OPEN ACCESS

SSTR2 positively associates with EGFR and predicts poor prognosis in nasopharyngeal carcinoma

Yue Xu ,[1] Zihan Quan,[1] Yuting Zhan,[1] Haihua Wang,[1] Jiadi Luo,[1] Weiyuan Wang,[2] Songqing Fan[1]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jcp-2023-208987).

[1]Pathology, The Second Xiangya Hospital of Central South University, Changsha, China
[2]Pathology, Xiangya Hospital of Central South University, Changsha, China

Correspondence to
Professor Songqing Fan;
songqingfan@csu.edu.cn

Received 29 May 2023
Accepted 1 September 2023
Published Online First
27 September 2023

ABSTRACT

Aims Epidermal growth factor receptor (EGFR) belongs to the receptor tyrosine kinases family and overexpression of EGFR has been linked to poor prognosis and cancer progression. Somatostatin receptor 2 (SSTR2) is a G-protein-coupled receptor (GPCR) with diverse biological functions in humans, and it is upregulated through the NF-KB signalling pathway in nasopharyngeal carcinomas (NPC). However, no studies have examined the EGFR and SSTR2 in NPC. This study aimed to investigate whether SSTR2 is associated with EGFR and clinicopathological features in NPC.

Methods Bioinformatics analysis was performed to assess the correlation between EGFR and SSTR2 based on the GEO database. The expression of SSTR2 and EGFR was evaluated by immunohistochemistry (IHC) in 491 cases of NPC and 50 cases of non-cancerous nasopharyngeal epithelium.

Results The bioinformatics analysis and IHC showed a positive correlation between SSTR2 and EGFR in NPC. High expression of SSTR2 and EGFR was significantly increased in NPC patients compared with non-cancerous nasopharyngeal epithelium. High expression of SSTR2 and/or EGFR was associated with a worse outcome and a higher risk of progression. The study found that patients receiving chemoradiotherapy (CR) with high expression of SSTR2, high expression of EGFR, and high coexpression of SSTR2 and EGFR had a poorer prognosis in both progression-free survival (PFS) and overall survival (OS). Interestingly, NPC patients with high expression of SSTR2, high expression of EGFR, high coexpression of EGFR and SSTR2, and EGFR/SSTR2 anyone high expression had a better prognosis with CR combined with targeted therapy. Cox multivariate analysis identified SSTR2 and EGFR as independent poor predictors of PFS.

Conclusion Our study is the first to shed light on the intricate relationship between SSTR2 and EGFR in NPC and provides new insights into the potential benefits of EGFR targeted therapy for patients with high SSTR2 expression. Additionally, SSTR2 has potential as a new biomarker for poor prognosis in NPC patients.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Recent studies have highlighted the effectiveness of epidermal growth factor receptor (EGFR)-targeted drugs in nasopharyngeal carcinomas (NPC), yet drug resistance has emerged as a challenge. SSTR2, highly expressed in NPC, is considered a potential tumour marker and therapeutic target.

WHAT THIS STUDY ADDS

⇒ This scientific article explores the correlation between SSTR2 and EGFR expression in NPC at the protein level and investigates their prognostic significance in response to different treatments. Through a retrospective analysis of clinical data and tissue samples, a significant correlation between SSTR2 and EGFR expression was observed, suggesting a potential functional relationship.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study emphasises the importance of considering the expression profiles of these receptors for personalised therapeutic approaches in NPC treatment and lays a foundation for the development of targeted drugs and signalling pathways involving EGFR and SSTR2.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is an epithelial cancer that occurs in the mucosa lining of the nasopharynx. This cancer is caused by a combination of factors, with the most significant being infection with Epstein-Barr virus (EBV). Persistently elevated EBV antibody levels are considered a major risk factor for NPC.[1–3] NPC is a regional cancer, with high incidence rates in southern China and Southeast Asia.[2 4] The disease is classified into two types based on histological analysis: non-keratinising squamous cell carcinoma and keratinising squamous cell carcinoma. The majority of NPC cases in China are non-keratinising squamous cell carcinoma and characterised by high levels of EBV antibodies.[2 5]

Somatostatin (SST) is a potent neuroendocrine hormone that is widely expressed in the human body and plays a crucial role in regulating cell proliferation. In addition to SST receptor 2 (SSTR2), SST has four membrane surface receptors collectively known as SSTRs.[6 7] It is widely accepted that SSTRs exert an antiproliferative effect on cells and trigger downstream signalling that promotes apoptosis and inhibits tumour growth factors.[8–10] SSTR2 is a G-protein-coupled receptor (GPCR) with diverse biological functions in humans. The activation of the SSTR2 pathway is known to cause cell cycle arrest or apoptosis in low-grade neuroendocrine tumours. However, the opposite occurs in high-grade neuroendocrine tumours and small-cell

Check for updates

© Author(s) (or their employer(s)) 2024. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Xu Y, Quan Z, Zhan Y, *et al*. *J Clin Pathol* 2024;**77**:829–834.

