The current status of clinical trials focusing on nasopharyngeal carcinoma: A comprehensive analysis of ClinicalTrials.gov database

Hao Peng¹, Lei Chen¹, Yu-Pei Chen¹, Wen-Fei Li¹, Ling-Long Tang¹, Ai-Hua Lin², Ying Sun¹, Jun Ma¹*

¹ Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in Southern China, Collaborative Innovation Center for Cancer Medicine, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangzhou, People’s Republic of China, ² Department of Medical Statistics and Epidemiology, School of Public Health, Sun Yat-sen University, Guangzhou, People’s Republic of China

* majun2@mail.sysu.edu.cn

Abstract

Purpose
Clinical Trials have emerged as the main force in driving the development of medicine. However, little is known about the current status of clinical trials regarding nasopharyngeal carcinoma (NPC). This study aimed at providing a comprehensive landscape of NPC-related trials on the basis of ClinicalTrials.gov database.

Patients and methods
We used the keyword “nasopharyngeal carcinoma” to search the ClinicalTrials.gov database and assessed the characteristics of these trials.

Results
Up to December 30, 2016, 462 eligible trials in total were identified, of which 222 (48.0%) recruited only NPC (NPC trials) and the other 240 (52.0%) recruited both NPC and other cancers (multiple cancer trials). Moreover, 47 (10.2%) were Epstein-Barr virus (EBV)-related trials and 267 (57.8%) focused on metastatic/recur rent disease. Compared with NPC trials, the multiple cancer trials had a higher percentage of phase 1 (26.7% vs. 6.7%, \( P < 0.001 \)) studies and more patients with metastatic/recur rent disease (72.5% vs. 41.9%, \( P < 0.001 \)). Notably, non-EBV trials had more phase 2 or 3 (78.4% vs. 48.8%, \( P < 0.001 \)) and interventional studies (89.5% vs. 70.7%, \( P = 0.002 \)) than EBV trials. Obviously, more phase 2/3 or 3 trials were conducted in patients with non-metastatic/recur rent disease (29.4% vs. 4.9%, \( P < 0.001 \)); however, metastatic/recur rent trials were more likely to be anti-cancer (94.6% vs. 63.6%, \( P < 0.001 \)).

Conclusions
The role of plasma EBV DNA in clinical trials is underestimated, and high-level randomized clinical trials should be performed for patients with metastatic/recur rent disease.
Introduction

Nasopharyngeal carcinoma (NPC) differs from other head and neck cancers for its epidemiology, clinical characteristics and therapy modality; it has an incidence rate of 20 per 100,000 persons in endemic regions such as South East Asia and Southern China [1], and radiotherapy has come as the only curative treatment as a result of the anatomic constraints and its sensitivity to irradiation. With the advancement of radiotherapy technique and combined therapy strategies of radiotherapy and chemotherapy over the last twenty years, outcomes for NPC have improved greatly, producing a 5-year overall survival rate of 84.7–87.4% [2–4]. However, control of advanced disease may be unsatisfactory, with an overall survival of 67–77% [5]. Furthermore, distant metastasis at initial diagnosis or after radical radiotherapy and recurrent NPC still remain the most serious challenges as the median overall survival of these patients is only 20 months [6]. Therefore, much effort are urgently needed to develop more effective treatment modalities.

Clinical trials have emerging as foundation of evidence-based medicine and the main force in driving the development of medicine. In September 2004, a consensus has been reached by the International Committee of Medical Journal Editors (ICMJE) that clinical trials should be registered in a public registry before recruiting patients to ensure transparency of the whole process. Later on, this policy was applied to all the clinical trials starting recruitment after July 1, 2005 [7]. ClinicalTrials.gov, developed and maintained by National Library of Medicine (NLM), is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. Currently, the ClinicalTrials.gov provides the most comprehensive source of information on ongoing and completed clinical studies worldwide.

As clinical trials usually represent the latest treatment modalities in the war against cancer, clinicians hope that these new drugs or technologies could be applied in clinical practice as soon as possible. Given the truth that we still lack a thorough understanding of current clinical studies regarding NPC, we therefore conducted this study aiming at providing a comprehensive landscape of NPC-related trials on the basis of ClinicalTrials.gov database and evaluating the characteristics of these studies.

Materials and methods

Data source and eligible study

Three oncologists (LC, YPC and WFL) at the Sun Yat-sen University Cancer Centre used the term “nasopharyngeal carcinoma” to search all the registered clinical trials in the ClinicalTrials.gov database separately. All the information of these searched clinical trials provided by the sponsors and/or collaborators were thoroughly gone through and kept. A fourth oncologist (HP) would review the data recorded by the three oncologists, and any disagreements were solved by consensus or referring to the fifth oncologist (JM) who has more than twenty years of experience in NPC clinical trials. Up to December 30, 2016, a total of 508 trials were identified. After carefully reviewing all the information presented by ClinicalTrials.gov database, 46 (9.1%) trials were excluded (Fig 1).

