PERGAMON

European Journal of Cancer 39 (2003) 2121–2135

European Journal of Cancer

www.ejconline.com

Review

Nasopharyngeal carcinomas: an update

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Received 10 March 2003; accepted 11 March 2003

Abstract

Among the group of head and neck cancers, nasopharyngeal carcinomas (NPC) represent a distinct entity in terms of their epidemiology, clinical presentation, biological markers, carcinogenic risk factors, prognostic factors, treatment and outcome. Undifferentiated NPC (UCNT), the most frequent histological type, is endemic in certain regions, especially in South East Asia. The disease has also been associated with the presence of the Epstein–Barr Virus (EBV). Although NPC is a radiosensitive and chemosensitive tumour, a substantial number of patients develop local recurrence or distant metastases. For patients with locoregional advanced disease, it is well known that conventional radiotherapy is insufficient in terms of both the local control rates and distant metastases. New techniques of radiation and new combined radiotherapy and chemotherapy modalities have been evaluated in numerous clinical trials in recent years. The purpose of this article is to review the current knowledge in terms of the epidemiology, biology, prognosis, management and outcome of patients with NPC.

Keywords: Nasopharyngeal carcinoma; Epstein–Bar virus; Prognosis; Combined modalities; Head and neck

1. Introduction

Nasopharyngeal Carcinoma (NPC) differs from other head and neck carcinomas, in terms of its epidemiology, pathology, clinical features, treatment and outcome. Many histological entities exist from Squamous Cell Carcinoma (SCC) to the more frequent Undifferentiated Carcinoma of the Nasopharyngeal Type (UCNT), and these entities share endemic areas throughout the world. UCNT is associated with the Epstein–Barr Virus (EBV). This is of interest not only for epidemiological reasons or diagnosis, but also for the monitoring of patients, prognosis of patients and therapeutic strategies for the patients [1–3]. NPC is also characterised by its relatively high sensitivity to radiation, although local recurrences and metastases are common events. In patients with locally advanced disease, chemotherapy in combination with radiotherapy has a proven efficiency in terms of the long-term disease-free survival rates [4] that have recently been reported in randomised trials [5,6]. This article reviews the current knowledge with regard to the epidemiology, the biology and the treatment experience and outcome of patients with NPC.

2. Epidemiology

NPC are rare in most countries, especially in Europe and North America (incidence below 1/100 000). However, it has a high incidence in several areas in Southern China, especially in the Cantonese region around Guangzhou, where the incidence is approximately 30–80/100 000 people per year [7]. Other areas of high incidence include Taiwan, Vietnam and the Philippines. In these areas, it is likely that diet plays a carcinogenic role as the population's diet consists of salt-cured fish

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doi:10.1016/S0959-8049(03)00367-8

and meat, and when such food is cooked volatile nitrosamines are likely to be released [8].

Outside of these specific areas, the incidence of NPC remains very low, especially in Western Europe or in the United States (US); in these countries, the main histological type is the differentiated type, that is related to tobacco use (incidence 0.5–2/100 000 people per year). An intermediate incidence is observed in Arabian populations of Northern Africa [9], Saudi Arabia [10], the Caribbean and the Eskimo population from Alaska and Greenland [11]. In North Africa, the incidence among males is approximately 4/100 000.

The male/female ratio is usually 2 or 3 to 1. The age distribution of NPC is not identical in South East Asia and North Africa. In Asia, the overwhelming majority of the cases occur in the fifth and sixth decades of life. In contrast, there is a bimodal distribution in North Africa, with a major peak of incidence around 50 years of age, similar to the single peak observed in Asia, and a minor peak in people aged between 10 and 25 years old. This juvenile form accounts for approximately 20% of the patients and has specific clinical and biological features [8,12].

EBV was first suspected to be linked with NPC on the basis of the serological observations by Old and colleagues [13] in 1966. This link was formally demonstrated a few years later by *in situ* hybridisation of the viral DNA in the nuclei of epithelial cells [14]. The full length EBV genome is contained in all malignant epithelial cells, but not in most infiltrating lymphocytes. The association with EBV is constant, regardless of the patient's geographical origin and is observed in World Health Organization (WHO) types II and III. However, the association of NPC type I with EBV has long been a matter of controversy. It is now clear that WHO type I tumours are frequently associated with EBV in endemic regions, but not in non-endemic regions, where they often result from tobacco and alcohol abuse [15]. More than 95% adults in all ethnic groups across the world are healthy carriers of EBV. This means that NPC oncogenesis is not simply a consequence of EBV infection. It probably results from a form of viral reactivation in combination with other events, such as cellular genetic lesions due to environmental carcinogens and/or some form of immune defects. Consistent with this hypothesis, is the fact that NPC generally occur several decades after EBV primary infection.

The contribution of other pathogenic factors, especially genetic and environmental factors, must be considered. A genetic predisposition for the disease has also been suggested, considering the high incidence of NPC in patients with specific histocompatibilty complex profiles, including HLA-A2, HLA-B Sin2 alleles or HLA haplotypes Aw19, Bw46 and B17 [16], and considering the fact that within a population that has been exposed to the same environmental factors, only some ethnic groups will develop UCNT [17]. According to these findings, Simons and colleagues have called the BW46 antigen the Singapore antigen, as its presence is associated with a high incidence of NPC [18,19].

Interestingly, recent case–control studies performed in Mediterranean countries have also found a higher incidence of NPC associated with some HLA alleles. However, these high-risk alleles are not identical to those previously described in South-East Asia, especially BW46 [20]. These findings are compatible with the presence of a disease susceptibility locus closely linked to the MHC region (chromosome 6), but distinct from the HLA genes [21]. In addition, a new susceptibility locus has just been mapped on chromosome 4 (D4S405 and D4S3002) by genome-wide scan using polymorphic satellite markers in 20 Cantonese families with multiple NPC cases [22]. Surprisingly, in this study, the authors have not found any obvious linkage to chromosome 6 which contains the MHC locus; this discrepancy has not yet been explained.

