The top 100 most impactful articles and recent trends in nasopharyngeal carcinoma from 1970 to 2018: a bibliometric analysis

QingWu Wu¹, Tian Yuan¹, Zongping Zhang², Qintai Yang¹, Mingyuan Chen³, Qiong Wang⁴, Huiyi Deng¹, Huijun Qiu¹, Xinyue Wang¹ and Xuekun Huang¹

Abstract
Objective: To identify the top 100 most impactful articles in nasopharyngeal carcinoma (NPC).
Methods: Articles on NPC from 1970 to 2018 were retrieved from the Web of Science (WoS). These articles were ranked in descending order based on the number of times they were cited, and all titles and abstracts were screened to identify the top 100 most-cited articles.
Results: The earliest and most recent articles were published in 1971 and 2016, respectively. The most prolific decade was the 2000s, with 51 articles published. The highest citation count reached 1223 and the lowest was 155. Thirty-four journals contributed to the 100 articles, with the International Journal of Radiation Oncology Biology Physics contributing the most articles (n=16). Notable contribution origins were Hong Kong (n=34), the United States (n=26), and China (mainland, n=12). The top three contributors were Chan ATC, Lee AWM, and Lo KW who were from Hong Kong. The types of articles included basic research (n=50), clinical research (n=36), and reviews (n=14).

¹Department of Otolaryngology-Head and Neck Surgery, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, P.R. China
²Department of Neurosurgery, Central Hospital of Guangdong Nongken, Zhanjiang, P.R. China
³Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, Guangzhou, P.R. China
⁴Department of Otolaryngology, Shiyan People's Hospital of Baoan District in Shenzhen City, Shenzhen, P.R. China

QingWu Wu, Tian Yuan, and Zongping Zhang contributed equally to this study.
Corresponding author:
Qintai Yang, Department of Otolaryngology-Head and Neck Surgery, The Third Affiliated Hospital of Sun Yat-sen University, 600 Tian He Road, Guangzhou, 510630, P.R. China
Email: yang.qt@163.com
Conclusions: This study identified the top 100 most impactful articles in NPC and stressed the multidisciplinary and multimodal nature of NPC management. Understanding historical articles may guide future NPC study.

Keywords
Bibliometric, citation analysis, Web of Science, radiotherapy, chemotherapy, nasopharyngeal carcinoma

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Introduction
Over the past decades, the mortality rate associated with nasopharyngeal carcinoma (NPC) has decreased,1 reflecting years of research that was focused on innovative techniques for controlling and managing NPC. However, an abundance of NPC literature involving different researchers, countries, specialties, and scientific journals has emerged and it is difficult to identify the important papers.

Citation analysis is a bibliometric analysis method2 that evaluates the influence and importance of an article in a certain field by analyzing the citation count.3 It is also an affirmation to authors, institutions, and countries that have made important contributions. This method has been frequently applied and widely recognized in various disciplines, such as orthopedics,4 neurosurgery,5 ophthalmology,6 and otolaryngology.7,8 However, few articles have analyzed the highly cited NPC papers. Therefore, we aimed to identify the top 100 most-cited NPC articles from 1970 to 2018 using citation analysis.

In addition, recently published papers may not have sufficient citations mainly because of the time-dependent citation analysis.9 For example, none of the clinical articles published from 2013 to 2018 were in our top 100 most-cited list. Therefore, to more comprehensively reveal the NPC development trend and research focus, we also conducted a corresponding analysis to identify the top 10 clinical research articles from 2013 to 2018.

Methods

Search strategy
We searched “TI=(nasopharyngeal carcinoma* OR nasopharyngeal cancer* OR nasopharyngeal neoplasm* OR nasopharyngeal tumor*)” on the Web of Science (WoS). The articles ranged from January 1970 to August 2018 and the document types were original articles and reviews. The retrieved articles were ranked from highest to lowest based on the number of citations. Two researchers reviewed and screened the title and abstract of the articles. If necessary, some studies with mixed NPC factors, such as head and neck cancer and Burkitt lymphoma, were excluded. Because no human subjects were enrolled, ethics approval was not required for this study.

Data extraction
After filtering the articles, we extracted the contents including the title of each article, the number of citations, the source journal,
the first author, and the research institute and its country. Next, based on the type of article, the literature records were further divided into basic research, clinical research, and review. We extracted the type of study and the clinical evidence.

**Statistical analysis**

Data were analyzed using IBM SPSS 22.0 package (IBM Corp., Armonk, NY, USA). Descriptive statistics are presented as the count or percentage of the parameters. This study did not involve statistically significant differences.

**Results**

Our literature search yielded 17,116 articles between 1970 and 2018, and the top 100 articles on AR were identified based on the number of times they were cited (Table 1).

There were 6675 articles between 2013 and 2018, and the top 10 most-cited clinical research papers were identified (Table 2).

**Number of articles published**

The Top 100 articles were mostly published from 1971 to 2016 (Figure 1). Among them, the greatest number of articles was published in the 2000s (n=51), followed by 1990s (n=24). The number of articles in the 2010s was equal to that in the 1980s (n=10) and the 1970s had the fewest articles (n=5).

**Number of articles cited**

In these articles, the highest and lowest citation counts were 1223 and 155, respectively. The average citation count for a single article in the 1970s, 1980s, 1990s, 2000s, and 2010s was 293.2, 239.0, 271.2, 274.5, and 195.3, respectively.

**Published journals**

The 100 most influential papers were published in 34 journals. Among these journals, those with more than one article published and their impact factor are presented in Table 3. The top three journals were *International Journal of Radiation Oncology Biology Physics* (n=16), *Journal of Clinical Oncology* (n=14), and *Cancer Research* (n=11).

**Origins**

These articles were mainly from 12 countries/regions (Figure 2). Among these countries/regions, the top three were Hong Kong (n=34), USA (n=26), and China (China mainland, n=12). The second tier of countries/regions were Britain (n=7), France (n=5), Taiwan (n=5), Sweden (n=3), and Singapore (n=3). An equal number of articles originated from Canada, Germany, Italy, and the Netherlands (n=1 each).

