of squamous differentiation with intercellular bridges and pearl-like terminal keratinization [25, 27].

Serological findings

One of the most fascinating aspects of NPC is its serological and biological link with EBV, first established by Old [13].

The characteristic EBV serologic profile in NPC is well established [19, 20, 28]. It consists of an elevation of IgA and IgG anti Viral Capsid antigen (VCA), Early antigen (EA)- and EBV-associated nuclear antigens (EBNA). IgA anti EA seems to be specific for early detection of NPC in high-risk patients (title £ 1/10) and also for this pathology [16, 19]. IgG anti VCA and EA levels may be related to tumor volume [18]. Follow-up serology, however, is not a good marker for cure, since many patients without evidence of disease continue to have elevated serologic levels after successful treatment [18, 30].

A recent review of the serology in suspected EBV-related epithelial cancers [31, 32] also addresses the issue of salivary gland lymphoepithelioma (eskimoma) [31, 32, 35, 36], and argues for a similarity and/or a relationship of tumors with a comparable histopathological picture and natural history or geographical distribution [32]. A slowly growing body of evidence indicates the existence of EBV-related undifferentiated carcinomas in other localizations such as larynx [46], parotid [41], tonsil [45], thymus [39], and lung [47]. The presence of the EBV genome in NPC cells was long believed to bear a direct relationship to the pathogenesis of the tumor [20, 31]. It is now known that the pharyngeal mucosa of the Waldeyer ring is the primary EBV infection site [34], and that EBV genome can be detected in normal nasopharyngeal mucosa. The quantity of EBV genome in carcinoma cells seems to be inversely proportional to the amount of epidermoid differentiation [33]. Furthermore, the same surface receptors for EBV virus found in B lymphocytes are present in nasopharyngeal epithelial cells [21]. This raises further questions concerning the possible relationship of NPC to EBV-related haematologic malignancies [35–36, 40, 42, 44].

<table>
<thead>
<tr>
<th>Table 1. TNM classifications.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNM HO 1970</td>
</tr>
<tr>
<td>Tx</td>
</tr>
<tr>
<td>T0</td>
</tr>
<tr>
<td>T1 Confined to NP</td>
</tr>
<tr>
<td>T2 T extended to nasal fossa,</td>
</tr>
<tr>
<td>T3 T extended below T2</td>
</tr>
<tr>
<td>T4</td>
</tr>
<tr>
<td>N0 No palpable node</td>
</tr>
<tr>
<td>N1 Upper cervical nodes*</td>
</tr>
<tr>
<td>N2 Lower cervical nodes**</td>
</tr>
<tr>
<td>N3 Supra clavicular nodes</td>
</tr>
<tr>
<td>N4 Skin involvement above</td>
</tr>
<tr>
<td>N5 Clavicles</td>
</tr>
<tr>
<td>Mx</td>
</tr>
<tr>
<td>M0 No distant metastasis</td>
</tr>
<tr>
<td>M1 Metastasis and/or</td>
</tr>
<tr>
<td>N6 Metastasis and/or</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>** Limited below by the neck crease extending laterally and backward from, or just below, the thyroid notch.</td>
</tr>
<tr>
<td># Limited below by a line joining the upper margin of the sternal end of the clavicle and the apex of an angle formed by the lateral surface of the neck and the superior margin of the trapezius.</td>
</tr>
</tbody>
</table>

Note: M0 = no distant metastasis; M1 = distant metastasis; N0 = no palpable node; N1 = single, homolateral; N2 = multiple, homolateral; N3 = ipsilateral; N4 = bilateral.

Staging

Different staging systems have been developed over the years [52–57].

The most important staging systems are those of HO [52], KYOTO [55] and the TNM-classification proposed by the UICC and the American Joint Committee in 1986. The first two are based on the topographic extent of the disease, whereas the latter considers the volume of the disease to be the main prognostic factor (Table 1). The TNM classification [57] is probably more appropriate since it incorporates new imaging techniques and recognizes the merit of the CTscan [60].