Epidemiological data of Chinese populations suggest that some environmental factors, especially diet factors, can be considered as carcinogenic factors for NPC. Salted fish and other preserved foods (full of nitrosamines) are important aetiological factors for NPC in the Chinese people [23]. The consumption of salted fish in rice porridge during weaning, but also drinking herbal tea have been shown to be significantly associated with a high risk of UCNT in China, whereas green vegetables seemed to be associated with a reduced risk [24]. A significantly increased risk was also found to be associated with a low educational status, a family history of NPC and even a history of nasal administration of traditional Chinese medicine; whereas vitamin E seems to have a protective effect. In Northern Africa, early exposure in life to preserved spiced meat, basic stewing preparations and hot pimento paste taken with bread have been reported to be associated with a higher incidence of NPC [9]. Concerning tobacco, its role remains controversial, and tobacco has not had the same impact on NPC carcinogenesis compared with other head and neck malignancies.

However, some studies have shown that in Northern US populations, smoking and alcohol intake can be risk factors for NPC, especially for histological type 1 NPC [25]. Recently, risk factors associated with certain professions were also suspected to be carcinogens for NPC. For example, an epidemiological study has recently suggested people working in the newspaper printing industry may have an increased risk of developing not only NPC, but also chronic infections of the head and neck area [26].

2.1. Virus–tumour and virus–host interactions

One to approximately 30 copies of the EBV genome are contained in the nuclei of malignant cells. Most of

these copies are in the form of circular 'minichromosomes' called 'episomes'. These episomes coexist, at least in some cases, with viral DNA copies that are integrated into the cellular chromosomes [27]. Presently, we have no idea whether these integration events occur at specific sites of integration. EBV viral particles are not detected by electron microscopy in NPC biopsies. This is consistent with the fact that most viral genes are silent in NPC cells. However, a small number of viral genes are consistently expressed in NPC cells. They can be classified in two categories. In the first category, are genes whose products can be detected using routine procedures in the pathology laboratories. They encode one nuclear protein, Epstein–Barr nuclear antigen 1 (EBNA 1), one membrane protein, Latent Membrane Protein 1 (LMP1) and two small untranslated nuclear RNAs called EBV-encoded RNA 1 and 2 (EBERs 1 and 2) [28]. EBNA 1 and EBERs 1 and 2 are present in the nuclei of all malignant epithelial cells in all NPC biopsies. The EBNA 1 protein is associated with cellular chromatin; the EBERs are contained in small ribonucleoparticles. LMP1 generally has a cytoplasmic distribution (it is mostly associated with internal membranes); it is present in approximately 50% of NPC biopsies; in these cases, it is contained in most of the malignant cells. For all four viral products—EBNA 1, LMP1 and EBERs 1 and 2—oncogenic activity has been demonstrated *in vitro*. EBERs 1 and 2 can restore the oncogenic phenotype of Burkitt's lymphoma cells which have been depleted of the EBV-genome *in vitro* [29]. Their oncogenic activity in epithelial cells is currently under investigation. EBNA 1 has the ability to induce the development of malignant lymphomas in transgenic mice [30]. This effect is mediated, in part, by BCl-X induction [31]. The oncogenic functions of EBNA 1 in epithelial cells have not yet been investigated. The transforming activity of LMP1 has been widely investigated in various cell types *in vitro*. It has multiple oncogenic functions: inhibition of senescence, apoptosis and epithelial maturation, enhancement of cell proliferation, cell migration and tissue invasion [32]. Further investigations will be required to determine which oncogenic functions of LMP1 are relevant to NPC development. There have been no reports demonstrating convincing differences between LMP1-positive and LMPI-negative NPC, in terms of clinical presentation or disease evolution [33]. However, this does not mean that LMP1 is not involved in NPC oncogenesis. Additional cellular gene alterations may substitute for the oncogenic role of LMP1 in LMP1-negative NPC. This type of scenario has been reported for Hodgkin's disease [34].

There are other viral genes which are consistently transcribed in NPC cells, but the corresponding proteins are either undetected or still under investigation [35,36]. One of this potentially interesting protein is BARF1 which also has oncogenic activity *in vitro* [37].

EBNA 1 and LMP1 can be detected in NPC tissue sections by immunohistochemistry, whereas the EBERs 1 and 2 are detected by *in situ* hybridisation. This latter procedure is regarded as being both highly sensitive and specific. Indeed, in contrast with most other cellular RNAs, the EBERs are quite stable even in paraffin-embedded tissue sections due to their strong association with nuclear proteins. Detection of the EBERs is sometimes used to connect a metastatic lesion of unknown origin to a primary NPC.

At the systemic level, there are substantial modifications of the interactions between EBV and the host organism, both prior and during NPC tumour development. Evidence of these changes is provided by an investigation of EBV-specific antibodies and viral DNA in peripheral blood.

Serological studies have shown that at the time of diagnosis of UCNT, high antibodies titres of proteins involved in the productive of the EB virus can be detected, like the early antigen EA before DNA replication and late structural antigens such as the Viral Capsid Antigen (VCA) [17]. Except for anti-EBNA 1 antibodies, most EBV-specific antibodies associated with NPC are directed to viral antigens which are not usually detectable in the malignant cells. This paradox might be partly explained by the fact that malignant cells expressing early or late EBV antigens are no longer actively proliferating and probably appear as privileged targets for cytotoxic lymphocytes.

Recently, the detection of cell-free EBV DNA in sera from patients with NPC [38], by a polymerase chain reaction (PCR)-based approach, has allowed the detection of recurrent disease in such a patient and can be considered a promising new technique to monitor these patients.

In conclusion, the main arguments for a contribution of the viral products to NPC oncogenesis are the following. (1) The consistency of the linkage of EBV to the disease, especially in WHO types II and III, regardless of the patient's geographical origin. (2) The expression in malignant cells of viral products which have oncogenic properties *in vitro*. (3) The detection of EBV-related serological alterations a long time prior to the presence of a clinically- or radiologically-detectable tumour. For instance, it has been shown that antibodies IgA anti-EBV, capsid antigen and neutralising antibodies against EBV-specific DNase were present before the onset of NPC and hence were predictive of NPC, in male patients in Taiwan [39]. After adjustment for age and family history of NPC, the relative risk of occurrence of NPC was 32.8 (95% CI: 7.3–147.2) for men with both markers ($P < 0.001$) and 4.0 (95% CI: 1.6–10.2) for men with only one marker ($P = 0.003$), in comparison to men with antibodies against neither marker [39].