**First authors**

There were 81 first authors who had contributed to these articles. Nine of the first authors had published more than one article. The top three authors were Chan ATC (n=6), Lee AWM (n=4), and Lo KW (n=4). They were followed by Kam MKM and Lo YMD (n=3 each) and by Lin JC, Pathmanathan R, Raab-Traub N, and Yu MC (n=2 each).

**Institutions**

These articles came from 55 institutions. There were 15 institutions with more than one published article (Table 4). Among them, the top three were the Prince of Wales Hospital (n=13), Sun Yat-Sen University Cancer Center (n=8), and Queen Elizabeth Hospital (n=5).
| Rank | Title                                                                 | Journal                                                      | Year | First Author | Institute                                      | Citation | Class |
|------|-----------------------------------------------------------------------|--------------------------------------------------------------|------|--------------|------------------------------------------------|----------|-------|
| 1    | Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: Phase III randomized intergroup study 0099 | Journal of Clinical Oncology                                   | 1998 | Al-Sarraf M  | Providence Cancer Center                        | 1223     | 2     |
| 2    | Nasopharyngeal carcinoma                                              | Lancet                                                       | 2005 | Wei WI       | Queen Mary Hospital                             | 724      | Review |
| 3    | Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: An update of the UCSF experience | International Journal of Radiation Oncology Biology Physics   | 2002 | Lee N        | University of California–San Francisco          | 638      | 4     |
| 4    | The enigmatic epidemiology of nasopharyngeal carcinoma               | Cancer Epidemiology Biomarkers and Prevention Biology         | 2006 | Chang ET     | Northern California Cancer Center               | 604      | Review |
| 5    | Epidemiology of nasopharyngeal carcinoma                             | Seminars in Cancer Biology                                   | 2002 | Yu MC        | Norris Comprehensive Cancer Center              | 517      | Review |
| 6    | Epstein-Barr virus-specific IgA serum antibodies as an outstanding feature of nasopharyngeal carcinoma | International Journal of Cancer                               | 1976 | Henle G      | the Children's Hospital of Philadelphia and School of Medicine | 491      | Technique |
| 7    | Retrospective analysis of 5037 patients with nasopharyngeal carcinoma treated during 1976-1985 - overall survival and patterns of failure | International Journal of Radiation Oncology Biology Physics   | 1992 | Lee AWM      | Queen Elizabeth Hospital                        | 446      | 4     |

(continued)
| Rank | Title                                                                 | Journal                                      | Year | First Author | Institute                             | Citation | Class |
|------|----------------------------------------------------------------------|----------------------------------------------|------|--------------|---------------------------------------|----------|-------|
| 8    | Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: Positive effect on overall and progression-free survival | Journal of Clinical Oncology                  | 2003 | Lin JC       | Taichung Veterans General Hospital    | 431      | 2     |
| 9    | Expression of Epstein-Barr virus-encoded proteins in nasopharyngeal carcinoma | International Journal of Cancer              | 1988 | Fahraeus R   | Karolinska Institute                 | 414      | Technique |
| 10   | EB viral genomes in epithelial nasopharyngeal carcinoma cells         | Nature-New Biology                           | 1973 | Wolf H       | University of Erlangen Nuremberg     | 413      | Technique |
| 11   | Epstein-Barr virus gene-expression in nasopharyngeal carcinoma       | Journal of General Virology                  | 1988 | Young LS     | University of Birmingham             | 411      | Technique |
| 12   | Quantitative analysis of cell-free Epstein-Barr virus DNA in plasma of patients with Nasopharyngeal carcinoma | Cancer Research                              | 1999 | Lo YMD       | The Chinese University of Hong Kong  | 407      | Technique |
| 13   | Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: Initial report on a randomized controlled clinical trial | International Journal of Radiation Oncology Biology Physics | 2006 | Pow Edmond HN | University of Hong Kong              | 392      | 2     |
| Rank | Title                                                                                     | Journal                                      | Year | First Author | Institute                      | Citation | Class |
|------|-------------------------------------------------------------------------------------------|----------------------------------------------|------|--------------|--------------------------------|----------|-------|
| 14   | Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients | Journal of Clinical Oncology                  | 2007 | Kam MKM      | Prince of Wales Hospital       | 386      | 2     |
| 15   | Epstein-Barr-virus latent gene-transcription in nasopharyngeal carcinoma-cells - coexpression of EBNA1, LMP1, and LMP2 transcripts | Journal of Virology                          | 1992 | Brooks L     | University of Binningham      | 383      | Technique |
| 16   | Clonal proliferations of cells infected with Epstein-Barr virus in preinvasive lesions related to nasopharyngeal carcinoma | New England Journal of Medicine               | 1995 | Pathmanathan R | University of North Carolina | 377      | Technique |
| 17   | Quantification of plasma Epstein-Barr virus DNA in patients with advanced nasopharyngeal carcinoma | New England Journal of Medicine               | 2004 | Lin JC       | Taichung Veterans General Hospital | 375      | Technique |
| 18   | Chemotherapy in locally advanced nasopharyngeal carcinoma: An individual patient data meta-analysis of eight randomized trials and 1753 patients | International Journal of Radiation Oncology Biology Physics | 2006 | Baujat B     | Institut Gustave Roussy       | 367      | 1     |
| Rank | Title                                                                                                                                                                                                 | Journal                                      | Year | First Author | Institute                                      | Citation | Class |
|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|------|--------------|------------------------------------------------|----------|-------|
| 19   | Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against Cancer stage III and IV Nasopharyngeal Cancer of the Endemic Variety | Journal of Clinical Oncology                  | 2005 | Wee J        | National University of Singapore               | 356      | 2     |
| 20   | Epstein-Barr virus in the pathogenesis of NPC                                                                                                                                                           | Seminars in Cancer Biology                  | 2002 | Raab-Traub N | Lineberger Comprehensive Cancer Center         | 346      | Review |
| 21   | Focus on nasopharyngeal carcinoma                                                                                                                                                                      | Cancer Cell                                  | 2004 | Lo KW        | Prince of Wales Hospital                       | 335      | Review |
| 22   | Treatment results for nasopharyngeal carcinoma in the modern era: The Hong Kong experience                                                                                                               | International Journal of Radiation Oncology | 2005 | Lee AWM      | Pamela Youde Nethersole Eastern Hospital       | 325      | 4     |
| 23   | Treatment of nasopharyngeal carcinoma with intensity-modulated radiotherapy: The Hong Kong experience                                                                                                 | International Journal of Radiation Oncology | 2004 | Kam MKM      | Prince of Wales Hospital                       | 313      | 4     |
| 24   | MicroRNA 29c is down-regulated in nasopharyngeal carcinomas, up-regulating mRNAs encoding extracellular matrix proteins                                                                                | Proceedings of the National Academy of      | 2008 | Sengupta Srikumar | National Cancer Institute                      | 297      | Technique |
|      | (continued)                                                                                                                                                                                            | Sciences of the United States of America   |      |              |                                                |          |       |
| Rank | Title                                                                                                                                                                                                 | Journal                                                      | Year | First Author | Institute                                           | Citation | Class |
|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|------|--------------|-----------------------------------------------------|----------|-------|
| 25   | How does intensity-modulated radiotherapy versus conventional two-dimensional radiotherapy influence the treatment results in nasopharyngeal carcinoma patients? | International Journal of Radiation Oncology Biology Physics | 2011 | Lai SZ       | Sun Yat-Sen University Cancer Center                | 285      | 4     |
| 26   | Intensity-modulated radiation therapy (IMRT) for nasopharynx cancer: Update of the memorial Sloan-Kettering experience                                                                 | International Journal of Radiation Oncology Biology Physics | 2006 | Wolden SL    | Memorial Sloan-Kettering Cancer Center              | 282      | 4     |
| 27   | Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: Radiation therapy oncology group phase II trial 0225 | Journal of Clinical Oncology                                  | 2009 | Lee Nancy    | Memorial Sloan-Kettering Cancer Center              | 280      | 3     |
| 28   | Concurrent chemotherapy-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: Progression-free survival analysis of a phase III randomized trial | Journal of Clinical Oncology                                  | 2002 | Chan ATC     | Prince of Wales Hospital                            | 278      | 2     |
| 29   | Identification of cancer stem cell-like side population cells in human nasopharyngeal carcinoma cell line                                                                                           | Cancer Research                                             | 2007 | Wang J       | Sun Yat-Sen University Cancer Center                | 262      | Technique |

