Molecular Biomarkers of Nasopharyngeal Carcinoma

Subjects: Oncology

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Nasopharyngeal carcinoma (NPC) is a cancer that arises from the squamous epithelial cells that cover the lateral wall of the nasopharynx. In contrast to head and neck cancers, NPC has a distinct epidemiology, pathology, clinical characteristics, and treatment response. NPC is an endemic form of malignancy in certain parts of the world.

Keywords: nasopharyngeal carcinoma (NPC) ; Epstein–Barr virus ; epigenetics ; biomarkers ; therapeutic resistance

1. Introduction

A well-known risk factor of NPC is the Epstein–Barr virus (EBV). Despite that, distinct ethnic and geographical dissemination of NPC indicates both genetic and environmental factors (diet and tobacco smoking) play an important role in its aetiology [1]. Complex interactions of multiple factors including viral infection, an individual's genetic susceptibility, environmental factors, and dietary factors have driven the pathogenesis of this malignancy.

Up to 80% of NPC patients are diagnosed at advanced stages (clinical stages III and IV) and 10% at distant metastasis, which is associated with unfavourable outcome and poor prognosis [2][3][4][5]. This is mainly due to the fact that it is asymptomatic in its early stages, its high metastatic rate, and its inaccessibility for examination, whereby examination of the local primary tumour in the small curved structure of the nasal cavity is difficult [6]. The common symptoms of NPC include epistaxis, nasal obstruction, hearing loss, otitis media, headache, diplopia, numbness, and neck lump [7][8].

In recent decades, the advancement of diagnostic imaging and the use of concurrent radio and systemic therapy have improved overall prognosis and treatment outcomes [2]. The tumour-node-metastasis (TNM) staging system developed by the American Joint Committee on Cancer and the National Comprehensive Cancer Network (NCCN) is used in treatment decisions for NPC patients at different stages. Radiotherapy (RT) is used as a standard treatment for early stage NPC, while concurrent chemotherapy (CT) followed by adjuvant chemotherapy is the preferred treatment for stages III and IV NPC.

Although overall survival (OS) has improved due to these advanced treatments, there are still many controversies regarding these treatment approaches. For example: (1) patients still encounter tumour recurrence or develop distant metastasis after undergoing RT, especially those in the advanced stages, resulting in death [1]; (2) most patients, especially those in the advanced stages of NPC, did not benefit from the abovementioned NPC treatments [9][10]; (3) a weak tolerance to the high toxic side effects of these therapeutics has led to a delay in treatment, and ultimately death (for example, nasopharynx haemorrhage, a dangerous and serious condition resulting from radiotherapy has led to 35.7% to 100% mortality [7][11]); (4) these treatments eventually allow for tumour progression and emergency due to radio- or chemo-resistance [12][13]; (5) the advanced stages of NPC are associated with poor prognosis and poor response towards the available treatments; and (6) the absence of a reliable prediction tool for NPC recurrence and metastasis. Treatment failure for advanced stages (distant metastasis) is the primary cause of mortality from NPC, accounting for 50,000 deaths annually [4]. Since the 10-year OS rate for stage I patients is as high as 98%, it seems that the mortality rate can be reduced if the NPC is diagnosed at an earlier stage [14]. Currently, the TNM staging system does not provide information on predicting or identifying the risk of NPC progression. This has highlighted the issues of NPC diagnosis and prognosis, as well as treatment. Hence, most studies now focus on uncovering the molecular biomarkers in NPC to improve the early diagnosis approaches and discover prognostic indicators. In the current review, we have reviewed the research status of biomarkers in NPC for early diagnosis and prognosis (metastasis and recurrence).

2. Diagnostic and Prognostic Biomarker Discovery for NPC

The use of biomarkers in cancer management has recently been increased with advancements in genomics, proteomics, and transcriptomics, as well as associated technologies. Studying the biomarkers involved in NPC progression and metastasis enables us to understand the disease, identify an individual's susceptibility to the disease, and predict or

monitor patients' response toward a therapeutic treatment. Based on their role in disease management, biomarkers can be categorised into two groups: (1) prognostics, which allow for the assessment of the risk of clinical outcomes including recurrence, metastasis, and progression; and (2) diagnostic markers, which identify whether an individual has the specific disease or condition.