One question which has long been asked is whether there are EBV strains which are associated with a higher

risk of NPC (as has been established for human papilloma virus (HPV) strains involved in cervical carcinomas). So far, there has been no formal demonstration of such a strain effect [40]. However, two groups have reported distinct polymorphisms in EBV isolates derived from NPC tissue and from the peripheral blood of the same individuals [41]. These findings are consistent with the idea that more aggressive EBV strains are often contained in NPC cells. However, similar differences have just been reported by investigators comparing viral polymorphisms in peripheral blood and throat washing samples of healthy EBV carriers [42]. This makes the interpretation of such data more complicated.

2.2. Cellular oncogenesis

In addition to Epstein–Barr-related products, alterations in cellular genes also play a major role in NPC oncogenesis. The most prevalent gene alterations are gene deletions (microdeletions or loss of heterozygosity) and hypermethylations. There are also gains of chromosomal material including gene amplifications. The chromosomal regions that are most often affected are 3p and 9p [43]. Inactivation of tumour suppressor genes in these regions often seems to result from a combination of allelic loss and hypermethylation of the remaining allele, although this is not fully documented. Allelic losses, in 3p, are reported in 96% of the cases. The minimally deleted region extends from chromosome 3p14 to 3p24.2. One tumour suppressor gene encompassed in this chromosomal segment encodes RASSF1, a protein which mediates the apoptotic effects of oncogenic ras. The *RASSF1* gene is frequently hypermethylated in NPC, but the percentage of tumours with loss of RASSF1 protein expression is not yet known. Allelic losses in 9p are reported in 85% of cases [43]. One important target gene in this region is the tumour suppressor gene encoding the p16-Ink 4, a physiological inhibitor of cell cycling. It can be inactivated by homozygous deletion, or promoter hypermethylation, possibly combined with deletion of one allele [44]. Both mechanisms of gene inactivation result in the loss of p16-Ink4 in 60% of NPC specimens [45]. Deletions of chromosome 14q are also highly prevalent, but at present, there is no data indicating a candidate tumour suppressor gene in this region [43]. Gain of chromosomal material has been reported for chromosome 12q [43]. According to Lo and colleagues [43], general microsatellite instability is infrequent in NPC. However, localised microsatellite instability has been reported, for example, in exon 3 of the transformation growth factor beta receptor type II gene on chromosome 11.

By methylation-specific PCR, Wong and colleagues [46] have shown that hypermethylation of the Death-associated Protein-kinase (DAP-kinase) promoter seems to be a common early event in NPC, that can be detected not only in tumour DNA, but also in circulating plasma DNA.

In contrast to data observed in squamous cell carcinomas, especially of the head and neck region, the *p53* gene is rarely mutated in NPC [47]. However, the p53 protein is often very abundantly expressed in NPC cells suggesting that indirect mechanisms of inactivation and stabilisation may be operating in these cells. Crook and colleagues [48] have reported data suggesting that wild-type p53 is inactivated in NPC cells by the short isoform of p63. One important aspect to note concerning cellular oncogenesis of NPC is that almost all the data presently available and summarised in this review were obtained from specimens collected in South-East Asia. There is an obvious need to perform more investigations on NPC specimens from North Africa.

3. Anatomy

The nasopharyngeal region is situated anteriorly in continuity to the nasal cavity through the posterior choanae, above the basisphenoid and the basiocciput that constitute the roof of the nasopharynx that comes down behind by the posterior wall, constituted itself by the first two cervical vertebrae. The eustachian tube ostium situated in the lateral walls of the nasopharynx and the lateral pharyngeal recess or fossa of Rosenmuller remain the most common site for the initial development of NPC. Above the nasopharynx, there is the palate. Histologically, the nasopharynx consists of a mucociliary columnar epithelium. The lymphatic drainage concerns all the levels of the neck, including the retropharyngeal nodes that are medial to the carotid artery [49].

4. Pathology

Pathology has an important impact on outcome and the WHO has classified NPC into three histological types: keratinising squamous cell carcinoma (type 1), non-keratinising carcinoma (type 2) and the most common tumour, the undifferentiated carcinoma UCNT (type 3) [50].

Other histological forms include lymphoma or plasmocytoma.

With regard to the histogenesis, despite numerous attempts, there has been no real characterisation of the premalignant lesions of the nasopharyngeal epithelium. In 1995, Pathmanathan and colleagues have reported 11 cases of NPC *in situ*, all of them expressed EBV-DNA, EBERs and LMP1 [51]. However, this study has remained controversial since several other groups have not been able to reproduce the data using their own specimens [52]. More recently, preliminary data reported by

Lo and colleagues suggest that chromosomal losses affecting chromosome 3p occur very early in the tumour process, at a pre-invasive stage [43]. This observation has prompted the drafting of new models of NPC oncogenesis. In these models, early dysplasia is associated with alterations in cellular genes occurring prior to EBV infection [53]. However, this scenario remains highly speculative; extensive biological and pathological investigations will be required for its validation.

5. Diagnosis

Most of time, NPC derives in the fossa of Rosenmuller and arises as a mass in the neck with symptoms such as hearing problems, serous otitis, tinnitus, nasal obstruction, anosmia, bleeding, difficulty in swallowing due to cranial nerve XII involvement or dysphonia if the nerve X is invaded by the tumour, even eye symptoms with diplopia (VI nerve invasion) and pain [54]. However, none of these symptoms is specific for NPC and sometimes NPC develops at the submucosal level and spreads outside of the anatomical limits of the nasopharynx. Often a bilateral and bulky tumour can also be found. The natural history of such a tumour is mainly dependent on the WHO histopathological classification. For instance, WHO type 1 is more often associated with uncontrolled local development and has a lower propensity to metastasise than WHO types 2 and 3. WHO type 1 is responsible for nodal involvement in approximately 60% of patients at diagnosis [55], whereas WHO types 2 and 3 are associated with nodal metastases in 80–90% of patients [56], and involvement of the bilateral neck nodes is also a common feature [57].