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| Rank | Title                                                                                                                                                                                                 | Journal                                      | Year | First Author | Institute                                      | Citation | Class |
|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|------|--------------|------------------------------------------------|----------|-------|
| 30   | Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma                                              | Journal of the National Cancer Institute     | 2005 | Chan ATC     | Prince of Wales Hospital                       | 262      | 2     |
| 31   | Bmi-1 is a novel molecular marker of nasopharyngeal carcinoma progression and immortalizes primary human nasopharyngeal epithelial cells                                                                             | Cancer Research                             | 2006 | Song LB      | Sun Yat-sen University Cancer Center           | 256      | Technique |
| 32   | Preliminary results of a randomized study on therapeutic gain by concurrent chemotherapy for regionally-advanced nasopharyngeal carcinoma: NPC-9901 trial by the Hong Kong nasopharyngeal cancer study group | Journal of Clinical Oncology                 | 2005 | Lee AWM      | Pamela Youde Nethersole Eastern Hospital       | 256      | 2     |
| 33   | Nasopharyngeal carcinoma cell line (C666-1) consistently harbouring Epstein-Barr virus                                                                                                                  | International Journal of Cancer             | 1999 | Cheung ST    | Prince of Wales Hospital                       | 249      | Technique |
| 34   | Mir-26a inhibits cell growth and tumorigenesis of nasopharyngeal carcinoma through repression of ezh2                                                                                                       | Cancer Research                             | 2011 | Lu J         | Nanfang Hospital                               | 247      | Technique |
| 35   | Serologic markers of Epstein-Barr virus infection and nasopharyngeal carcinoma in Taiwanese men                                                                                                             | New England Journal of Medicine             | 2001 | Chien YC     | National Taiwan University                     | 243      | Technique |

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| Rank | Title                                                                 | Journal                      | Year | First Author | Institute                              | Citation | Class |
|------|-----------------------------------------------------------------------|------------------------------|------|--------------|----------------------------------------|----------|-------|
| 36   | High frequency of promoter hypermethylation of rassfla in nasopharyngeal carcinoma | Cancer Research              | 2001 | Lo KW        | Prince of Wales Hospital               | 242      | Technique |
| 37   | Results of a prospective randomized trial comparing neo-adjuvant chemotherapy plus radiotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma | Journal of Clinical Oncology  | 2001 | Ma J         | Sun Yat-Sen University Cancer Center   | 242      | 2     |
| 38   | Quantitative and temporal correlation between circulating cell-free Epstein-Barr virus DNA and tumor recurrence in nasopharyngeal carcinoma | Cancer Research              | 1999 | Lo YMD       | The Chinese University of Hong Kong    | 241      | Technique |
| 39   | Abundant expression of eber I small nuclear-RNA in nasopharyngeal carcinoma - a morphologically distinctive target for detection of Epstein-Barr virus in formalin-fixed paraffin-embedded carcinoma specimens | American Journal of Pathology | 1991 | Wu TC        | Johns Hopkins School of Medicine       | 240      | Technique |
| 40   | The additional value of chemotherapy to radiotherapy in locally advanced nasopharyngeal carcinoma: A meta-analysis of the published literature | Journal of Clinical Oncology  | 2004 | Langendijk JA | University Hospital Vrije Universiteit | 235      | 1     |