Therefore, biomarkers can improve the early diagnosis and prognosis approaches by assisting in identifying patients who are susceptible to developing NPC or who are at a high risk or distant metastasis or recurrence. Biomarkers are the key to preventing NPC progression, recurrence, and metastasis, as well as to developing effective therapeutic treatments. With the aid of high throughput 'omics' technologies, knowledge on the aetiology, tumorigenesis, and progression of NPC has progressed much faster, thus allowing researchers to identify potential molecular biomarkers. Several types of potential NPC molecular biomarker, including DNA (genomic), mRNA (transcriptomic), protein (proteomic), and metabolite (metabolomics) biomarkers, have been identified (**Table 1**).

Table 1. Potential biomarkers for early diagnosis of NPC.

Biomolecules	Full Name	Role	Aberration	Sources
Genomic biomarkers				
COX-2	***Cyclooxygenase-2***	**Cell proliferation, apoptosis**	**Polymorphism in rs5275**	[15]
MCP-1	***Monocyte chemoattractant protein-1***	**Monocytes or macrophages migration and infiltration**	**Polymorphism in rs1024611**	[16]
GRP78	***Glucose-regulated protein***	**Apoptosis**	**Polymorphism in rs3216733**	[17]
DC-SIGN	***Dendritic cells specific intercellular adhesion molecule 3-grabbing nonintegrin***	**Induced immune cells**	**Polymorphism in rs7252229, rs735240, rs4804803 or rs2287886**	[18][19]
HLA-A2-B46 **(Chinese)**	***Human leukocyte antigen-A2-B46***	**Immune response**	**Polymorphism in chromosome 6p21**	[20][21]
HLA-A2-B-17 **(Chinese)**	***Human leukocyte antigen-A2-B-17***	**Immune response**		
HLA-B5 **(Caucasians)**	***Human leukocyte antigen-B5***	**Immune response**		
IL-13	***Interleukin-13***		**Polymorphism in rs20541 (TT genotype)**	[22]
Chromosome 3p and 9p	**N/A**	**N/A**	**Chromosomal loss**	[23]
Chromosome 12	**N/A**	**N/A**	**Gain number**	[24]
RASSF1	**Ras association (RalGDS/AF-6) domain family member 1A**	**Tumour suppression, cell growth, proliferation**	**copy number variant in in 3p21**	[25]
CDKN2A**,** ***CDKN2B***	**Cyclin-dependent kinase inhibitor 2A, 2B**	**Tumour suppression, cell cycle**	**Allelic deletion in 9p21.3**	[26]
EGFR	**Epidermal growth factor receptor**	**Cell proliferation, cell cycles, apoptosis**	**Upregulation**	[27][28]
BamH1-W	***Bacillus amyloliquefaciens 1 WZhet***	**Viral replicative cycle**	**Upregulation**	[29][30]
A73	**N/A**	**Cell proliferation and angiogenesis**	**Polymorphism in A157154C**	[14][31]
RPMS1	**N/A**	**Cell proliferation and angiogenesis**	**Polymorphism in G155391A**	
BALF2	**N/A**	**Viral infection and replication**	**EBV variants with 162476_C or 163364_T**	[32]
miRNA biomarkers				