J Clin Pathol: first published as 10.1136/jcp-2023-208987 on 27 September 2023. Downloaded from http://jcp.bmj.com/ on May 25, 2025 at Department GEZ-LTA Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

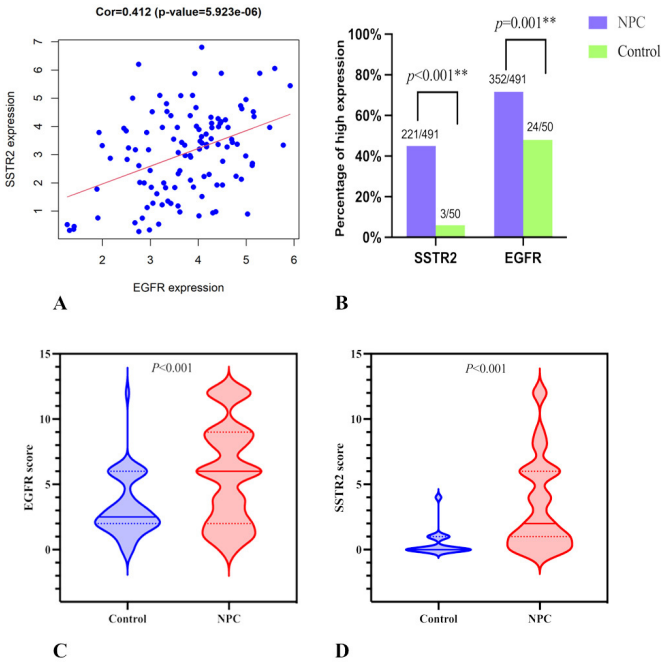

Figure 1 Bioinformatics analysis and patients with NPC and non-NPC expressing different levels of SSTR2 and EGFR. (A) Scatter plot demonstrating a positive correlation between EGFR and SSTR2 at the mRNA level in the GEO database (R=0.412). (B) Bar graphs showing the expression levels of SSTR2 and EGFR in patients with NPC (n=491) and non-NPC (n=50) control group, as determined by immunohistochemistry. (C) Violin plots depicting the distribution of SSTR2 and EGFR scores between the NPC and control groups. The NPC group had a significantly higher proportion of patients with high SSTR2 and EGFR expression. EGFR, epidermal growth factor receptor; NPC, nasopharyngeal carcinomas. （*p<0.05,** p<0.01 ）

lung cancers, where SSTR2 is upregulated, leading to tumour growth.[1 11 12]

Epidermal growth factor receptor (EGFR) belongs to the receptor tyrosine kinases family and overexpression of EGFR has been linked to poor prognosis and cancer progression. The EGFR plays a crucial role in maintaining homeostasis in epithelial tissues during normal physiological conditions. However, mutations or overexpression of EGFR occurred frequently in

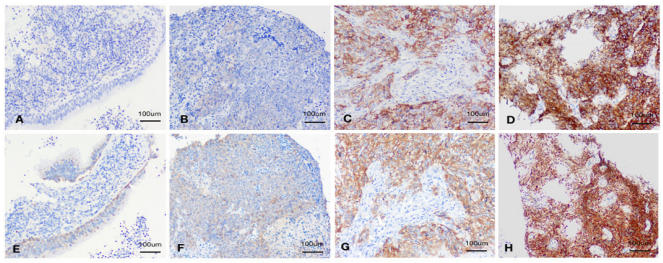

Figure 2 Representative IHC images of SSTR2 and EGFR protein expression in NPC and non-cancerous nasopharyngeal epithelium. (A, E) weak expression of SSTR2 and EGFR in non-cancer nasopharyngeal epithelium, while (B, F) weak expression of SSTR2 and EGFR in NPC. (C, G) Moderate expression of SSTR2 and EGFR in NPC, and (D, H) strong expression of SSTR2 and EGFR in NPC. The magnification of the light microscope used for these images is ×100x. EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; NPC, nasopharyngeal carcinomas.

pathological conditions, leading to the development of tumours including head and neck squamous cell carcinomas. EGFR activates various signalling pathways that transmit signals from the cell surface to the nucleus, promoting cellular survival, proliferation and differentiation.[13 14] Anti-human EGFR monoclonal antibodies have been developed as a treatment option for cancers such as NPC. The combination of chemoradiotherapy (CR) and EGFR-targeted therapy has been shown to significantly improve survival rates. LMP1, a proteins product of EBV, governs proliferative signalling pathways, including those associated with EGFR and NF-KB. In NPC, NF-KB signalling has been demonstrated to regulate SSTR2 expression, and additionally, EGFR-mediated MAPK/ERK signalling has also been shown to regulate SSTR2.[1 5 8 15–17] However, the potential relationship between EGFR and SSTR2 has not been thoroughly investigated in NPC. Our study is the first to shed light on the intricate relationship between SSTR2 and EGFR in NPC and provides new insights into the potential benefits of EGFR targeted therapy for patients with high SSTR2 expression. In addition, SSTR2 has potential as a new biomarker for poor prognosis in NPC patients. These findings could potentially offer a theoretical foundation for investigating signalling pathways and advancing the development of future targeted therapeutic agents.