In fact, the initial clinical exam must include a complete examination of all levels of neck, of all cranial nerve functions, of all multiple nodal areas including the retropharyngeal pathway. Basically, an examination and biopsies of the tumour and the nasopharynx are performed by a direct flexible fibreoptic endoscopic examination. This is one of the most important skills in the diagnosis and monitoring of NPC [58].

5.1. Serological and biological diagnosis

The presence of EBV in epithelial and in B lymphocyte cells provokes a humoral immune response including antibodies encoding latent or replicative antigens [59,60]; the typical anti-EBV serological profile of NPC patients consists of an increase in both IgG and IgA antibodies against the VCA and Early antigen (EA) and anti-EBNA IgG. Antibodies against the EBV replication activator protein or ZEBRA, that triggers the virus from a latent to a productive mode, are often used to diagnose NPC; indeed, anti-Zebra IgG antibodies have been detected in 75% of NPC patients who were positive for anti-VCA and in 25% of NPC patients with sera that was negative for anti-VCA IgA, providing an identification of the early stages of NPC [61]. The detection of EBV DNA can be made in situ by using PCR. Hybridisation can localise the virus in infected tumour cells [62]. PCR techniques can also be performed in patients with unknown primary neck nodes allowing NPC to be diagnosed [63]. Recently, genomic microarrays have also been used to detect the amplification of oncogenes associated with NPC [64] and, by methylation-specific PCR, Wong and colleagues [46] have recently shown that hypermethylation of the DAP-kinase promoter appears to be a common early event in NPC development and its detection in sera might be a tumour marker for the diagnosis of NPC.

5.2. Radiological examination

Imaging remains one of the most important exams for NPC evaluation and staging. However, different techniques of imaging are used for treatment by radiation and for the detection of locoregional recurrences and especially for nodal involvement. Computed Tomography (CT) and magnetic resonance imaging (MRI) remain the most sensitive exams which are essential to measure the accurate extension of the tumour [65,66]. The density of NPC tissue is similar to that of soft tissue; so the diagnosis of the tumour depends on displacement or erosion of the normal anatomy and the uptake by the tumour of the iodinated intravenous product.

CT detects the tumour and its extension to the different spaces of the neck. Lymph node involvement is suspected when the size of the nodes exceeds 10 mm and when there is a peripheral ring enhancement contrast with a central hypodensity [67]. Recently, Doppler sonography, frequently used in the assessment of cervical nodes, has been used as a new way to diagnose lymph node involvement. This technique, in the supraclavicular region, may distinguish tuberculosis involvement from metastatic carcinoma nodes, depending on the vascularity and the capsular integrity of the nodes [68], with a capsular or mixed vascularity with high resistance for metastatic nodes.

MRI provides accurate anatomical information, due to its better contrast and multiplanar capability [69], especially for the contours and locoregional extensions of the tumour.

Generally, both methods, CT and MRI, are necessary and seem to provide convergent results about the tumour and lymph node staging. Nevertheless, CT seems to be better in detecting cortical bone erosion, whereas MRI appears more accurate when examining an eventual bone marrow extension (normal high fatty signal of the marrow is replaced by a lower signal

intensity). Moreover, MRI seems of use when visualising the tumours limits and the cranial nerve infiltration through the foramen of the base of skull, especially the foramen ovale.

6. Staging

There are several clinical staging systems used in this disease, depending on the country. For instance, the most common classification used in Asia is derived from the Ho clinical study [70] whereas the International Union Against Cancer/American Joint Committee on Cancer (UICC-AJCC) system [71] remains the most frequently used system in countries other than Asia (Table 1). Anyway, there seems to be no difference between these staging systems, except in one study where the Ho staging system appeared superior to the others in terms of disease-free survival [72]. Although a new staging system, based on modern imaging techniques, was proposed in China [73], requiring prospective validation. The 1997 AJCC staging system was recently considered prognostically useful for Chinese patients and has a subdivision based on parapharyngeal extension for overall survival and relapse-free survival [74].

6.1. Prognostic factors

Better characterisation of the tumour has provided prognostic factors and also predictive information allowing the determination of the optimal treatment sequence.

6.2. TN stage

Most studies have shown no differences in clinical outcome between patients with T1 and T2 UICC stages, except for the recent study of Ma and colleagues [74], that proposed a subdivision for T2 para-oropharyngeal extension which appeared as an independently significant prognostic factor for overall survival, for local recurrence and recurrent metastases. Local failure is higher for those with T3 and T4 staging than those with T1 and T2 staging and the prognosis depends on the structures involved [75,76]; for instance, intracranial involvement (T4) was found to have a significant negative impact on survival and cranial nerve invasion seemed to have a negative impact not only on survival, but also on local control [77].

As for lymph node involvement, this remains one of the most important prognostic factors for disease-free survival and overall survival, and is associated with an increased local failure rate, a poor outcome, especially for N3 disease, according to both the HO and UICC staging systems [78]. However, bilateral nodal involvement according to the median localisation of the NPC, has no major impact on prognosis [10].

Metastatic nodes in NPC seemed to be more vascularised than in other head and neck squamous carcinomas, implying the disease may have a better response to chemotherapy, and the results of a CT-scan after the injection of contrast medium seems to predict the outcome following neoadjuvant cisplatin-based chemotherapy [79].

Table 1
TNM staging of NPC according to 5th UICC

T1—tumour limited to one subsite
T2—tumour invades more than one subsite of the nasopharynx
T3—tumour invades nasal cavity and/or oropharynx
T4—tumour invades skull or cranial nerve(s)
N1—ipsilateral node, single, equal or less than 3 cm
N2
N2a—ipsilateral node, single, >3–6 cm
N2b—ipsilateral, multiple nodes, >3–6 cm
N2c—bilateral or controlateral node(s), equal or less than 6 cm
N3—node(s) >6 cm

UICC, International Union Against Cancer; NPC, nasopharyngeal carcinoma.