Biomolecules	Full Name	Role	Aberration	Sources
Genomic biomarkers				
miR17-92	MicroRNA17-92	Targeting PTEN and apoptosis protein	Upregulation	[33]
miR-155	MicroRNA-155	Leucosis	Upregulation	[34]
miR-378	MicroRNA-378	Affect tumour suppression, cell cycle	Upregulation	[35][36]
miR-141	MicroRNA-141			
miR144-3p	MicroRNA-144-3p	Targeting PTEN/Akt, cell cycle, apoptosis	Upregulation	[37]
miR-17-5p	MicroRNA-17-5p			
miR-20a-5p	MicroRNA-20a-5p			
miR-20b-5p	MicroRNA-20b-5p			
miR-205-5p	MicroRNA-205-5p			
miR-16	MicroRNA-16	Cell proliferation, invasion	Upregulation	[34]
miR-21	MicroRNA-21	Targets PDCD4, PTEN, SPRY, ERCK, and Bcl-2 family proteins		
miR-24	MicroRNA-24	Epithelial-to-mesenchymal transition	Upregulation	
miR-146a		Inflammation	Upregulation	[38]
miR-34	MicroRNA-34	Tumour suppression	Downregulation	[33]
miR-143	MicroRNA-143	Tumour suppression		
miR-145	MicroRNA-145	Tumour suppression		
let-7b-5p	MicroRNA let-7b-5p	Cell proliferation	Downregulation	[37]
miR-140-3p	MicroRNA-140-3p	Cell proliferation		
Platelet miR-34c-3p	MicroRNA-34c-3p	Tumour suppression	Upregulation	[22]
Platelet miR-18a-5p	MicroRNA-18a-5p	Tumour suppression		
MALAT1	metastasis associated with lung adenocarcinoma transcript 1	Invasion	Upregulation	[39]
AFAP1-AS1	actin filament-associated protein 1-antisense RNA1	Invasion		
AL359062	N/A	N/A		
EBER	Epstein–Barr encoding region	Cell proliferation, apoptosis, innate immunity	Four base deletion SNPs	[40]
miR-BART7-3p	BamH1 A rightward transcript 7-3p	Cell proliferation targeting NF-κB signalling, angiogenesis targeting AMPK/mTOR/HIF1 signalling	Upregulation	[2][41][42]
miR-BART13-3p	BamH1 A rightward transcript 13-3p	Cell proliferation targeting NF-κB signalling, angiogenesis targeting AMPK/mTOR/HIF1 signalling		
Protein biomarkers				
PAI-1	Plasminogen activator inhibitor 1	Angiogenesis, signalling activities	Upregulation	[43]
Fibronectin	N/A	Cell adhesion		
Mac-2 BP	Mac-2-binding protein	Cell adhesion		

Biomolecules	Full Name	Role	Aberration	Sources
Genomic biomarkers				
CTSD	Cathepsin D	Apoptosis	Upregulation	[44]
POSTN	Periostin	Cell adhesion	Upregulation	[45]
CK18	Cytokeratin 18	Transcription	Upregulation	[46]
KRT8	Keratin-8	Tumour necrosis factor-mediated signaling pathway, cell differentiation	Upregulation	[44]
STMN1	Stathmin-1	Signal transduction		
LCP1	L-plastin	Cell differentiation	Upregulation	[47]
LGALS1	Galectin-1	Apoptosis	Upregulation	[48]
S100A9	S100 calcium-binding protein A9	Cell proliferation, innate immunity, apoptosis	Upregulation	[47]
CCL5	C-C motif chemokine 5	Cell adhesion, migration, apoptosis	Upregulation	[49]
CLIC1	Chloride intracellular channel 1	Cell cycle, signal transduction	Upregulation	[50]
LMP1	Latent membrane protein	Signalling activities	Upregulation	[51]
P-Thr-sv-5	N/A	Gene expression (sub-variant of EBNA1)	subvariant of EBNA1	[52]
EBNA1/IgA	EBV nuclear antigens immunoglobulin A	Antibody against EBV antigen	Increased level	[53][54]
VCA/IgA	Viral capsid antigen immunoglobulin A	Antibody against EBV antigen		
BALF2/Ab	BALF2 antibodies	Antibody against EBV antigen	Increased level	[32]
Metabolite biomarkers				
kynurenine	N/A	Metabolism	Upregulation	[55]
N-acetylglucosaminylamine	N/A	Metabolism		
N-acetylglucosamine hydroxyphenylpyruvate	N/A	Metabolism		
Pyroglutamate	N/A	Metabolism	Upregulation	[56]
Glucose	N/A	Metabolism		
Glutamate	N/A	Metabolism		
Glycerol 1-hexadecanoate	N/A	Metabolism	Upregulation	[57]
b-hydroxybutyrate	N/A	Metabolism		
Arachidonic acid	N/A	Metabolism		
Stearic acid	N/A	Metabolism		
Linoleic acid	N/A	Metabolism		
Proline	N/A	Metabolism		

N/A. Not available.