MATERIALS AND METHODS

Bioinformatics analysis

It was obtained mRNA-seq data from 113 patients with NPC (GSE102349) from the GEO database (https://www.ncbi.nlm.nih.gov/geo/). We normalised and analysed this data to investigate the correlation between EGFR and SSTR2.

Tissue specimens and clinical data

This study included 491 NPC samples and 50 non-cancerous nasopharyngeal epithelium samples. All samples were collected between 2016 and 2021 at The Second Xiangya Hospital in Changsha, China. Among the 491 NPC cases, 65 were clinically early (stages I and II) and 426 were clinically advanced (stages III and IV). A totall of 433 cases had lymph node metastases, and 37 cases had distant metastases. All participants had received a biopsy tissue prior to CR, and complete medical records as well as follow-up records were available. The pathological diagnosis of all specimens was made according to the latest WHO classification for head and neck tumours, and the patients were categorised according to the eighth edition of the UICC (Union Internationale Contre le Cancer) /AJCC (American Joint Committee on Cancer) .

Immunohistochemistry and scores

Immunohistochemistry (IHC) staining was conducted on paraffin-embedded of the NPC and non-cancerous nasopharyngeal epithelium tissues sections (4 µm). The tissues were first dewaxed and hydrated, followed by heating with EDTA repair solution for 7 min. Endogenous peroxidase was blocked using H_2O_2 (3%) for 30 min. Incubation with primary antibodies for SSTR2 (1:200; Rabbit monoclonal antibody; EP149; MXB) and EGFR (ready-to-use antibody; Rabbit monoclonal antibody; EP38Y; MXB) followed, and then secondary antibody incubation. The visualisation signal was obtained with 3, 3'-diaminobenzidine tetrachloride. We assessed staining only in epithelial cells of benign or malignant tissue and not lymphoid tissue. The staining revealed positive expression of SSTR2 and EGFR on the cytoplasm and cell membrane. The evaluation of protein expression was based on staining intensity and extent,

J Clin Pathol: first published as 10.1136/jcp-2023-208987 on 27 September 2023. Downloaded from http://jcp.bmj.com/ on May 25, 2025 at Department GEZ-LTA Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Table 1 Univariate and multivariate Cox regression analysis for PFS in NPC patients

	Univariate analysis			Multivariate analysis		
Parameters	**Average survival time (SE)/ Months**	**95% CI**	**P value**	**Exp(B)**	**95% CI**	**P value**
SSTR2			0.003**	1.68	1.01 to 2.78	0.045*
Low expression	58.83 (1.52)	55.86 to 61.80				
High expression	55.19 (2.72)	49.86 to 60.53				
EGFR			0.001**	1.96	1.05 to 3.68	0.036*
Low expression	61.89 (1.84)	58.29 to 65.49				
High expression	56.51 (2.45)	51.72 to 61.30				
Gender			0.436	1.13	0.69 to 1.84	0.644
Male	58.90 (2.47)	54.06 to 63.74				
Female	62.67 (2.52)	57.73 to 67.61				
Age			0.052	1.12	0.69 to 1.87	0.628
≤45	65.50 (2.34)	60.93 to 70.08				
>45	58.18 (2.30)	53.67 to 62.70				
T stage			0.001**	0.71	0.43 to 1.15	0.159
T1 and T2	68.62 (2.02)	64.66 to 72.59				
T3 and T4	50.65 (1.77)	47.18 to 54.11				
N stage			0.018*	0.74	0.29 to 1.88	0.527
N0	59.13 (2.46)	54.31 to 63.96				
N1/2/3	58.58 (1.96)	54.75 to 62.42				
M stage			0.001**	4.44	2.67 to 7.98	0.001**
M0	62.72 (1.97)	58.86 to 66.59				
M1	28.34 (3.42)	21.65 to 35.04				
Treatment therapy			0.001**	0.41	0.23 to 0.73	0.002**
CR	51.03 (1.98)	47.16 to 54.9				
CR and targeted therapy	56.03 (2.09)	52.06 to 57.80				

Analysis of Cox regression, *p<0.05, **p<0.01.
CR, chemoradiotherapy; eGFR, epidermal growth factor receptor; NPC, nasopharyngeal carcinomas; PFS, progression-free survival.