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| Rank | Title                                                                 | Journal                          | Year | First Author       | Institute                                      | Citation | Class |
|------|----------------------------------------------------------------------|----------------------------------|------|-------------------|-----------------------------------------------|----------|-------|
| 41   | Norepinephrine up-regulates the expression of vascular endothelial    | Cancer Research                  | 2006 | Yang Eric V.      | The Ohio State University Medical Center      | 234      | Technique |
|      | growth factor, matrix metalloproteinase (MMP)-2, and MMP-9 in        |                                  |      |                   |                                               |          |       |
|      | nasopharyngeal carcinoma tumor cells                                |                                  |      |                   |                                               |          |       |
| 42   | Nasopharyngeal carcinoma: Molecular biomarker discovery and progress | Molecular Cancer                 | 2007 | Cho William Chi-  | Queen Elizabeth Hospital                      | 230      | Review |
|      |                                                                      |                                  |      | shing             |                                               |          |       |
| 43   | Coexpression of hypoxia-inducible factors 1 alpha and 2 alpha,     | Clinical Cancer Research         | 2002 | Hui EP            | Prince of Wales Hospital                      | 230      | Technique |
|      | carbonic anhydrase ix, and vascular endothelial growth factor in    |                                  |      |                   |                                               |          |       |
|      | nasopharyngeal carcinoma and relationship to survival               |                                  |      |                   |                                               |          |       |
| 44   | Treatment of nasopharyngeal carcinoma with Epstein-Barr virus-     | Blood                            | 2005 | Straathof KCM     | Baylor College of Medicine                    | 226      | 4     |
|      | specific T lymphocytes                                              |                                  |      |                   |                                               |          |       |
| 45   | Nasopharyngeal carcinoma                                            | Annals of Oncology               | 2002 | Chan ATC          | Prince of Wales Hospital                      | 226      | Review |
| 46   | The differentiated form of nasopharyngeal carcinoma contains        | International Journal of Cancer  | 1987 | Raab-Traub        | Lineberger Cancer Research Center              | 223      | Technique |
|      | Epstein-Barr virus-DNA                                              |                                  |      | N                 |                                               |          |       |
| 47   | Randomized phase II trial of concurrent cisplatin-radiotherapy with | Journal of Clinical Oncology      | 2009 | Hui Edwin P       | Prince of Wales Hospital                      | 221      | 2     |
|      | or without neoadjuvant docetaxel and cisplatin in advanced naso-     |                                  |      |                   |                                               |          |       |
|      | pharyngeal carcinoma                                                |                                  |      |                   |                                               |          |       |

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| Rank | Title                                                                 | Journal                                           | Year | First Author  | Institute                      | Citation | Class |
|------|----------------------------------------------------------------------|---------------------------------------------------|------|---------------|--------------------------------|----------|-------|
| 48   | Isolation and sequencing of the Epstein-Barr virus bnlf-1 gene (LMP1) from a Chinese nasopharyngeal carcinoma | Journal of General Virology                        | 1991 | Hu LF         | Karolinska Institute            | 219      |       |
| 49   | Modulation of LMP1 protein expression by EBV-encoded miRNAs          | Proceedings of The National Academy of Sciences of the United States of America | 2007 | Lo Angela KF  | Sidney Kimmel Cancer Center     | 214      |       |
| 50   | An unusual virus in cultures from a human nasopharyngeal carcinoma   | Journal of the National Cancer Institute           | 1971 | Achong BG     | University of Bristol Medical School | 213      |       |
| 51   | The infratemporal fossa approach for nasopharyngeal tumors           | Laryngoscope                                      | 1983 | Fisch U       | University of Zurich Kantonsspital | 211      |       |
| 52   | Plasma Epstein-Barr virus DNA and residual disease after radiotherapy for undifferentiated nasopharyngeal carcinoma | Journal of the National Cancer Institute           | 2002 | Chan ATC      | Prince of Wales Hospital        | 208      |       |
| 53   | Cantonese-style salted fish as a cause of nasopharyngeal carcinoma - report of a case-control study in Hong-Kong | Cancer Research                                   | 1986 | Yu MC         | University of Southern California | 207      |       |
| 54   | Bcl-2 proto-oncogene expression in Epstein-Barr virus-associated nasopharyngeal carcinoma | International Journal of Cancer                   | 1993 | Lu QL         | Imperial Cancer Research Fund    | 205      |       |
| 55   | Comparison of treatment plans involving intensity-modulated radiotherapy for nasopharyngeal carcinoma | International Journal of Radiation Oncology Biology Physics | 2000 | Xia P         | University of California        | 201      |       |

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| Rank | Title                                                                 | Journal                                      | Year | First Author | Institute                     | Citation | Class |
|------|------------------------------------------------------------------------|----------------------------------------------|------|--------------|-------------------------------|----------|-------|
| 56   | MicroRNA deregulation and pathway alterations in nasopharyngeal carcinoma | British Journal of Cancer                     | 2009 | Chen HC      | Chang Gung University          | 200      | Technique |
| 57   | A prospective randomized study of chemotherapy adjunctive to definitive radiotherapy in advanced nasopharyngeal carcinoma | International Journal of Radiation Oncology Biology Physics | 1995 | Chan ATC     | Prince of Wales Hospital       | 200      | 2     |
| 58   | A genome-wide association study of nasopharyngeal carcinoma identifies three new susceptibility loci | Nature Genetics                             | 2010 | Bei JX       | Sun Yat-sen University Cancer Center | 199      | Technique |
| 59   | Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: A phase 3 multicentre randomised controlled trial | Lancet Oncology                             | 2012 | Chen L       | Sun Yat-sen University Cancer Center | 198      | 2     |
| 60   | Preliminary report of the Asian-Oceanian clinical oncology association randomized trial comparing cisplatin and epirubicin followed by radiotherapy versus radiotherapy alone in the treatment of patients with locoregionally advanced nasopharyngeal carcinoma | Cancer                                      | 1998 | Chua DTT     | Queen Mary Hospital            | 198      | 2     |