3. NPC Diagnostic Biomarkers

Consistent findings have revealed that NPC diagnostic accuracy could be enhanced by using a panel of miRNA biomarkers. Liu et al. (2013) reported the sensitivity and specificity of an NPC diagnostic method using five plasma miRNAs (miR-16, miR-21, miR-24, miR-155, and miR-378) were 87.7% and 82.0%, respectively [34]. Another study compiling 12-miRNA signatures for early diagnosis of NPC demonstrated an accuracy of up to 100% [58]. These 12-miRNA were found to play an important role in NPC development by modulating its target genes to inhibit NF-κB kinase regulator apoptosis and regulate platelet-derived growth factor receptor α. Collectively, these findings have provided an encouraging message on the use of miRNA as a biomarker for the early diagnosis of NPC.

Recently, tumour-educated platelets that have accurate diagnostic efficiency in various other types of cancer look like a promising avenue for NPC diagnostic marker discovery. Two platelet miRNAs, namely miR-34c-3p and miR-18a-5p, which have been detected in NPC patients and healthy controls, were found to have high diagnostic ability with a sensitivity of 92.59% and specificity of 86.11% [22]. However, further functional and validation studies were not carried out. Nevertheless, it still seems to be promising as the platelets can alter the transcriptome and molecular signal by affecting its pre-mRNA splicing upon instructions given by the tumour [59]. Additionally, in contrast to other samples, its RNA expression is not affected by the genomic DNA, thus the RNA expression truly corresponds to the pathological condition of the cancer.

Proteins are found to be involved in regulating many physiological processes, including immune response, metabolism, and cellular signalling pathways, while tumour cells can utilise the protein by-product to make their favourite proteins, thus affecting anabolism and catabolism, eventually leading to an alteration of protein expression patterns. Therefore, these tumour synthesised oncogenic proteins can be used to reflect the real time state of diseases and used for NPC biomarker research.

Most of these studies have used high throughput mass spectrometry technology, data processing, system integration, cluster index analysis, and integration with information modelling to look for metabolites that reflect clinical disease phenotypes [60]. Numerous metabolites, including kynurenine, N-acetylglucosaminylamine, N-acetylglucosamine hydroxyphenylpyruvate, pyroglutamate, glucose, and glutamate, have been evaluated as potential biomarkers for early NPC diagnosis [55][56]. Further studies conducted in larger NPC cohorts also validated that a panel of seven metabolites including glycerol 1-hexadecanoate, b-hydroxybutyrate, linoleic acid, arachidonic acid, stearic acid, glucose, and proline provided strong NPC diagnosis from disease free controls, with a sensitivity of 88.0% and a specificity of 92.0% [57].

4. NPC Prognosis Biomarkers

Up to 40% of NPC patients have disease recurrence or distant metastasis even after they receive a series of CT or RT [61]. This indicates that tumour cells are able to recover from damaged cells and survive by having resistance to current therapies (CT or RT). Therefore, prediction of NPC recurrence or metastasis risk after treatment is crucial since it is the major cause of mortality in NPC patients. Particularly, molecular components that are metastasis susceptible or capable of affecting the radio- or chemo-sensitivity can be used as a prognosis biomarker (**Table 2**).

Table 2. Potential prognosis and predictive biomarkers for NPC therapeutic resistance or metastasis and recurrence after treatment.

Biomolecules	Name	Role	Aberration	Sources
β-catenin 1	**Beta-catenin1**	**Activate multiple downstream growth signalling components such as cyclin D1 and c-Myc**	**Polymorphism in rs1880481 or rs3864004**	
GSK-3*β*	***glycogen synthase kinase-3β***	**Cell growth, metabolism, gene transcription, protein translation, cytoskeletal organisation**	**Polymorphism in rs3755557**	**[62]**
APC	***adenomatous polyposis coli***	**Cell adhesion**	**Polymorphism in rs454886**	