which were semiquantitatively assessed under light microscopy by scorers who were blinded to the case data.[18–20] Staining intensity was graded as 0 (negative), 1 (weak), 2 (moderate) and 3 (strong), while staining extent was graded as 0 (0%), 1 (1%–25%), 2 (26%–50%), 3 (51%–75%) and 4 (76%–100%). Scores were calculated by multiplying the staining intensity and extent. A score ≤2 for SSTR2 was considered low expression, while a score >2 was considered high expression. Similarly, an EGFR score of >2 was considered high expression based on data collected for NPC and previous studies.[21–24]

Statistical analysis

The statistical analyses and graphing in this study were performed using a variety of methods, including χ^2 tests, Spearman correlations, univariate Cox regression and multivariate Cox regression

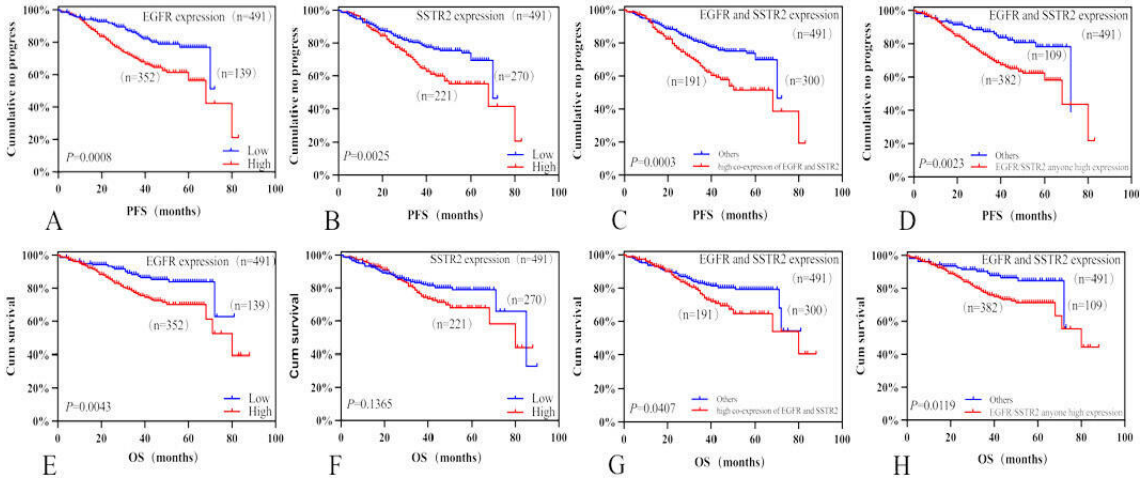

Figure 3 Kaplan-Meier analysis of a cohort of 491 patients with NPC, evaluating the effect of different levels of SSTR2 and EGFR on PFS and OS. EGFR/SSTR2 anyone high expression includes EGFR (high) and SSTR2 (high), EGFR (high) and SSTR2 (low), and EGFR (low) and SSTR2 (high). EGFR, epidermal growth factor receptor; NPC, nasopharyngeal carcinomas; OS, overall survival; PFS, progression-free survival.

J Clin Pathol: first published as 10.1136/jcp-2023-208987 on 27 September 2023. Downloaded from http://jcp.bmj.com/ on May 25, 2025 at Department GEZ-LTA Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