The role of staging will probably be changed by therapeutic advances and newly discovered prognostic factors. Two such models have already been proposed by Neel et al. [58] and the NCI Milan [59].
Treatment

Radiation therapy

Radiation therapy is the classical treatment for this disease. Radiation treatments normally employ two parallel lateral opposed fields for the nasopharynx, base of the skull, middle ear, and posterior cervical chains. Anterior fields are used for lower and supraclavicular cervical lymph nodes [4, 10] with an adjunctive anterior nasal field for facial or ethmoidal extensions [5, 63, 64]. The usual dose schedule is 1, 8 to 2 Gys/day, 5 days/week. The usual dose delivered to the primary tumor is 55–75 Gy: clinically-positive lymph node-bearing areas above the clavicle receive 60 Gy and negative necks are treated with 50 Gy [10, 11]. The tumor is highly radiosensitive, but its radioresistance is dependent upon tumor volume and delivered dose. Less than 50 Gy to the nasopharynx result in a significant percentage of tumor persistence and recurrence [7, 9, 65].

Radiation therapy is performed according to the logistical and technical possibilities of the treating centers in high-incidence areas (China, North Africa).

There is a 70%-90% definitive locoregional control with appropriate sources, doses, and techniques. Treatment-related, acute and chronic side effects are often important (77–78), especially in the youngest patients [67] or when the dose per fraction increases (78). Several published pediatric series [69, 75] suggest the use of lower doses (55-65 Gy) in the hope of bestowing the same locoregional control with fewer long-term complications. Hyperfractionation seems to be better than normal fractionation in the hands of C.C. Wang [79], who has the only meaningful series with this treatment modality in NPC.

Chemotherapy

The use of systemic cytotoxics is not a novelty in the management of NPC, especially in the UCNT variety. Until recently, however, series were scattered, non-homogeneous, and mostly based on adjuvant treatments. Methodologically acceptable single-agent Phase II data are not available but some extrapolations with regard to single-agent activity can be made. Adriamycin [86, 87], CDDP [6, 87, 88], and bleomycin [87, 89] seem to be active agents. Vinca alcaloids, methotrexate and 5FU seem to be somewhat less active [87, 89]. Alkylating agents produce short-lived responses [87, 90, 91] and their use has recently been discontinued, epirubicin has been used in the Far East [92, 93] with apparently good antitumor activity.

We have reviewed the available adult and pediatric literature. Proper analysis is hampered by a mixture of histological types (squamous NPC and UCNT), an absence of detailed staging information and variations in the use of chemotherapy (concomitantly with radiation, adjuvant post-radiation, neoadjuvant chemotherapy) [68, 69, 95–107]. Asiatic series are large in number, but lack detailed information about work-up and staging. Western series are much smaller and are generally the result of retrospective analyses over many years. Therefore, although providing more detailed data, they fail to provide definite conclusions about a possible therapeutic gain.

There are only a few reports from studies based on a homogeneous approach and a sufficient number of patients. Their conclusions can be summarized as follows:

a) The Milan trial [96] and the Princess Margaret [69] series show no advantage for adjuvant chemotherapy. The evaluation of the former, however, is hampered by inadequate drug doses, compliance and evaluability problems. Tannock's acute analysis [69] represents a comparison between a retrospective analysis and a historical control. His caution against premature optimism should nevertheless be heeded.

b) The Quebec experience [107] showed no increase in survival rate with chemoradiotherapy, but their chemotherapy does not encompass the most active drugs in NPC, and furthermore, only one course was given.

c) The Taiwan experience seems somewhat more positive [102]. Huang et al. [102] have clearly adopted the neoadjuvant approach, and find evidence of its superiority over his own historical controls. He reports a 64% 5-year survival rate in N2c-N3 patients treated with chemotherapy (cyclophosphamide, methotrexate, bleomycin, CDDP) versus 49% treated with radiation only.

d) The pediatric literature allows a more optimistic viewpoint. Recent publications have reported that adjuvant and neoadjuvant chemotherapy increased long-term survival as compared with historical controls [68, 104]. Moreover, in cases of a complete response to chemotherapy, smaller radiation doses became possible with good local control [68, 101].

e) Recently published American experiences seem to favor neoadjuvant chemotherapy to increase the percentage of rapid response [100, 106] and of disease-free long-term survivors [103, 115].

In summary, there is a dearth of meaningful prospectively controlled trials and they are badly needed to test the real efficacy of chemotherapy in the treatment of this tumor, which seems to be even more chemo-sensitive than the rest of the neoplasms of the head-and-neck region.