7. Pathology

The pathological type is a prognostic factor. In Western countries, squamous cell carcinoma (WHO type 1) has a worse outcome in terms of local control and overall survival than WHO types 2–3 [55,78]. However, a high proportion of dendritic cells and macrophages in lymphoid infiltrations has been shown to be associated with a better prognosis [80].

7.1. Age and gender

At diagnosis, the impact of age on prognosis remains controversial; on the one hand, some studies have reported a better outcome in childhood, with higher advanced stages [81], on the other hand, Martin and colleagues and Huang and colleagues have reported a worse prognosis for patients aged 20 and 14 years old, respectively [82,83].

In most studies, when gender was considered as a prognostic factor, females had a better outcome. In fact, the evidence overall suggests that there is no difference of prognosis between males and females, or for the age at diagnosis.

7.2. Biological prognostic factors

Detection of cell-free EBV genomes in the sera of the patients with NPC could be a screening and surveillance tool [1], but could also be used to assess the prognosis of the disease [3] and hence to evaluate the risk of a disease recurrence [38]. However, nowadays, it is generally not

used. Some others have also shown that, after a complete remission, an increase in IgG and IgA EA titres is highly significant for predictor of a relapse [84] and increasing levels of ZEBRA antibodies, after an initial posttreatment decrease, seem to be predictive of a distant metastatic recurrence.

Concerning other biological markers, a high Fas ligand expression in NPC cells seems to be associated with a significantly higher incidence of skull base involvement than is seen in patients with a low Fas ligand expression [85]. A high expression of the met protein in NPC cells appears to be correlated with a poorer survival rate in late-stage NPC patients and seems to be an independent prognostic factor [86]. Finally, a low haemoglobin level has also been demonstrated to be associated with a poorer outcome, as has been observed in other head and neck cancer patients receiving radiation therapy [11].

8. Treatment

NPC remains a relatively radiosensitive tumour and thus radiation therapy remains the standard treatment for almost all NPC patients. By contrast, surgery is generally not feasible due to potentially inadequate margins of resection. Despite improvements in treatment modalities, regional recurrences are not uncommon and the pattern of failure for patients with NPC differs from that of other cancer sites of the head and neck, with a higher distant failure rate [75]. Thus, chemotherapy is indicated for recurrent or metastatic disease. The concurrent combination of radiotherapy and chemotherapy has been studied to try to improve local control rates and overall survival rates. In spite of encouraging results in terms of response rates, the survival rates remained disappointing [87].

8.1. Radiotherapy

As CT and MRI enable disease extensions to be identified accurately, the radiation therapy fields are defined accordingly to their results. Generally, two opposed isocentric lateral fields are used for the nasopharynx and upper neck, using 4–6 MV particle accelerator photon beams. The whole tumour dose delivered is generally 65–75 Gy, given in daily fractions of 1.8–2 Gy for 7–8 weeks. A third anterior field is planed in case of a nasal extension or a small tumour (T1–T2).

For parapharyngeal extensions, a prognostic factor in terms of local control, some authors have divided into categories this area extension using CT results [88]. Type 1 extension is defined as the disease extending up to a line from the medial pterygoid plate to the lateral carotid artery. Type 2 extension refers to an area that is beyond type 1, up to a line from the medial pterygoid to the styloid process. Type 3 extension is up to a line from the lateral pterygoid to the posterior aspect to the ramus of the mandible. The degree of extension remains very important, even within the T4 stage patient group. Concerning the upper lymphatic extension (cervical, jugular, spinal and retropharyngeal nodes), these regions are treated within these lateral fields. After 42–45 Gy, a spinal cord exclusion is necessary with a special personalised shield for an adequate coverage above the retropharyngeal extension. Hence, the upper and posterior lymphatic cervical areas are treated by electron beams, with an energy of 6–15 MeV. A bulky posterior node requires oblique posterior photon beams.

The bilateral lower neck and supraclavicular regions are treated by a single anterior field, matched with the lateral zones, with a median shield to protect the larynx and the spinal cord; the dose delivered depends on involvement of the nodes. Generally, the prophylactic dose delivered is approximately 50 Gy over 5 weeks and this is increased up to 65–70 Gy in cases of clinical or scannographic nodal involvement.

There are some studies that suggest that radiation therapy in a concomitant boost during the last 2–2.5 weeks of radiation would provide better local control [89,90]; in fact, the total dose would be increased with a shortened overall time, producing an enhanced biological effect.

Better imaging procedures have been shown to improve the outcome of the disease, yielding a better local control and providing a better adapted radiation therapy, as mentioned in the studies of Lee and colleagues [91], with an improvement in survival. In Cellai and colleagues' [92] study patients' therapy before and after 1978 was compared and a stage migration phenomenon was detected, due to better imaging and thorough workups. With better imaging of tumours by CT, they are often upstaged and treated accordingly.

8.2. Radiotherapy results

The local control rates for stages T1 and T2 remains generally acceptable (80–90%), whereas higher locally advanced disease results in a worse outcome with 20–40% failure rates and a higher risk of distant metastases. However, it is necessary to wait 2 or 3 months after the completion of the therapy to observe definitive results, particularly in cases of an initial bulky lymph node involvement. A reduced time to recurrence or the persistence of such nodal disease is generally associated with a local relapse or a metastatic recurrence [65].

At 5 years, in terms of the local recurrence rates, several studies have reported important variations, with most relapses occurring within 3 years after the completion of the radiation therapy, a very poor tumour control in advanced T stages (T3–T4), in WHO type 1 compared with WHO types 2–3 and also in cases involving the skull

base (Table 2). Approximately 5% of the local recurrences can also occur between 5 and 15 years following treatment [93].

The local recurrence rates are approximately 15–25% for stages T1–T2 and 30–55% for stages T3–T4 [10,91,93–102]. Erkal and colleagues showed that the radiation dose correlated with the tumour control, the nodal control and the survival rates [102].