Biomolecules	Name	Role	Aberration	Sources
XRCC1	X-ray repair cross-complementing 1	DNA repair	Polymorphism in rs25489 or Codon399	[63][64][65]
CT	*Calcitonin receptor*	Calcium homeostasis	Polymorphism in rs2528521	[66]
VCP	*Valosin-containing protein*	Proteolysis	Polymorphism in rs2074549	
IL-13	*Interleukin-13*	Chinese population with IL-13 rs20541	Polymorphisms in rs20541	[22]
ERCC1	*Excision repair 1 endonuclease non-catalytic subunit*	DNA repair	Polymorphism with C118T genotype	[67]
EBV-DNA	Epstein–Barr virus-DNA	EBV genome	Upregulation	[28]
YBX3	Y-Box Binding Protein 3	Apoptosis, Gene expression		
CBR3	Carbonyl reductase 3	Xenobiotic metabolic process		
LRIG1	Leucine-rich repeats and immunoglobulin-like domains 1	Negative regulator of tyrosine kinases signalling	Upregulation	
CXCL10	Chemokine C-X-C motif ligand 10	Chemokine receptors recruit tumour infiltrating T-lymphocytes, tumour microenvironment		
DCTN1	Dynactin-1	G2/M transition of mitotic cell cycle		
GRM4	Glutamate metabotropic receptor 4	Tumour suppression		
HDLBP	High density lipoprotein binding protein	Cholesterol metabolic process		[68]
ANXA1	Annexin	Cell cycle, apoptosis		
POLR2M	RNA polymerase II subunit M	Negative regulator of transcriptional	Downregulation	
CLASP1	Cytoplasmic linker associated protein 1	Dynamic microtubules stabilization		
FNDC3B	Fibronectin type III domain-containing protein 3B	Positive regulator of adipogenesis		
WSB2	WD repeat and SOCS box-containing protein 2	Protein ubiquitination, post-translation modification		
WNK1	lysine deficient protein kinase 1	T-cell receptor signalling pathway		
miR-203	MicroRNA-203	Targeting IL-8/Akt signalling	Downregulation	[69]
miR-324-3p	MicroRNA-324-3p	Tumour suppression		
miR-93-3p	MicroRNA-93-3p	Targeting Wnt/β-catenin signalling	Downregulation	
miR-4501	MicroRNA-4501	Cellular process		
miR-371a-5p	MicroRNA-371a-5p	Cellular pathway, apoptosis		[70][71]
miR-34c-5p	MicroRNA-34c-5p	Cell proliferation, apoptosis, targeting JAK2/STAT3 signalling pathway	Upregulation	
miR-1323	MicroRNA-1323	DNA repair		
miR-9	MicroRNA-9	MHC class I and interferon-regulated gene expression	Downregulation	[72]
miR-92a	MicroRNA-92a	Invasion, migration	Upregulation	[73]
miR-574-5p	MicroRNA-574-5p	Mesenchymal transition	Downregulation	[3]
miR-296-3p	Micro-296-3p	Cytoplasmic Translocation of c-Myc	Downregulation	[74][75]

Biomolecules	Name	Role	Aberration	Sources
RNA_0000285		homeodomain interacting protein kinase 3 (HIPK3)	Upregulation	[76]
EGFR	Epidermal growth factor receptor	Cell proliferation, cell cycles, apoptosis	Upregulation	[77]
GSTP1	Glutathione S-transferase P1	Cell adhesion, apoptosis, negative regulator of NF-kB signaling	Methylation	[78]
IGF-1R	Insulin-like growth factor-1 receptor	Cell proliferation, cell cycles and apoptosis	Upregulation	[77]
Jab1	C-Jun activation domain-binding protein-1	Cell proliferation, targeting negative regulator proteins and tumour suppressors (p27 and p53)	Upregulation	[79]
EMT	Epithelial-to-mesenchymal transition	Carcinogenesis and metastatic progression	Upregulation	[80]
β-catenin	N/A	Activate multiple downstream growth signalling components such as cyclin D1 and c-Myc	Upregulation	[81]
E-cadherin	N/A	Cell adhesion, tumour suppression	Downregulation	
GnT-V	N-acetylglucosaminyltransferase-V	Protein glycosylation, cell proliferation	Upregulation	[82]
Bcl2	B-cell lymphoma 2	Apoptosis	Upregulation	[83][84]
SPARC	Secreted protein acidic and Cysteine rich	Extracellular matrix synthesis, cell shape		
ERPIND1	Serpin family D member 1S	Invasion		
C4B	Complement C4B	Component of the classical activation pathway	Upregulation	[85]
PPIB	Ppeptidylprolyl Isomerase B	Cyclosporine A-mediated immunosuppression		
FAM173A	Family with sequence similarity 173 member A	Adenine nucleotide translocase		
Maspin	Mammary serine protease inhibitor	Tumour suppression		
GRP78	Glucose-regulated protein	Apoptosis	Upregulation	[86][87]
Mn-SOD	Manganese superoxide dismutase	Apoptosis		
14-3-3σ	14-3-3 protein sigma	Cell cycle arrest, DNA damage response, signal transduction	Downregulation	
ANXA1,3	Annexin A1, A3	Cell cycle, apoptosis	Downregulation	[88][89][90]
Nm23 H1	Non-metastatic clone 23, isoform H1	TGF-β signaling	Upregulation	
KRT1	Keratin 1	Angiogenesis	Upregulation	[91]
SAA	Serum amyloid A	MAPK activities, innate immune response	Downregulation	[92]
HSP27	Heat shock protein 27	Apoptosis, cell differentiation	Upregulation	[93]