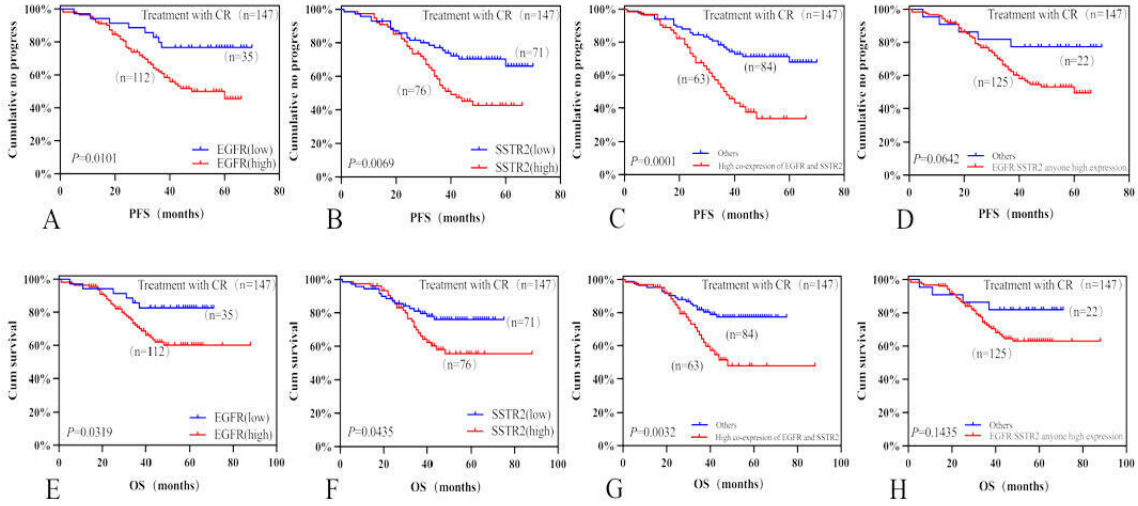

Figure 4 Kaplan-Meier analysis of a cohort of 147 patients with NPC who underwent CR, evaluating the effect of different levels of SSTR2 and EGFR on PFS and OS. EGFR/SSTR2 anyone high expression includes EGFR (high) and SSTR2 (high), EGFR (high) and SSTR2 (low), and EGFR (low) and SSTR2 (high). CR, chemoradiotherapy; EGFR, epidermal growth factor receptor; NPC, nasopharyngeal carcinomas; OS, overall survival; PFS, progression-free survival.

analysis, all of which were performed using SPSS Statistics V.26 (SPSS) for macOS. Kaplan-Meier analysis, Bar graphs and Violin plots were conducted with GraphPad Prism V.9.4.1 (GraphPad, La Jolla, California, USA) for macOS. The progression-free survival (PFS) is defined as the period from the date of diagnosis until the patient dies or the disease progresses further. The overall survival (OS) is defined as the period from the date of diagnosis to the date of death or the last known date alive. The p values were analysed as two-sided statistics, and a $p<0.05$ was considered statistically significant.

RESULTS

Patients with NPC and those with non-cancerous nasopharyngeal epithelium exhibit differential expression levels of SSTR2 and EGFR

Initially, we performed bioinformatics analysis using the GEO database, which revealed a positive correlation between SSTR2 and EGFR in NPC (R=0.412, moderate positive association) (figure 1A). Subsequently, we investigated the expression levels of SSTR2 and EGFR proteins using IHC. The study demonstrated that patients diagnosed with NPC exhibited a significantly higher expression rate of SSTR2 (45.0%, 221 out of 491) and EGFR (71.7%, 352 out of 491) in high expression compared with the control group, which exhibited a SSTR2 high expression rate of only 6.0% (3 out of 50) and an EGFR high expression rate of 48.0% (24 out of 50) (figure 1B). Furthermore, the distribution of SSTR2 and EGFR scores between the NPC and control groups were represented using violin plots, which showed significant differences between the two groups ($p<0.001$) (figure 1C,D). These findings suggest that high expression levels of SSTR2 and EGFR are significantly associated with NPC rather than non-cancerous nasopharyngeal epithelium ($p<0.05$). Here, we present a partial IHC image of SSTR2 and EGFR protein expression in NPC and non-cancerous nasopharyngeal epithelium (figure 2).

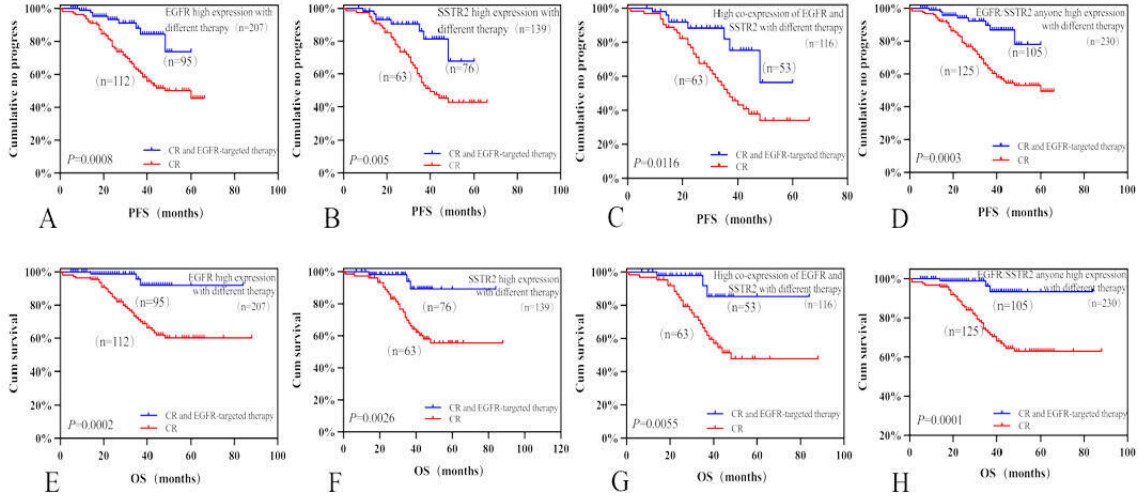

Figure 5 Kaplan-Meier analysis of different treatment options for NPC, evaluating the effect of different levels of SSTR2 and EGFR on PFS and OS. EGFR/SSTR2 anyone high expression includes EGFR (high) and SSTR2 (high), EGFR (high) and SSTR2 (low), and EGFR (low) and SSTR2 (high). EGFR, epidermal growth factor receptor; NPC, nasopharyngeal carcinomas; OS, overall survival; PFS, progression-free survival.