Institute Gustave Roussy experience

The increased incidence of systemic metastatic disease in NPC as compared to other head and neck malignancies was already perceived a few years ago [48, 51, 76]. While in the squamous (WHO 1) variety this could be partly attributed to the higher proportion of advanced locoregional stages at presentation, in the undifferentiated tumors (UCNT) the proportion was even greater. There are four published autopsy series [48, 50, 76, 81], with an overall metastatic incidence of 87%. Bone, lung and liver are the most common sites.

We did thorough work-ups on, and closely followed the last 110 recurrent and/or metastatic patients with NPC who were seen at the Institute Gustave Roussy (IGR) from October 1985 to July 1989 to establish a natural history data
been recently described by our group and are present in metastasis. Hypertropic osteoarthropathy has been described [84], usually associated with pulmonary or hilar disease. This intensive work-up and regular follow-up have prompted the following observations:

a) The metastatic incidence is clearly related to nodal status. Our own data show that an intensive work-up in N3 (UICC-AJC 1986) patients will yield 40% of asymptomatic metastatic disease [82]. More than 90% of N3 patients die with metastatic disease. Metastatic spread, however, may be discovered by appropriate work-up in all clinical stages of disease.

b) The natural history of progressive disease is short, with most metastases (78%) being diagnosed within 18 months after the appearance of the first symptoms of primary tumor. Thirty-one patients had local recurrence and metastatic disease (28%), while metastasis without local recurrence developed in 60 patients (54%). Only 19 patients had local recurrence without concomitant metastatic disease (17%). We therefore believe that patients with local recurrence should be aggressively managed [116, 117, 118].

c) Bone marrow invasion, which was not previously described, is common (23%) and linked to bone metastasis [83, 85]. It is a sign of poor prognosis and widespread disease.

d) Liver metastases (diagnosed in 30% of cases) are initially clinically and biochemically silent. Generally they can be detected easily by echography. They also represent a poor-prognosis factor.

e) Bone metastasis is the most common site in NPC, with a 63% incidence in our series [50, 109, 110]. It can be clinically indolent in about 20% of patients. In these cases the metastatic pattern is exclusively osseous. Patients with a few isolated bone metastases (12% of cases in our series) constitute a good-prognosis group when chemotherapy and radiotherapy are used concomitantly.

f) Lung metastases (20%) may sometimes have a slow evolution. They have been frequently associated with the Pierre-Marie syndrome.

g) Nodal recurrences are rare, and tend to occur subcutaneously and to show a diffuse skin infiltration. They are particularly difficult to treat and respond poorly to chemotherapy and/or irradiation.

h) T stage has little correlation with metastatic potential, but determines local evolution. In cases of significant bone erosion of the base of the skull (T4) or of bulky tumor the disease is difficult to control, even with a high dose of radiation.

i) Several paraneoplastic syndromes are associated with this disease. Hypertropic osteoarthropathy has been described [84], usually associated with pulmonary or hilar metastasis.

j) Leukemoid reaction and tumor-specific fever have been recently described by our group and are present in 15%-20% of high tumor volume cases [85].

Chemotherapy for metastatic and recurrent disease

It has been recognized for more than 20 years that this tumor is chemo-sensitive. However, systematic trials have only recently been carried out due to the lack of resources in the countries where UCNT is prevalent and the limited involvement thus far by medical oncologists. That there were a number of scattered long-term survivors after chemotherapy for metastatic disease was already known [66, 74]. In our institution we found three such cases out of several hundred patients treated over a 15-year period (1970-1985). In a first step we decided to treat recurrent or metastatic disease by the same chemotherapy protocol.

Our first protocol, PBF (between October 1985 and December 1986) [109] consisted of CDDP 100 mg/m² D1, bleomycin 15 mg i.v. push + 16 mg/m² D by continuous i.v. for 5 days, and 5FU 650 mg/m²/D x 5 days by continuous i.v. The treatment was repeated every 4 weeks for 3 cycles. Encouraged by Phase II data [92, 93] from Singapore and Hong Kong, in the second protocol (BEC) (from January 1987 till August 1989) we substituted 5FU for epirubicin 80 mg/m² D1 and shortened the interval between cycles to 3 weeks.