(continued)
| Rank | Title                                                                 | Journal                                      | Year | First Author | Institute                               | Citation | Class |
|------|----------------------------------------------------------------------|----------------------------------------------|------|--------------|-----------------------------------------|----------|-------|
| 61   | Reirradiation of recurrent nasopharyngeal carcinoma - treatment techniques and results | International Journal of Radiation Oncology Biology Physics | 1987 | Wang CC      | Massachusetts General Hospital Cancer Center | 198      | 4     |
| 62   | Adjuvant chemotherapy with vincristine, cyclophosphamide, and doxorubicin after radiotherapy in local-regional nasopharyngeal cancer - results of a 4-year multicenter randomized study | Journal of Clinical Oncology                 | 1988 | Rossi A      | Istituto Nazionale Tumori                | 197      | 2     |
| 63   | Induction of cyclooxygenase-2 by Epstein-Barr virus latent membrane protein 1 is involved in vascular endothelial growth factor production in nasopharyngeal carcinoma cells | Proceedings of The National Academy of Sciences of The United States of America | 2001 | Murono S     | Lineberger Comprehensive Cancer Center | 195      | Technique |
| 64   | Molecular prognostication of nasopharyngeal carcinoma by quantitative analysis of circulating Epstein-Barr virus DNA | Cancer Research                              | 2000 | Lo YMD       | The Chinese University of Hong Kong      | 195      | Technique |
| 65   | Preliminary results of a randomized trial comparing neoadjuvant chemotherapy (cisplatin, epirubicin, bleomycin) plus radiotherapy vs radiotherapy alone in stage IV (\(n=2, m=0\)) undifferentiated nasopharyngeal carcinoma: a positive effect on progression-free survival | International Journal of Radiation Oncology Biology Physics | 1996 | Cvitkovic E   | Institute Gustave Roussy                 | 193      | 2     |
Table 1. Continued.

| Rank | Title                                                                 | Journal                                                                 | Year | First Author | Institute                          | Citation | Class |
|------|------------------------------------------------------------------------|-------------------------------------------------------------------------|------|--------------|------------------------------------|----------|-------|
| 66   | Deletions within the LMP1 oncogene of Epstein-Barr virus are clustered in Hodgkin's-disease and identical to those observed in nasopharyngeal carcinoma | Blood                                                                   | 1993 | Knecht H     | CHUV University Hospital            | 190      |       |
| 67   | Carcinoma of the nasopharynx treated by radiotherapy alone: Determinants of local and regional control | International Journal of Radiation Oncology Biology Physics              | 1997 | Sanguineti G | M.D. Anderson Cancer Center         | 187      | 4     |
| 68   | Linkage of a nasopharyngeal carcinoma susceptibility locus to the HLA region | Nature                                                                  | 1990 | Lu SJ        | People's Regional Hospital          | 186      |       |
| 69   | Analysis of 1379 patients with nasopharyngeal carcinoma treated by radiation | Cancer                                                                  | 1988 | Qin DX       | Chinese Academy of Medical Sciences | 186      |       |
| 70   | Histo-pathology of nasopharyngeal carcinoma - correlations with epidemiology, survival rates and other biological characteristics | Cancer                                                                  | 1979 | Shanmugaratnam K | University of Singapore           | 186      |       |
| 71   | Nasopharyngeal cancer detection based on blood plasma surface-enhanced Raman spectroscopy and multivariate analysis | Biosensors & Bioelectronics                                              | 2010 | Feng SY      | Fujian Normal University            | 184      |       |
| 72   | Intensity-modulated radiotherapy in nasopharyngeal carcinoma: Dosimetric advantage over conventional plans and feasibility of dose escalation | International Journal of Radiation Oncology Biology Physics              | 2003 | Kam MKM      | Prince of Wales Hospital            | 184      | 4     |

(continued)
| Rank | Title                                                                 | Journal                               | Year | First Author            | Institute                            | Citation | Class       |
|------|-----------------------------------------------------------------------|---------------------------------------|------|-------------------------|--------------------------------------|----------|-------------|
| 73   | Blood diffusion and th1-suppressive effects of galectin-9-containing exosomes released by Epstein-Barr virus-infected nasopharyngeal carcinoma cells | Blood                                 | 2009 | Klibi Jihene            | Universite Paris-Sud                  | 183      | Technique   |
| 74   | miR-218 suppresses nasopharyngeal cancer progression through downregulation of survivin and the SLIT2-ROBO1 pathway | Cancer Research                       | 2011 | Alajez Nehad M          | Ontario Cancer Institute              | 182      | Technique   |
| 75   | Cloning and characterization of the latent membrane-protein (LMP) of a specific Epstein-Barr virus variant derived from the nasopharyngeal carcinoma in the Taiwanese population | Oncogene                              | 1992 | Chen ML                 | Chang-Gung Medical College            | 182      | Technique   |
| 76   | Establishment and characterization of 3 transplantable EBV-containing nasopharyngeal carcinomas | International Journal of Cancer      | 1988 | Busson P                | Institut Gustave Roussy               | 182      | Technique   |
| 77   | Nasopharyngeal carcinoma - review of the molecular mechanisms of tumorigenesis | Head and Neck-Journal for the Sciences and Specialties of the Head and Neck | 2008 | Chou Josephine          | University of California              | 180      | Review      |

(continued)
| Rank | Title                                                                 | Journal                                      | Year | First Author | Institute                                      | Citation | Class |
|------|----------------------------------------------------------------------|----------------------------------------------|------|--------------|------------------------------------------------|----------|-------|
| 78   | A prospective, randomized study comparing outcomes and toxicities of intensity-modulated radiotherapy vs. conventional two-dimensional radiotherapy for the treatment of nasopharyngeal carcinoma | Radiotherapy and Oncology                    | 2012 | Peng G       | Cancer Center of Union Hospital                 | 179      | 2     |
| 79   | Undifferentiated, nonkeratinizing, and squamous-cell carcinoma of the nasopharynx - variants of Epstein-Barr virus-infected neoplasia | American Journal of Pathology                 | 1995 | Pathmanathan R | Lineberger Comprehensive Cancer Center           | 178      | Technique |
| 80   | Significant prognosticators after primary radiotherapy in 903 nondisseminated nasopharyngeal carcinoma evaluated by computer tomography | International Journal of Radiation Oncology Biology Physics | 1996 | Teo P        | Prince of Wales Hospital                         | 175      | Technique |
| 81   | Nasopharyngeal carcinoma                                             | Lancet                                       | 1997 | Vokes EE     | The University of Chicago                         | 174      | Review |
| 82   | Three-dimensional intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: The university of California-San Francisco experience | International Journal of Radiation Oncology Biology Physics | 2000 | Sultanem K    | University of California                        | 173      | 4     |
| 83   | Etiology of nasopharyngeal carcinoma - a review                      | Epidemiologic Reviews                        | 1993 | Hildesheim A  | National Cancer Institute                        | 172      | Review |
| 84   | Genome-wide scan for familial nasopharyngeal carcinoma reveals evidence of linkage to chromosome 4 | Nature Genetics                              | 2002 | Feng BJ       | Sun Yat-sen University Cancer Center             | 171      | Technique |