J Clin Pathol: first published as 10.1136/jcp-2023-208987 on 27 September 2023. Downloaded from http://jcp.bmj.com/ on May 25, 2025 at Department GEZ-LTA Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

EGFR and SSTR2 proteins expression and clinicopathological features

First, we classified and analysed NPC patients based on various factors, including age, sex, clinical stage and TNM stage. The resulting table (online supplemental table 1) revealed that NPC is more prevalent in older age groups and male. Furthermore, our study cohort included a larger proportion of patients with advanced clinical stages and lymph node metastases, while distant metastases were relatively rare. Subsequently, we investigated the correlation between SSTR2 and/or EGFR protein expression and clinicopathological features, such as gender, age, TNM stage, treatment strategy and disease progression. Online supplemental table 2 shows that patients with advanced T stage, lymph node metastases and distant metastases tended to exhibit higher expression levels of SSTR2 and/or EGFR than those with early T stage and no metastases, although this was not statistically significant ($p>0.05$). Furthermore, high expression levels of SSTR2 and EGFR were significantly associated with worse outcomes and a higher risk of progression ($p<0.05$).

Prognosis and correlation of SSTR2 and EGFR

The influence of various variables on PFS and OS was assessed using Cox univariate analysis, and the corresponding tables were created (table 1 and online supplemental table 3). Our findings revealed that high EGFR expression, advanced T stage, lymph node metastasis, distant metastasis and general CR were associated with a poor prognosis for both PFS and OS. However, high SSTR2 expression was identified as a poor prognostic factor only for PFS, while older age was found to be a poor prognostic factor solely for OS. Moreover, multivariate Cox analysis (table 1 and online supplemental table 3) was conducted to determine independent prognostic factors, which revealed that both M stage and treatment strategy were significant factors for both PFS and OS. However, SSTR2 and EGFR were independent prognostic factors only for PFS. Furthermore, K-M analysis was performed on a cohort of 491 patients (figure 3), which indicated that patients with high expression of EGFR, high coexpression of EGFR and SSTR2, and EGFR/SSTR2 anyone high expression had a poorer prognosis for both PFS and OS and high expression of SSTR2 had a poorer prognosis for PFS ($p<0.05$). Based on these studies, overexpression of SSTR2 and EGFR is detrimental to patients with NPC. SSTR2 has the potential to serve as a new biomarker for poor prognosis in patients with NPC. Additionally, we found a positive correlation between EGFR and SSTR2 at the mRNA level using the GEO database ($R=0.412$) as described previously. We also demonstrated that SSTR2 correlates with EGFR at the protein level via IHC ($R=0.296$, weak positive association) (data not shown).

EGFR-targeted therapy affected the prognosis associated with SSTR2 expression

Our study cohort consisted of 288 patients who were treated and reviewed at our institution, providing us with comprehensive and timely clinical information. Among the patients, 147 received only CR, while 141 received CR along with EGFR targeted therapy. We evaluated the clinical prognosis of these patients. First, the study found that patients receiving general CR with high expression of SSTR2, high expression of EGFR and high coexpression of both had a poorer prognosis in both PFS and OS ($p<0.05$). Although the prognosis did not reach a statistical difference between the EGFR/SSTR2 anyone high expression and others (low coexpression of EGFR and SSTR2) in PFS and OS, low coexpression had a better prognosis ($p>0.05$) (figure 4). Subsequently, we examined the prognosis of NPC patients treated with general CR combined with targeted therapy and found no significant differences in EGFR expression levels ($p>0.05$), indicating that EGFR targeted drugs improved the poor prognosis arising from high EGFR expression. Surprisingly, there was also no statistical difference in SSTR2 expression levels, between EGFR/SSTR2 anyone high expression and others (low coexpression of EGFR and SSTR2) in PFS and OS, and between high coexpression of EGFR and SSTR2 and other factors in OS (online supplemental figure 1). This finding led us to speculate whether EGFR targeted therapy could also improve the poor prognosis of NPC patients associated with high SSTR2 expression. To investigate further, we compared the prognosis of both treatment therapies and found that NPC patients with high expression of SSTR2, high expression of EGFR, high coexpression of EGFR and SSTR2, and EGFR/SSTR2 anyone high expression all had a better prognosis with CR combined with targeted therapy, with a significant statistical difference ($p<0.05$) (figure 5). Our findings suggest that CR combined with EGFR targeted therapy is more effective for NPC with high SSTR2 expression and high EGFR expression. EGFR targeted therapy significantly improves the poor prognosis of NPC patients with high expression of SSTR2 and EGFR.