Table 2. Patient characteristics in patients with metastatic UCNT treated with PBF and BEC.

<table>
<thead>
<tr>
<th>Chemotherapy regimen</th>
<th>PBF</th>
<th>BEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>49</td>
<td>51</td>
</tr>
<tr>
<td>Sex</td>
<td>36M/13F</td>
<td>38M/13F</td>
</tr>
<tr>
<td>Median age</td>
<td>37.7 (16-61)</td>
<td>36 (16-77)</td>
</tr>
<tr>
<td>Previous chemotherapy</td>
<td>15/49</td>
<td>27/51</td>
</tr>
<tr>
<td>Bone metastasis</td>
<td>37/49</td>
<td>28/51</td>
</tr>
<tr>
<td>Bone marrow metastasis</td>
<td>12/49</td>
<td>8/51</td>
</tr>
<tr>
<td>Lung metastasis</td>
<td>10/49</td>
<td>13/51</td>
</tr>
<tr>
<td>Liver metastasis</td>
<td>11/49</td>
<td>16/51</td>
</tr>
<tr>
<td>Extra regional metastatic lymph nodes</td>
<td>10/49</td>
<td>9/51</td>
</tr>
</tbody>
</table>

PBF: cisplatin, bleomycin and 5-fluorouracil combination chemotherapy.
BEC: bleomycin, 4-epidoxorubicin (epirubicin) and cisplatin.

In the PBF regimen chemotherapy was given for 3 cycles, whereas in the BEC protocol 6 cycles were given, the last 3 without bleomycin. All patients received a complete pretherapeutic work-up and response was assessed after the third cycle. Patient characteristics (Table 2) show that in the BEC protocol there were more pretreated patients and somewhat more visceral and less bone metas-
tasis than in the PBF protocol. The results of the two studies are comparable, with an 80% overall response rate (Table 3). CR was obtained in 20% of the patients on the PBF regimen: most of these had less than three bone metastatic sites, and they received a consolidation treatment with radiation flashes (13-26 Gy) in two to four sessions. In the BEC regimen there were only 13% CRs, three of them in patients with liver metastasis. The responses lasted 3 to 12 months. There was moderate hematologic toxicity in the BEC regimen with some grade 3 episodes lasting an average of 3 to 4 days. Two patients died after grade 4 toxicity. Five of the nine CRs obtained in our first protocol are still NED 34 to 40 months after treatment [110]. As of August 1989, 14 patients treated by the BEC regimen are alive: 5 are NED, 4 stable following PR without further treatment after 9, 9, 10 and 11 months, and 5 are alive with disease. The existence of at least a few long-term disease-free survivors with prior metastatic disease [108] is, in our opinion, a significant indicator of the curability of the disease.

Table 3. Results of chemotherapy in patients with metastatic UCNT.

<table>
<thead>
<tr>
<th>Chemotherapy regimen</th>
<th>Number of patients</th>
<th>Evaluable patients</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>Alive (%)</th>
<th>NED (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBF</td>
<td>49</td>
<td>49</td>
<td>9/49 (20%)</td>
<td>30/49 (60%)</td>
<td>5/49 (24+ - 40+)</td>
<td>5/49</td>
</tr>
<tr>
<td>BEC</td>
<td>51</td>
<td>47</td>
<td>7/47 (13%)</td>
<td>33/47 (65%)</td>
<td>14/47 (14+ - 20+)</td>
<td>5/47</td>
</tr>
</tbody>
</table>

* 2 Dead of Treatment (DOT), 2 Treatment Refusals.

PBF: cisplatin, bleomycin and 5-fluorouracil combination chemotherapy.
BEC: bleomycin, 4-epidoxorubicin (epirubicin) and cisplatin.

Adjuvant chemotherapy

From January 1983 to December 1984, in a first experience we treated 38 patients (group A) with a non-metastatic UCNT with a sequential combination of radiotherapy and chemotherapy [94]. Radiotherapy consisted of 70 Gy/7 weeks on the tumor, 65 Gy/5 weeks to the node-positive areas, and 50 Gy in clinically-negative necks. Chemotherapy was started 3 weeks after completion of radiation. The protocol consisted of the combination of cisplatinum 150 mg i.v. continuous perfusion, doxorubicin 40 mg i.v.D, and vindesin 2 mg i.v., on day 1, bleomycin 15 mg on day 1 and day 2, and cyclophosphamide 300 mg day 1, 2, 3 and 4 i.v., given monthly for a maximum of 6 cycles.