(continued)
| Rank | Title                                                                 | Journal                          | Year | First Author | Institute                        | Citation | Class |
|------|----------------------------------------------------------------------|----------------------------------|------|--------------|----------------------------------|----------|-------|
| 85   | Nasopharyngeal carcinoma                                             | Lancet                           | 2016 | Chua MLK     | National Cancer Centre Singapore  | 167      | Review|
| 86   | Genetic and epigenetic changes in nasopharyngeal carcinoma           | Seminars in Cancer Biology       | 2002 | Lo KW        | Prince of Wales Hospital          | 166      | Technique|
| 87   | Promoter hypermethylation of multiple genes in nasopharyngeal cancer | Clinical Cancer Research          | 2002 | Kwong J      | The Chinese University of Hong Kong | 164      | Technique|
| 88   | Concurrent and adjuvant chemotherapy for nasopharyngeal cancer       | Journal of Clinical Oncology      | 2004 | Kwong DLW    | Queen Mary Hospital               | 163      | 2     |
| 89   | Demonstration of Epstein-Barr virus-associated nuclear antigen in nasopharyngeal carcinoma from fresh biopsies | International Journal of Cancer  | 1974 | Huang DP     | Queen Elizabeth Hospital          | 163      | Technique|
| 90   | Hypermethylation of the p16 gene in nasopharyngeal carcinoma         | Cancer Research                  | 1996 | Lo KW        | Prince of Wales Hospital          | 162      | Technique|
| 91   | Nasopharyngeal cancer - epidemiology, staging, and treatment         | Seminars in Oncology             | 1994 | Fandi A      | Institute Gustave Roussy          | 162      | Review|
| 92   | 2 epithelial tumor-cell lines (HNE-1 and HONE-1) latently infected with Epstein-Barr virus that were derived from nasopharyngeal carcinomas | Proceedings of the National Academy of Sciences of the United States of America | 1989 | Glaser R     | The Ohio State University Medical Center | 161      | Technique|
| 93   | High level expression of delta n-p63: A mechanism for the inactivation of p53 in undifferentiated nasopharyngeal carcinoma (NPC)? | Oncogene                         | 2000 | Crook T      | Imperial College of Science, Technology and Medicine | 160      | Technique|

(continued)
| Rank | Title                                                                 | Journal                                   | Year | First Author | Institute                        | Citation | Class |
|------|-----------------------------------------------------------------------|-------------------------------------------|------|--------------|----------------------------------|----------|-------|
| 94   | Prognostic factors of nasopharyngeal carcinoma - a review of 759 patients | British Journal of Radiology              | 1990 | Sham JST     | Queen Mary Hospital               | 160      | Review |
| 95   | Identification of serum amyloid a protein as a potentially useful biomarker to monitor relapse of nasopharyngeal cancer by serum proteomic profiling | Clinical Cancer Research                   | 2004 | Cho WCS      | Queen Elizabeth Hospital          | 159      | Technique |
| 96   | Plasma Epstein-Barr viral deoxyribonucleic acid quantitation complements tumor-node-metastasis staging prognostication in nasopharyngeal carcinoma | Journal of Clinical Oncology               | 2006 | Leung SF     | Sir YK Pao Centre for Cancer      | 158      | Technique |
| 97   | Multicenter, phase II study of cetuximab in combination with carboplatin in patients with recurrent or metastatic nasopharyngeal carcinoma | Journal of Clinical Oncology               | 2005 | Chan ATC     | Prince of Wales Hospital          | 158      | 4     |
| 98   | Prognostic value of a microRNA signature in nasopharyngeal carcinoma: A microRNA expression analysis | Lancet Oncology                           | 2012 | Liu N        | Sun Yat-sen University Cancer Center | 157      | Technique |
| 99   | Randomized trial of radiotherapy plus concurrent-adjuvant chemotherapy vs radiotherapy alone for regionally advanced nasopharyngeal carcinoma | JNCI-Journal of the National Cancer Institute | 2010 | Lee AWM      | Pamela Youde Nethersole Eastern Hospital | 155      | 2     |
| 100  | The aetiology of nasopharyngeal carcinoma                            | Clinical Otolaryngology                   | 2001 | McDermott AL | Queen Elizabeth Hospital          | 155      | Review |
| Rank | Title | Journal | Year | First Author | Institute | Citation | Class |
|------|-------|---------|------|--------------|-----------|----------|-------|
| 1    | Long-term outcomes of intensity-modulated radiotherapy for 868 patients with nasopharyngeal carcinoma: An analysis of survival and treatment toxicities | Radiotherapy and Oncology | 2014 | Sun XM | Sun Yat-sen University Cancer Center | 135 | 4 |
| 2    | Chemotherapy and radiotherapy in nasopharyngeal carcinoma: An update of the MAC-NPC meta-analysis | Lancet Oncology | 2015 | Blanchard P | Paris-Saclay University | 130 | 1 |
| 3    | Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: A phase 3, multicentre, randomised controlled trial | Lancet Oncology | 2016 | Sun Y | Sun Yat-sen University Cancer Centre | 84 | 2 |
| 4    | Concurrent chemo-radiation with or without induction gemcitabine, carboplatin, and paclitaxel: A randomized, phase 2/3 trial in locally advanced nasopharyngeal carcinoma | International Journal of Radiation Oncology Biology Physics | 2015 | Tan T | National Cancer Centre Singapore | 71 | 2 |
| 5    | Adoptive T-cell transfer and chemotherapy in the first-line treatment of metastatic and/or locally recurrent nasopharyngeal carcinoma | Molecular Therapy | 2014 | Chia WK | National Cancer Centre Singapore | 70 | 4 |