8.3. Side-effects of radiotherapy

Improving outcome must be linked with an acceptable toxicity, especially in terms of xerostomia and central nervous system (CNS) toxicity. In terms of acute toxicity, the most frequent complication remains mucositis that occurs most commonly between the second and third week of treatment. Other acute side-effects observed, in common with other head and neck tumours, are dermatitis (generally grades 1–2), alterations in taste and problems with saliva (i.e. dry mouth).

Late toxicities are relatively frequent and may be underreported. The most frequent complication is salivary dysfunction, with a hyposialosis being observed in most patients [103]. The patients are often young at diagnosis and therefore are followed for a long period of time. Another late complication of radiotherapy is the risk of trismus that may be seen in as many as 35% of the patients, secondary to a sclerosis of the pterygoid muscle and mandibular joint. In the series of the Gustave Roussy Institute (IGR) [103], the risk of trismus may be reduced by adding an anterior field, when it is possible; trismus seems to be severe in 15–20% of cases (<15 mm interdental space). Dental complications, partly related to the xerostomia, can also be frequent and must be prevented by the use of prophylactic topical Fluor applications. Another complication must be known: toxicity related to cranial nerve impairment or lesions. Furthermore, a loco-regional recurrence is often difficult to distinguish from posttreatment fibrosis. Some radio-induced sarcomas (osteosarcoma), an osteonecrosis like a temporal necrosis [91,101], hypothalamic alterations and a hypopituitarism can occur, but remain relatively uncommon [104].

Table 2
Results in terms of local recurrence rates of the main series using radiation therapy alone

Author, year [Ref.]	Patients (*N*)	Local control rates (%)
Laramore, 1998 [10]	166	26 (T1–T2) 45 (T3–T4)
Lee, 1992 [71]	5037	30
Bedwinek, 1980 [73]	111	9.5 (T1–T2) 38.1 (T3) 54 (T4)
Huang, 1980 [74]	1605	15.7
Mesic, 1981 [75]	251	19.5
Qin, 1988 [76]	1379	29
Schwaab, 1983 [77]	143	35
Teo, 1989 [78]	403	17.3
Wikram, 1985 [79]	107	30
Yan, 1983 [80]	811	9.6
Zhang, 1989 [81]	1302	18.4
Erkal, 2001 [82]	308	22

The quality of life (QOL) of patients with carcinoma of head and neck [105] has been reported in several studies, which has also recently focused on the QOL of NPC patients [106]. The most noteworthy problems were hypoacousia, difficulties in chewing and xerostomia; but, in fact, overall QOL seemed acceptable. This latter study emphasised the fact that NPC concerns mostly younger patients (without severe alcohol and tobacco abuse) compared with other carcinomas of the head and neck region. These patients present with less comorbidity and a better performance status at diagnosis. Moreover, tolerance to radiotherapy may be improved due to new conformal radiotherapy techniques that protect the salivary glands and temporal bone.

8.4. Improved modalities of radiation

Attempts to reduce salivary gland and CNS toxicity, without compromising the patient's outcome, have resulted in the use of three-dimensional (3D) conformal radiation therapy or intracavitary boost delivery for localised tumours [107] or proton beam therapy [108] that enables an increased dose to the tumour, with a significant reduction in the doses given to the surrounding normal tissues, compared with photon beam therapy. For conformal radiation therapy, with the potential use of 3D treatment planning, some preliminary results are encouraging in terms of coverage of the tumour and the sparing of the salivary glands and CNS from radiation [102,109].

Improving results are often at the expense of unacceptable toxicity: hyperfractionated radiation therapy has the potential of an improved control and survival [110]. However, consistent with the results of Teo and colleagues [111,112], the local control and overall survival may be equivalent when hyperfractionated radiation therapy is compared with conventional radiotherapy [112], even though there may be a higher risk of toxicity and unacceptable CNS complications, when accelerated and hyperfractionated radiation therapies are used. If the outcome for NPC can be improved by delivering higher radiation doses, then brachytherapy may be of interest. However, there is no randomised study that had shown the promise of escalating the dose by brachytherapy after conventional external radiation. In a retrospective study by Wang [107], a significant improvement for T1–T3 (UICC) patients was suggested when a brachytherapy boost of 10–15 Gy was added

after cobalt 60 external radiotherapy. Recently, Ozyar and colleagues [113] have compared in 144 T1–T4 (UICC) NPC patients, the local control and survival rates reached following either external beam radiation therapy (EBRT) and an adjuvant high dose-rate brachytherapy (HDR) or EBRT alone, and have shown no difference in the local control rates between the two groups. The administration of an adjuvant HDR brachytherapy was not an independent prognostic factor in multivariate analysis. For some authors, brachytherapy has been used systematically for T1–T2 (UICC) tumours [114], or with chemotherapy by others [115]. A correlation between the tumour dose and the local control in NPC remains controversial, even though doses below 60 Gy over 6 weeks are known to be less efficient with regard to local tumour control [116]; definitive conclusions are impossible to draw without data from a randomised trial taking into account possible dose–response relationships. Perhaps 3D-conformal radiation therapy could answer this question.

Prospective studies have also examined the modulation of the efficacy of radiotherapy through new molecular cell targets that are involved in DNA repair, signal transduction or cell-cycle regulation and apoptosis [117]. For instance, Blank and colleagues [118] have demonstrated the central role of *p53* and *bcl2* as modulators of apoptosis after radiation therapy. We have mentioned in this review that the expression of the Fas ligand in tumour NPC cells seemed to correlate with a higher frequency of skull base involvement. Recently, a French study has shown that a high expression level of Fas ligand in EBV-positive human NPC cells may result in increased apoptosis of cells after radiation with doses as low as 2 Gy [119]. These preliminary data suggest a new type of therapeutic strategy that may be used to improve patients' outcome.

9. Chemotherapy

Although radiation therapy remains the mainstay treatment, some pathological types of NPC (types 2 and 3) have been shown to be chemosensitive in all stages of the disease [120–122]. Moreover, some cases of NPC can be locally controlled by chemotherapy alone [120]. Although complete response rates (CRs) are generally higher in UCNT patients with a similar or greater stage tumour than in other head and neck SCC patients, the local recurrence rates and rates of distant metastases remain relatively important. In order to improve the treatment outcome, concurrent combinations of chemotherapy and radiotherapy have been studied. The most active drugs used in NPC patients are cisplatin, bleomycin, doxorubicin, epirubicin, 5-fluorouracil (5-FU), methotrexate [123,124] and mitoxantrone [125].