We compared the results of this group of patients with a simultaneously treated group of 38 patients with the same TNM characteristics, who received radiotherapy only during the same period (simultaneous, group B). A comparison with a matched historical group seen between 1979 and 1981 and treated by radiotherapy only (historical, group C) as well as comparison with group B, shows more disease-free survivors and a decrease in the percentage of later metastatic spread in the patients (group A) receiving the sequential combination of radio- and chemotherapy.

These data are, however, to be taken cautiously. Not only is the study not randomized, but many other factors (sub-optimal staging procedures and chemotherapy regimen, long delay before start of chemotherapy) may have influenced the outcome.

Neo-adjuvant chemotherapy

The efficacy of the PBF chemotherapy in patients with metastatic UCNT encouraged us to use the same combination in a neo-adjuvant approach in patients with locoregionally advanced disease. We have treated only patients with nodal staging greater than or equal to N2c (UICC, AJC 1986), since the main prognostic factor is the nodal status.

So far we have used 2 different schemes of alternating radiotherapy and chemotherapy (Fig. 1) in patients with locoregionally advanced UCNT [2] after an extensive negative work-up. The first protocol was initiated with two cycles of PBF given 4 weeks apart. The third cycle of chemotherapy was then administered in the interval between 2 series of locoregional radiotherapy of 35 Gy given over a 3 1/2 week period. Our second-generation program replaced 5FU with epirubicin and radiotherapy was given after the end of chemotherapy (Fig. 1). Three cycles of chemotherapy are given every 3 weeks and the locoregional radiotherapy is started 2 weeks after the third cycle of chemotherapy, with 70 Gy given in 7 weeks at 5 fractions of 2 Gy/week.

PBF/alternated RT

Between February 1986 and October 1987, we treated 30 consecutive patients with locoregionally advanced non-metastatic disease (Table 4) with an alternating PBF regimen. All of the patients had a nodal status greater than or equal to N2c (UICC-AJC 86), 18 patients had nodes equal or greater than 8 cm in diameter, and paraneoplastic symptoms were found in 7 patients. This treatment met with a good general overall tolerance. A total of 89 cycles were given. Substantial nausea and vomiting were common despite an antiemetic treatment. There was a very good

Table 3. Results of chemotherapy in patients with metastatic UCNT.
hematologic tolerance with only one Grade 3 toxicity episode. At the end of radiotherapy, all of the patients had Grade 3 mucositis. Sixteen patients had reversible 10% weight losses and 1 patients had 5FU angor. One patient had a sub-clinical pulmonary function disorder. Six months after treatment one patient had post-radiation myelitis and there was one bilateral lower jaw osteoradionecrosis secondary to a surgical attempt to improve trismus. Another patient had late deafness. After the second chemotherapy cycle and before radiotherapy all of the patients were evaluated with an ENT exam and CTscan. Of the 30 patients in the protocol, one was non-evaluable (he refused treatment after the first cycle of chemotherapy) and 29 were evaluable. There were 3 CR, (confirmed by biopsy) and 22 PR (83% objective responses), with 2 minor responses and 2 patients with progressive disease (Table 5). Two months after radiotherapy another work-up was done on the 28 evaluable patients: one patient with a partial response died of Leriche syndrome before RT, one patient developed liver metastasis at the end of treatment, and another had a very large unsterilized tumor (bulky T4). Twenty-five patients had local control or complete response (83%).

The current status (December 1989) of the 30 patients entered in the protocol: 28 were appropriately treated, 19 are still alive, 2 with metastasis and 17 disease-free (two had isolated metastases managed by salvage treatment). The mean follow-up is 34 months with a minimum of 27 months and a maximum of 46 months. The current overall survival rate is 63% and disease-free survival is 56% [112].