(continued)
| Rank | Title                                                                                                                                                                                                 | Journal                        | Year | First Author | Institute                                | Citation | Class |
|------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|------|--------------|------------------------------------------|----------|-------|
| 6    | Significant efficacies of neoadjuvant and adjuvant chemotherapy for nasopharyngeal carcinoma by meta-analysis of published literature-based randomized, controlled trials | Annals of Oncology             | 2013 | OuYang PY    | Sun Yat-sen University Cancer Center     | 69       | 1     |
| 7    | Evolution of treatment for nasopharyngeal cancer - success and setback in the intensity-modulated radiotherapy era                                                                                  | Radiotherapy and Oncology      | 2014 | Lee AWM      | University of Hong Kong-Shenzhen Hospital | 66       | 4     |
| 8    | Progress report of a randomized trial comparing long-term survival and late toxicity of concurrent chemoradiotherapy with adjuvant chemotherapy versus radiotherapy alone in patients with stage III to IVB nasopharyngeal carcinoma from endemic regions of China | Cancer                         | 2013 | Chen Y       | Sun Yat-sen University Cancer Center     | 65       | 2     |

(continued)
| Rank | Title                                                                 | Journal          | Year | First Author | Institute                                      | Citation | Class |
|------|----------------------------------------------------------------------|------------------|------|--------------|-----------------------------------------------|----------|-------|
| 9    | Preliminary results of trial NPC-0501 evaluating the therapeutic gain by changing from concurrent-adjuvant to induction-concurrent chemoradiotherapy, changing from fluorouracil to capecitabine, and changing from conventional to accelerated radiotherapy fractionation in patients with locoregionally advanced nasopharyngeal carcinoma | Cancer           | 2015 | Lee AWM      | Pamela Youde Nethersole Eastern Hospital       | 61       | 2     |
| 10   | Phase I trial of recombinant modified vaccinia ankara encoding Epstein-Barr viral tumor antigens in nasopharyngeal carcinoma patients | Cancer research  | 2013 | Hui EP       | The Chinese University of Hong Kong            | 55       | 4     |
The type of articles

Among the 100 articles, the number of articles on basic research, clinical research, and reviews was 50, 36, and 14, respectively. Most of the basic research articles focused on the pathogenesis, detection, and diagnosis of NPC (Figure 3).
The types of studies were 36 clinical articles, of which most were randomized trials (n=18), followed by case-series (n=15), systematic reviews (n=2), and non-randomized controlled cohort study (n=1).

Table 4. Institutions contributing to more than one published article.

| Institutions                                      | Number of Articles (n=58) |
|--------------------------------------------------|---------------------------|
| Prince of Wales Hospital                          | 17                        |
| Sun Yat-Sen University Cancer Center             | 8                         |
| Queen Elizabeth Hospital                         | 5                         |
| Institute Gustave Roussy                         | 4                         |
| Queen Mary Hospital                              | 4                         |
| The Chinese University of Hong Kong              | 4                         |
| Lineberger Comprehensive Cancer Center           | 3                         |
| Pamela Youde Nethersole Eastern Hospital         | 3                         |
| Memorial Sloan-Kettering Cancer Center           | 2                         |
| National Cancer Institute                        | 2                         |
| Taichung Veterans General Hospital               | 2                         |
| The Ohio State University Medical Center         | 2                         |
| University of Binningham                         | 2                         |

Figure 2. Origins of the top 100 most impactful articles on NPC.
The level of evidence

Among the 36 clinical articles, two, 18, one, and 15 articles were graded as having Level 1, 2, 3, and 4 evidence, respectively, based on “The Oxford 2011 Levels of Evidence” (Figure 4).

Classification of treatment methods

The 36 clinical articles were mainly divided into nine treatment categories (Table 5). The top three were concurrent chemotherapy (n=11), intensity-modulated radiation therapy (IMRT, n=10), concurrent chemoradiotherapy plus adjuvant chemotherapy (n=4), and radiotherapy (n=4).

Comparison between 1970–2018 and 2013–2018 in the top 10 most-cited clinical articles

Based on the level of clinical evidence, the ratios (1970–2018 vs. 2013–2018) of Level 1, Level 2, and Level 4 evidence were 1:2, 5:4, and 4:4, respectively. None of the top 10 most-cited articles described Level 3 evidence (non-randomize controlled cohorts).

Comparing the clinical treatment patterns, the ratios (1970–2018 vs. 2013–2018) of concurrent chemotherapy, IMRT, radiotherapy, neoadjuvant chemotherapy, T lymphocytes, and recombinant vaccinia virus were 4:5, 4:2, 2:0, 0:1, 0:1, and 0:1, respectively.

Discussion

In our study, bibliometric analysis was used to identify the top 100 most impactful articles in NPC. These articles are representative of the many landmarks that have taken place in NPC over the past decades.

Our study showed that the highest ranking article was published by the Journal of Clinical Oncology in 1998. It suggested that concurrent chemoradiotherapy was superior to radiotherapy alone and that patients benefited from progression-free survival and overall survival. Because it had a large enough sample size and was a randomized controlled trial, it provided reliable evidence for clinicians to use for treating patients with NPC in the future.

The second highest ranking article was a review of NPC that was published by The Lancet in 2005. It provided researchers with a notable and useful summary of the
pathology, clinical symptoms, diagnosis, tumor grading system, and treatment methods for NPC, and thus, it was well accepted and cited by other researchers.

The third highest ranking article was the application of IMRT in NPC, which was published by the International Journal of Radiation Oncology Biology Physics in 2002. It showed that IMRT can better control the recurrence of primary tumors and can protect salivary glands and adjacent important tissues to the greatest extent. Thus, this result had a significant impact on the future application of IMRT in NPC.