Different therapy approaches include: neoadjuvant, adjuvant or concomitant chemotherapy with radiotherapy.

9.1. Neoadjuvant chemotherapy

Neoadjuvant chemotherapy is generally used in order to reduce the sub-clinical metastases and to improve local control by shrinking the tumoral volume before radiation therapy. As we have already mentioned above, complete response rates after a chemotherapeutic regimen in NPC patients are generally higher than those obtained in other head and neck SCC patients with an equivalent tumour stage. CRs after neoadjuvant chemotherapy may reach 10–66%, with objective responses rates ranging from 75 to 98% [124]. Indeed, response rates depend on the pathological types and stage of the tumours and the type of chemotherapeutic regimen.

In the phase II setting, as in Dimery's study [124], neoadjuvant chemotherapy consisting of three cycles of 5-FU and cisplatin before radiation, has resulted in CRs of 20.5% and a local control rate of 86.4% after all the combined treatments. The 4-year actuarial disease-free and overall survival rates were 65.6 and 71.6%, respectively, and the rate of recurrence (including the local recurrences and distant metastases) was 27%.

The IGR used two consecutive regimens in locally advanced nodal disease (N2-N3 UICC-AJC 1986); first, in 30 N3 UCNT patients treated by bleomycin, cisplatin and 5-FU [126]. The overall response rate was 83% (10% CR; 73% PR) for a 4-year disease-free survival rate of 35%. In the second study, 67 patients with locally advanced UCNT received three cycles of bleomycin, epirubicin and cisplatin before the radiation therapy; the overall response rate was 98% after chemotherapy, with 66% CR and the 4-year disease-free survival was 66%, with an overall survival rate of 60% [127,128].

The first large scale phase III multicentre study [6] was conducted between 1989 and 1993 by the International Nasopharynx Cancer Study Group (INCSG, VUMCA I trial) and included 339 patients from different countries from Southern Europe, Northern Africa and the Middle East. WHO pathological types were II and III and the stages were N2–N3 (UICC-AJC 1986) and M0. Patients were randomised between an arm consisting of three cycles of bleomycin, epirubicin, cisplatin (days 1, 22 and 43) followed 3 weeks later by radiation therapy of 70 Gy over 7 weeks, and an arm including just radiation therapy of 70 Gy over 7 weeks. This study showed a benefit of adding chemotherapy to the radiotherapy treatment, with a significant increase in disease-free survival, but not in overall survival, for the combined arm (40% versus 46%, respectively). With a median duration of follow-up of 49 months, the rate

of recurrence or progression was 32.7% in the chemotherapy and radiotherapy group and 54.7% for the group who received radiation therapy alone ($P < 0.001$)

A second randomised study [129] was conducted between 1989 and 1993 by the Asian-Oceanic Clinical Oncology Association (AOCOA) and enrolled 334 patients with T3, N2–N3 UCNT (Ho classification). Patients were randomised between a conventional radiation therapy of 66–74 Gy over 6.5–7.5 weeks alone and the same radiation therapy preceded by 2–3 cycles of cisplatin (60 mg/m^2, day 1) and epirubicin (110 mg/m^2, day 1). After a median follow-up of 44 months, there was no significant difference between the two arms in terms of disease-free survival and overall survival. Disease-free survival rates were 48 and 42% in the combined modality and radiation therapy alone arms, respectively. However, in this study, there was a significant trend of benefit (improved relapse-free survival) in patients with 'bulky' lymph nodes, that represented a smaller subgroup compared with the same subgroup in the INCSG trial; for these 49 patients, with a nodal size greater than 6 cm, the relapse-free survival at 3 years was 63% versus 28% ($P = 0.02$) in favour of the combined modality arm.

A randomised study comparing 2–3 cycles of cisplatin (100 mg/m^2, day 1), bleomycin (10 mg/m^2, days 1 and 5), and fluorouracil (800 mg/m^2, days 1–5, continuous intravenous (i.v.) infusion), every 3 weeks, followed by radiotherapy (68–72 Gy, 2-Gy fraction per day, split-field technique), with the same radiation therapy given alone, was recently reported re Ref. [130]. There was no difference in terms of the 5-year overall survival rate between the two arms; however, there was a significant statistical difference ($P = 0.05$) between the two arms in terms of 5-year relapse-free survival (59% versus 49% for the combined treatment and the radiotherapy alone group, respectively).

In conclusion, in this neoadjuvant chemotherapy setting before radiation therapy, no overall survival benefit was observed in NPC patients, the overall survival did not reach significance. However, a significantly increased relapse-free survival rate in favour of the combined modality arm was observed, especially in patients with bulky lymph nodes. Currently, there is not any other published randomised trials that have shown a superiority of neoadjuvant chemotherapy before radiotherapy compared with radiotherapy alone.

9.2. Adjuvant chemotherapy

The main goal of this strategy is usually to reduce the risk of distant metastases. A few phase II studies, where the results of patients receiving radiotherapy followed by adjuvant chemotherapy were matched with those of a historical radiotherapy alone control group, have shown a potential benefit of using adjuvant chemotherapy, although definitive conclusions have not been drawn ([131–133], Table 3).

The potential interest of adding chemotherapy after radiotherapy in NPC patients was also evaluated in randomised trials. Rossi and colleagues [134] using adjuvant chemotherapy with vincristine, cyclophosphamide and doxorubicin administered or not after 60–70 Gy of radiation therapy, did not show any benefit in terms of relapse-free survival and 4-year-disease free survival. However, the results of this study should be interpreted with caution, as the regimen did not include cisplatin and the number of patients with distant metastases was not examined at the start of chemotherapy.