N/A. Not available

One study acknowledged the value of EBV-DNA for early NPC recurrence after treatment [94]. Most of the patients had EBV-DNA elevated prior to the disease recurrence [28]. The accuracy, sensitivity, and specificity of recurrence diagnostic using EBV-DNA were 87.0%, 82.3%, and 80.0%, respectively [28]. In another study, the circulating EBV-DNA concentration was found to be higher in recurrent NPC plasma compared to primary NPC plasma, thus implying that recurrence risk can be predicted by detecting the circulating EBV-DNA [95]. The National Comprehensive Cancer Network also recommends monitoring NPC patients with EBV-DNA [96]. This EBV-DNA biomarker was further strengthened by combination with a predictive tool, namely distant metastasis gene signature (DMGN), which constitutes 13 genes including DCTN1 , YBX3 ,

GRM4 , HDLBP, POLR2M , CLASP1 , CBR3 , FNDC3B , WSB2 , LRIG1 , ANXA1 , WNK1 , and CXCL10 to examine whether the patients can benefit from concurrent CT. The patients with the higher predicted metastasis risk would have less sensitivity to concurrent CT [68].

Moreover, by looking at mRNA involved in NPC progression, the subtype of disease, prognosis, and therapeutic effect in NPC could be predicted [97][98][99]. For example, analysed miRNA expression profile of radioresistant and radiosensitive NPC cell lines by next generation deep sequencing have revealed that downregulation of miR-203, miR-324-3p, miR-93-3p, and miR-4501 and upregulation of miR-371a-5p, miR-34c-5p, and miR-1323 contribute to mediating radio-resistance in NPC [69][70][88]. Additionally, miR-574-5p, miR-9 and miR92a, which modulate the expression of MHC class I and interferon-regulated genes associated with NPC metastasis, could potentially be non-invasive blood-based biomarkers for metastasis prediction [72][73]. RNA sequencing of NPC patients' peripheral blood mononuclear cells (PBMC) before and after RT has revealed 11 potential mRNA prognostic biomarkers for NPC for post-RT evaluation [100]. RNA_0000285 at homeodomain interacting protein kinase 3 (HIPK3) was observed in high level radio-resistance NPC patients and low radiosensitive NPC patients, thus showing its ability to predict NPC radiosensitivity [76].

Furthermore, as mentioned previously, the residue of cigarette smoke promotes cancer progression. Cigarette smoke was found to be associated with poor prognosis of chemotherapy and radiotherapy. Nicotine in cigarette smoke promoted chemoresistance by affecting the ATP-biding cassette transporter G2 via downregulation of miR-296-3p and Akt-mediated pathways [74][75]. Furthermore, hypoxia induced through smoking can facilitate tumour angiogenesis, invasion, reoccurrence, and metastasis. Therefore, the downregulation of miR-296-3p in patients could be a potential prognosis or predictive biomarker for recurrence and metastasis.

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