With the exception of the 2010s, the number of articles increased by decades. Thus, over half of the articles in our study were published in the 2000s. The finding is consistent with those of other bibliometric studies. The result demonstrates that new articles with novel discoveries and advanced technologies continue to be published.

Based on the average citation count for a single article over the past decades, the highest citation count was the 1970s, whereas the lowest count was the 2010s. This finding shows that because of the time-dependent citation analysis, previous articles have more citations compared with current articles.

Some bibliometric studies reported that journals with high impact factors, such as NEJM and The Lancet, were the leading journals. However, we found that the International Journal of Radiation Oncology Biology Physics was the most productive journal, despite having an impact factor of 5.6. This result shows that highly impactful articles are published in a specialized journal and are not limited to well-known general medical journals.

It has been shown that the most productive authors and institutions were always from the USA. In our study, Hong Kong was the most prolific region and Chan ATC, who contributed six articles, was from the Prince of Wales Hospital in Hong Kong. NPC has regional characteristics such as being common in the eastern and southeastern parts of Asia and eastern Africa. Thus, there are enough clinical research cases in Hong Kong. The findings indicate that Hong Kong has advanced technology and management concepts, and this region is good for researchers to learn and collaborate.

For the type of article, basic research articles on NPC accounted for half of the articles. They were mostly concerned with the epidemiology, pathogenesis, detection, and diagnostic techniques, such as

### Table 5. Treatment reported by 36 clinical articles on the top 100 list.

| Treatment                                                                 | Number of Articles (n=36) |
|---------------------------------------------------------------------------|---------------------------|
| Concurrent chemotherapy                                                   | 11                        |
| IMRT                                                                      | 10                        |
| Concurrent chemoradiotherapy plus adjuvant chemotherapy                    | 4                         |
| Radiotherapy                                                              | 4                         |
| Neoadjuvant chemotherapy                                                 | 3                         |
| Surgery                                                                   | 1                         |
| T lymphocytes                                                            | 1                         |
| Chemotherapy after recurrent tumor                                        | 1                         |
| Radiotherapy after recurrent tumor                                        | 1                         |

IMRT, intensity-modulated radiation therapy.
Epstein–Barr virus (EBV)-associated DNA, microRNA, and its associated genomes. Among them, a noteworthy article was published in 1976 by Henle and Henle\textsuperscript{18} in the International Journal of Cancer, which was a study on NPC and EBV. It revealed the close relationship between EBV-related immunoglobulin A and NPC in serum, which was a milestone and laid the foundation for the determining the diagnosis and prognosis of NPC.

Some bibliometric articles on surgical tumors reported that more than half of the articles were of low-quality (Level 4).\textsuperscript{19} In our study, most clinical articles were scored as Levels 1 or 2 on the level-of-evidence grading scale. These results indicate that a high-quality NPC study was relatively easy to conduct and receive more citations compared with a low-quality study.

One of the Level 1 articles\textsuperscript{20} showed that concurrent chemoradiotherapy can confer survival benefits to patients with NPC, which was consistent with another highly cited article.\textsuperscript{21} This article also pointed out that the efficacy of induction chemotherapy and intensive chemotherapy before concurrent chemoradiotherapy would need to be further confirmed.

Based on the only article regarding surgery in the top 100 articles, the NPC tumor in patients with stage T1 or T2 did not disappear after radiotherapy, and radical resection of the tumor can prolong their survival time. For patients with stage T4 NPC, palliative cytoreductive surgery failed to confer benefits because of extensive tumor invasion of the skull base and cranial nerves.\textsuperscript{22} However, surgery is mostly used for some patients who needed a biopsy to confirm the diagnosis or who had tumor recurrence after radiotherapy based on a recent guideline (NCCN Clinical Practice Guidelines for Head and Neck Cancer, Version 3, 2019).\textsuperscript{23}

Among the top 10 clinical articles from 1970 to 2018, one article on retrospective analysis written by Lee AWM in 1992 suggested that radiotherapy can increase the local tumor control rate and prolong overall survival and progression-free survival.\textsuperscript{24} His subsequent and highly cited article published in 2005 described a retrospective analysis of 2687 patients in Hong Kong, and confirmed the therapeutic effect of radiotherapy.\textsuperscript{25} Therefore, his articles provided a basis for future randomized clinical trials of IMRT.

For the top 10 clinical articles from 2013 to 2018, half were focused on concurrent chemoradiotherapy, while IMRT was described in only 20% of these articles. The findings show that the effect of IMRT was confirmed\textsuperscript{26,27} and related research was reduced accordingly. Additionally, neoadjuvant chemotherapy,\textsuperscript{28} T-lymphocyte immunotherapy,\textsuperscript{29} and recombinant vaccinia virus gene therapy\textsuperscript{30} had emerged. The results show that these new therapies are the current research priorities and the trends for future treatments.

There are some limitations in this paper. First, the citation count used for the citation analysis did not include self-citation. Second, because of the influence of certain time factors, it would be unfavorable for the most recently published articles in the citation analysis. Third, the database used in this article was the WoS. Although it is the most commonly used database with citation analysis capabilities, a small number of articles may have been missed.

**Conclusions**

To the best of our knowledge, this study is the first bibliometric study to identify the most impactful articles in the area of NPC. The findings indicate that articles with novel discoveries, advanced technologies, and a high quality level of evidence will receive more citations. Recognition of
important historical contributions to this field may guide future investigations into NPC.

**Author contributions**

All authors were involved in the study. Q.-T. Yang and M.-Y. Chen conceived and designed the study. Q.-W. Wu, T. Yuan, and Z.-P. Zhang analyzed the data and wrote the paper. Q. Wang, H.-Y. Deng, and H.-J. Qiu performed the search strategy. X.-Y. Wang, and X.-K. Huang collected the data.

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**Declaration of conflicting interest**

The authors declare that there is no conflict of interest.

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**ORCID iD**

Qintai Yang http://orcid.org/0000-0003-3377-737X

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