**BEC regimen**

From January 1987 until August 1989, 51 consecutive previously untreated patients (Table 4) with negative metastatic work-up, were treated by the BEC protocol followed by radiotherapy. Eighty-four percent of the patients had a nodal status greater than or equal to N2c (UICC/AJCC 1986 classification). Toxicity was well tolerated in the 152 cycles of chemotherapy given. Hematologic toxicity (WHO 3-4), with a brief duration of 3 to 4 days, was seen in 16 patients, generally after the third cycle. All of the patients had Grade 3 mucositis at the end of radiotherapy. One patient had non-symptomatic pulmonary toxicity after 2 cycles. One year after treatment one patient had a secondary osteoradionecrosis.

Chemotherapeutic activity was evaluated by ENT exam and CTscan after the third cycle and before radiotherapy. This showed 32/51 patients (63%) with complete response, and 18/51 with good partial responses (more than 80% decrease in measurable disease) for an overall 98% objective response rate (Table 5). One patient had a minor response [113]. Two months after radiotherapy another evaluation was done. Two patients had died of treatment-related causes before completion of radiotherapy. Forty-nine patients were complete responders after sequential treatment.

**Table 4. Patient characteristics in locally advanced UCNT.**

<table>
<thead>
<tr>
<th>Chemotherapy regimen</th>
<th>PBF</th>
<th>BEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>30</td>
<td>51</td>
</tr>
<tr>
<td>Sex M/F</td>
<td>27M/3F</td>
<td>35M/16F</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>37 (17-71)</td>
<td>37 (9-60)</td>
</tr>
<tr>
<td>T (UICC/AJCC 1986)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>T2</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>T3</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td>T4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>N (UICC/AJCC 1986)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2a</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>N2b</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>N2c</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>N3</td>
<td>27</td>
<td>27</td>
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</tbody>
</table>

**Table 5. Results of neoadjuvant chemotherapy in locally advanced UCNT.**

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>CR</td>
<td>3/29</td>
<td>32/51</td>
</tr>
<tr>
<td>PR</td>
<td>22/29 (85%)</td>
<td>18/51</td>
</tr>
<tr>
<td>MR</td>
<td>2/29</td>
<td>1/51</td>
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<tr>
<td>PROG</td>
<td>2/29</td>
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<table>
<thead>
<tr>
<th>Results after RT</th>
<th>PBF</th>
<th>BEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>25/28</td>
<td>49/49</td>
</tr>
<tr>
<td>PR</td>
<td>3/28</td>
<td></td>
</tr>
</tbody>
</table>

* After 2 cycles (Day 1 = Day 28 for PBF regimen).
  After 3 cycles (Day 1 = Day 21 for BEC regimen).

PBF: cisplatin, bleomycin and 5-fluorouracil combination chemotherapy.
BEC: bleomycin, 4-epidoxrubin (epirubicin) and cisplatin.

The current status (December 1989) of the 51 patients entered in the protocol: 49 were appropriately treated, 2 have died of non-neoplastic causes, and 45 patients are alive, two of them with metastasis. Forty-two patients are disease-free (78%) (1 had local recurrent disease managed by salvage treatment). The mean follow-up is 19 months with a minimum of 10 months and a maximum of 32 months [114]. We believe that these results, obtained in a group of patients with such advanced locoregional disease, would justify a controlled prospective assessment of chemotherapy against radiotherapy only.

**Conclusion**

The object of this review is to present this fascinating disease to medical oncologists. This carcinoma constitutes one aspect of the phenotypic expression and possible clinical behavior of epidermoid cancers. It is an excellent model for the development of therapeutic strategies.

We have presented a literature review as well as data showing its chemosensitivity and potential curability by
combined-modality treatment. One of the first fruits of this work has been the implementation of an International Nasopharynx Cancer Study Group which in a comparative trial will test chemotherapy (with bleomycin, epirubicin, and cisplatinum) followed by radiotherapy versus radiotherapy alone in locoregionally advanced undifferentiated nasopharyngeal cancer (UCNT). The countries participating in this trial are France, Algeria, Morocco, Spain, Italy, Portugal, Greece, and Saudi Arabia.

The Gustave Roussy experience allows some optimism. An eighty percent response rate in a metastatic disease with about 10% unmaintained long-term survivors and about 2/3 of complete responses in locally advanced disease treated with BEC argue for a primary role of chemotherapy in the treatment of this disease. Moreover, we believe that NPC can be envisaged as a potentially curable disease in the near future.

References


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