DISCUSSION

The SSTR2 receptor plays a critical role in regulating cell proliferation and acts as a growth suppressor in various biological processes. Several studies have shown that SSTR2 can inhibit tumour growth in low-grade neuroendocrine tumours and prostate cancer. However, high levels of SSTR2 expression have been linked to promoting tumour growth in high-grade neuroendocrine tumours and small cell lung cancer. The study of EGFR proteins has gained significant attention in recent years due to their involvement in activating various signalling pathways and regulating cell proliferation and survival.[15 25–28] The findings of our study have significant implications for the identification of SSTR2 and EGFR as biomarkers associated with poor prognosis provides opportunities for targeted therapies. Targeting SSTR2 could be a potential strategy to improve the survival outcomes of NPC patients, particularly those with high SSTR2 expression. However, our results also suggest that the use of EGFR targeted therapy in combination with chemotherapy could be a more effective approach for patients with high SSTR2 and EGFR expression levels.

The surprising result of EGFR targeted therapy suppressing the effects of high SSTR2 expression warrants further investigation. It is possible that EGFR targeted therapy indirectly affects SSTR2 expression or that it inhibits signalling pathways that promote tumour growth in SSTR2 overexpressing cells. These findings could pave the way for developing novel treatment strategies that target both EGFR and SSTR2 in NPC patients.

In conclusion, our study provides valuable insights into the role of SSTR2 and EGFR in the prognosis of NPC patients. Our results suggest that targeting both biomarkers could be a promising strategy to improve the survival outcomes of NPC patients. Further studies are needed to validate our findings and to explore the mechanisms underlying the interaction between EGFR and SSTR2 in NPC.

Compared with previous research on the role of SSTR2 in NPC, our study stands out with a larger sample size of 491 patients. Overall, our study is the first to shed light on the intricate relationship between SSTR2 and EGFR in NPC and provides new insights into the potential benefits of EGFR targeted

J Clin Pathol: first published as 10.1136/jcp-2023-208987 on 27 September 2023. Downloaded from http://jcp.bmj.com/ on May 25, 2025 at Department GEZ-LTA Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

therapy for patients with high SSTR2 expression. Future studies could further investigate the molecular mechanisms underlying this relationship and explore potential alternative therapies for patients with high SSTR2 expression. Additionally, efforts should be made to address the toxicity concerns associated with EGFR targeted therapy and optimise treatment strategies to improve patient outcomes.[15]

Handling editor Munita Bal.

Contributors YX and SF conceived the research. YX wrote the main manuscript text and JL prepared figures. ZQ, YZ and HW collected the literature. SF and WW made significant revisions to the manuscript. All authors reviewed the manuscript. SF is responsible for the overall content as guarantor.

Funding The work included data collection, sample processing and data analysis, was funded by the National Natural Sciences Foundations of China (No. 81972838; 82272722; 82200019; 82102805), and the independent exploration and innovation project of central south university (2023ZZTS0843).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the Ethical Review Committee of Xiangya Second Hospital of Central South University approved the study protocols (Scientific and Research Ethics Committee, No. K022). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD

Yue Xu http://orcid.org/0009-0004-3620-6788

REFERENCES

1 Emanuel O, Liu J, Schartinger VH, *et al*. SSTR2 in nasopharyngeal carcinoma: relationship with latent EBV infection and potential as a therapeutic target. *Cancers (Basel)* 2021;13:4944.
2 Yoshizaki T, Kondo S, Wakisaka N, *et al*. Pathogenic role of Epstein-Barr virus latent membrane protein-1 in the development of nasopharyngeal carcinoma. *Cancer Lett* 2013;337:1–7.
3 Chen Y-P, Chan ATC, Le Q-T, *et al*. Nasopharyngeal carcinoma. *The Lancet* 2019;394:64–80.
4 Lao TD, Truong PK, Thieu HH, *et al*. Simultaneously both expression of LMP-1 and methylation of E-Cadherin: molecular biomarker in stage IV of nasopharyngeal carcinoma patients. *Balkan J Med Genet* 2021;24:57–66.
5 Tao L, Chen Y, Huang Y, *et al*. SSTR2A is constantly expressed in lymphoepithelioma-like carcinoma with squamous differentiation other than that with glandular differentiation. *J Clin Pathol* 2021;74:704–8.
6 Murakami E, Shionoya T, Komenoi S, *et al*. Cloning and characterization of novel testis-specific diacylglycerol kinase H splice variants 3 and 4. *PLoS One* 2016;11:e0162997.
7 Torrisani J, Hanoun N, Laurell H, *et al*. Identification of an upstream promoter of the human somatostatin receptor, HSSTR2, which is controlled by epigenetic modifications. *Endocrinology* 2008;149:3137–47.
8 Lechner M, Schartinger VH, Steele CD, *et al*. Somatostatin receptor 2 expression in nasopharyngeal cancer is induced by Epstein Barr virus infection: impact on prognosis, imaging and therapy. *Nat Commun* 2021;12:117.
9 Shen Z, Chen X, Li Q, *et al*. SSTR2 promoter hypermethylation is associated with the risk and progression of laryngeal squamous cell carcinoma in males. *Diagn Pathol* 2016;11:10.
10 Theodoropoulou M, Stalla GK. Somatostatin receptors: from signaling to clinical practice. *Front Neuroendocrinol* 2013;34:228–52.
11 Viswanathan K, Sadow PM. Somatostatin receptor 2 is highly sensitive and specific for Epstein-Barr virus-associated nasopharyngeal carcinoma. *Hum Pathol* 2021;117:88–100.
12 Roden AC, Rakshit S, Johnson GB, *et al*. Correlation of somatostatin receptor 2 expression, 68Ga-DOTATATE PET scan and octreotide treatment in thymic epithelial tumors. *Front Oncol* 2022;12:823667.
13 Sigismund S, Avanzato D, Lanzetti L. Emerging functions of the EGFR in cancer. *Mol Oncol* 2018;12:3–20.
14 Byeon HK, Ku M, Yang J. Beyond EGFR inhibition: multilateral combat strategies to stop the progression of head and neck cancer. *Exp Mol Med* 2019;51:8.
15 Chen X, Liang R, Zhu X. Anti-EGFR therapies in nasopharyngeal carcinoma. *Biomedicine & Pharmacotherapy* 2020;131:110649.
16 Xie L, Shi F, Li Y, *et al*. DRP1-dependent remodeling of mitochondrial morphology triggered by EBV-LMP1 increases cisplatin resistance. *Signal Transduct Target Ther* 2020;5:56.
17 Tsang CM, Lui VWY, Bruce JP, *et al*. Translational genomics of nasopharyngeal cancer. *Semin Cancer Biol* 2020;61:84–100.
18 Rufini V, Lorusso M, Inzani F, *et al*. Correction to: correlation of somatostatin receptor PET/CT imaging features and immunohistochemistry in neuroendocrine tumors of the lung: a retrospective observational study. *Eur J Nucl Med Mol Imaging* 2022;49:4289.
19 Feng J, Xie G, Zhan Y, *et al*. Elevated HSP90 Associates with expression of HIF-1A and P-AKT and is predictive of poor prognosis in nasopharyngeal carcinoma. *Histopathology* 2019;75:202–12.
20 Modi S, Jacot W, Yamashita T, *et al*. Trastuzumab deruxtecan in previously treated HER2-Low advanced breast cancer. *N Engl J Med* 2022;387:9–20.
21 Chen X, Gao A, Zhang F, *et al*. ILT4 inhibition prevents TAM- and dysfunctional T cell-mediated immunosuppression and enhances the efficacy of anti-PD-L1 therapy in NSCLC with EGFR activation. *Theranostics* 2021;11:3392–416.
22 Majala S, Vesterinen T, Seppänen H, *et al*. Correlation of somatostatin receptor 1–5 expression, [68Ga]Ga-DOTANOC, [18F]F-FDG PET/CT and clinical outcome in a prospective cohort of pancreatic neuroendocrine neoplasms. *Cancers* 2022;14:162.
23 Marx AH, Zielinski M, Kowitz C-M, *et al*. Homogeneous EGFR amplification defines a subset of aggressive Barrett's adenocarcinomas with poor prognosis. *Histopathology* 2010;57:418–26.
24 Wildemberg LEA, Vieira Neto L, Costa DF, *et al*. Validation of immunohistochemistry for somatostatin receptor subtype 2A in human somatotropinomas: comparison between quantitative real time RT-PCR and immunohistochemistry. *J Endocrinol Invest* 2012;35:580–4.
25 Jia J, Cui Y, Lu M, *et al*. The relation of EGFR expression by immunohistochemical staining and clinical response of combination treatment of nimotuzumab and chemotherapy in esophageal squamous cell carcinoma. *Clin Transl Oncol* 2016;18:592–8.
26 Kung C-P, Raab-Traub N. Epstein-Barr virus latent membrane protein 1 modulates distinctive NF-KB pathways through C-terminus-activating region 1 to regulate epidermal growth factor receptor expression. *J Virol* 2010;84:6605–14.
27 Dawson CW, Tramountanis G, Eliopoulos AG, *et al*. Epstein-Barr virus latent membrane protein 1 (LMP1) activates the phosphatidylinositol 3-kinase/AKT pathway to promote cell survival and induce actin filament remodeling. *J Biol Chem* 2003;278:3694–704.
28 Deledda A, Annunziata G, Tenore GC, *et al*. Diet-derived antioxidants and their role in inflammation, obesity and gut microbiota modulation. *Antioxidants (Basel)* 2021;10:708.

J Clin Pathol: first published as 10.1136/jcp-2023-208987 on 27 September 2023. Downloaded from http://jcp.bmj.com/ on May 25, 2025 at Department GEZ-LTA Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.