A second randomised study has evaluated neoadjuvant chemotherapy, plus adjuvant chemotherapy with radiation therapy alone in advanced NPC patients [135]. This trial was conducted between 1988 and 1991 at the Prince of Wales Hospital of Hong Kong and compared radiotherapy alone with a combination of two cycles of cisplatin plus 5-FU as neoadjuvant treatment followed by radiotherapy then four more cycles of the same chemotherapy regimen were administered. There was no significant difference between the two arms in terms of disease-free and overall survival rates.

9.3. Concomitant radio-chemotherapy

The principal aim of adding concomitant chemotherapy to radiotherapy is to increase not only the local control, but also to decrease the probability of distant metastases, as has been already shown in the treatment of other head and neck cancers [136].

The South Western Oncology Group (SWOG), Radiation Therapy Oncology Group (RTOG) and Eastern Cooperative Oncology Group (ECOG) intergroup trials [137] evaluated the value of adding concomitant and adjuvant chemotherapies to radiotherapy treatment. This consisted of three cycles of cisplatin (100 mg/m^2, day 1) and 5-FU (1 g/m^2, days 1–5) after a total radiation dose of 70 Gy over 7 weeks, and with a cisplatin chemotherapy regimen (100 mg/m^2, day 1) concomitant to the radiation, compared with radiation therapy alone (70 Gy over 7 weeks). After a median

Table 3
Phase II clinical studies of NPC patients treated with radiation therapy followed by adjuvant chemotherapy

Author, year [Ref.]	Patients (*N*)	Year, DFS (%)	*P* value
Rahima, 1986 [131]	25	77 (3-year DFS)	<0.05
	20	50 (3-year DFS)[a]	
Droz, 1987 [132]	38	71 (3-year DFS)	<0.05
	20	47 (3-year DFS)[a]	
Altun, 1992 [133]	59	57 (5-year OS)	NS
	70	37 (5-year OS)	

DFS, disease-free survival; OS, overall survival; NS, non-significant.
[a] Historical radiation alone group.

follow-up of 4 years for 150 patients with III-IV stage NPC, this study showed a superiority in terms of the 3-year survival rate in favour of the chemotherapy arm (76% versus 46%, $P<0.001$) and a significant benefit in the 3-year overall survival ($P=0.005$). Surprisingly, the disease-free and overall survival rates observed in the reference arm (radiotherapy alone) were worse than in other large scale published series of conventional radiation therapy, including a large number of SCC NPC, but not UCNT, patients.

Recently, taking account of these above results, Chan and colleagues [138] have led a new randomised trial in N1–N2–N3 (Ho's classification) NPC patients, comparing concurrent chemotherapy–radiotherapy, using cisplatin (40 mg/m^2, weekly up to 8 weeks concurrently with radiotherapy), with radiation alone. Although, there was no statistical difference between the two arms in terms of progression-free survival and overall survival, a significant benefit was observed in favour of the combined arm for the stage T3 subgroup ($P=0.007$).

10. Treatment of recurrent disease

The main cause of death in NPC patients remains distant failure. Metastases can occur in different sites, with a preferential skeletal spread. A relationship was even demonstrated between local recurrences and metastasis [139]. For patients with local recurrence, a second course radiotherapy may be administered with caution. Many therapeutic techniques have been evaluated, e.g. external re-irradiation, brachytherapy, surgery and chemotherapy or combined modalities. A second course of radiotherapy appears feasible, providing the size and shape of the treated volume, including the minimal margin of the tumour is taken into account and re-irradiation of the spinal cord is avoided [140]. The risk of complications is increased after this second course of radiation (salivary dysfunction, dental complications, trismus). The concomitant use of chemotherapy during this re-irradiation might be considered. In a brachytherapy approach, radiation sources used are 137 caesium, 192 iridium and 125 iodine or 198 gold permanent implant [141]. In selected recurrent NPC, brachytherapy can be used at high doses, with encouraging results, or combined with external beam radiation [142]. Otherwise, another strategy might be surgical resection that could be proposed in patients with a very localised recurrent tumour below the base of the skull.

In metastatic disease, the most effective combinations are cisplatin-based regimens. Most phase II results have shown high response rates, with a substantial proportion of complete responses, but with a small proportion of long-term disease-free survival [49]. The most effective agents are the same as those mentioned above.

From the IGR experience, one of the most effective regimens remains the combination of cisplatin, bleomycin and 5-FU, with an overall response rate of 86%, including a 20% complete response rate [143]. It should also be noted that 4 patients with bone metastases reached long-term disease-free survival rates of 52–58 months.

The use of the new chemotherapeutic agent gemcitabine has been evaluated in chemonaïve or previously treated NPC metastatic patients (1250 mg/m^2, days 1 and 8 of a 3-week cycle). Gemcitabine seemed to have a moderate activity in these patients; none the less, this agent might be considered as an effective salvage possibility in patients who have relapsed after conventional therapies [144]. Of interest, it has recently been shown that low doses of paclitaxel [145] can inhibit the growth of NPC cells and induce apoptosis, possibly through the upregulation of p53. When high doses of paclitaxel were used, the cell growth and apoptotic processes were independent of p53 expression.

11. Conclusions

NPC are a very distinct type of head and neck cancer, in terms of their epidemiology, clinical presentation, outcome and treatment strategy. Some prognostic factors, such as locoregional extension, are well known. NPC are relatively radiosensitive and chemosensitive when compared with other head and neck cancers. Treatment strategies are multidisciplinary, combining radiotherapy with chemotherapy. The most important issue in NPC advanced patients is the high rate of treatment failure, with a high risk of local recurrence and distant metastases. However, the benefits of chemotherapy in the treatment of patients with locally advanced NPC have been demonstrated; although overall survival has not improved in randomised trials, disease-free survival rates are significantly increased following combined chemotherapy treatments, especially in the neoadjuvant setting.

Future developments may rely on improvements of the technical devices used in radiotherapy treatments; for example, intensity modulation (IMRT) to reduce the sequelae of treatments by minimising the dose given to the surrounding tissues. New drugs, new combinations of treatments or the biological modulation of response by using radiation therapy or chemotherapy are also likely future areas of improvement in the management and treatment of NPC patients.

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