Therefore, 462 (90.9%) trials were left for further analysis (S1 File). This study was approved by the Research Ethics Committee of Sun Yat-sen university cancer center.

Study variables

Before searching, we set up recording standards for each study variable and the following characteristics provided by ClinicalTrials.gov database were assessed: registered number, registered
time, Epstein-Barr virus (EBV)-related trials (yes or no), time perspective (prospective or retrospective), tumor stage (non-metastasis/recurrent or metastasis/recurrent or both or health population), tumor category (nasopharyngeal carcinoma only or multiple), the phase of trial (none or phase 0/1 or phase 1/2 or phase 2/3 or phase 4), study type (interventional or observational), interventional phase (none or prior to radiotherapy or during radiotherapy or after radiotherapy or metastatic/recurrent disease), interventional measure (none or anticancer or non-anticancer), anticancer drug (none or chemotherapy or targeted therapy or radiotherapy or immunotherapy or other), endpoint classification (efficacy or safety or efficacy/safety or
other), masking (none or open label or blind), allocation (none or randomized or non-randomized), study arm (none or one or two or more), funding source (industry or national cancer institute or other), study sample (< 50 or 50–100 or > 100), participant age (< 18y or ≥ 18y or both), region (Unite states/Canada or European or Asia or other) and center (one or two or more).

The definition of EBV-related trials was that pre-treatment plasma EBV DNA was one of the inclusion criteria or therapy targeted EBV-related antigens such as latent membrane protein 1 (LMP1). If a trial included both NPC and other kinds of cancer types, it would be grouped into a “multiple” category. With regard to interventional stage, the trial would be classified as “metastatic/recurrent disease” if only patients with recurrent/metastatic disease were recruited; otherwise, the trial was categorized according to the order of intervention and radiotherapy for newly diagnosed, non-disseminated disease. For retrospective or observational studies, the phase of trial, interventional stage, interventional measure, anticancer drug, masking, allocation and study arm were considered as “none”, and the endpoint classification was “other”. Funding sources were categorized as industry, national cancer institute (NCI) or other academic groups based on the sponsor or collaborators [8]. If an industry was listed as the sponsor or collaborators, the trial would be treated as funded by industry. When NCI was the lead sponsor or collaborators, the trial was considered as NCI-funded. Furthermore, the region of the trial mainly depends on the location of lead sponsor.

Statistical analysis
The characteristics of clinical trials were summarized by descriptive statistics: continuous variables were characterized as median and interquartile ranges (IQR) and categorical variables were reported as frequencies and percentages. Pearson Chi-square test was used to compare the characteristics difference between different kinds of NPC-related trials, and Fisher’s exact test would also be applied if indicated. Any missing value would be excluded from analysis. All statistical tests were performed using STATA version 13.0 (Stata Corporation LP, College Station, TX, USA), and a two-sided \( P < 0.05 \) was considered statistically significant.

Results
Basic characteristics of included trials
Among the 462 eligible trials, 222 (48.0%) were identified as NPC trials and the other 240 (52.0%) were multiple cancer trials. The distribution of these two kinds of trials according to registered time was summarized in Fig 2.

Obviously, the number of NPC trials increased greatly after 2004, and the number of multiple cancer trials decreased and remained stable after 2011. The baseline characteristics of 462 trials were presented in Table 1. Although plasma EBV DNA has been documented to be a reliable biomarker in prognosis predicting and decisions making in NPC since 2004 [9], its role in clinical trials still remains slight (10.2%). Intriguingly, more than half of trials (57.8%) focused on metastatic or recurrent disease and only 40.5% recruited non-disseminated NPC at initial diagnosis. Notably, the primary purpose of most trials (72%) was anticancer intervention, and much attention was paid to chemotherapy (30.7%) and targeted therapy (23.4%). Moreover, 51.3% of the trials were registered in Unite States (US)/Canada where NPC has a very low rate of incidence, and most of these studies were multiple cancer trials which mainly focused on other head and neck cancers.
NPC trials and multiple cancer trials

Table 2 summarized the study characteristics of NPC trials and multiple cancer trials registered with ClinicalTrials.gov database. Difference in the number of EBV-related trials was apparent: NPC trials had an obviously higher rate of EBV-related trials (18.5% vs. 2.5%, \( P < 0.001 \)) compared with multiple cancer trials. Moreover, NPC trials were more likely to focus on non-metastatic/recurrent disease at initiation diagnosis (55.0% vs. 27.1%, \( P < 0.001 \)), while multiple cancer trials mainly recruited patients with metastatic/recurrent disease (55.0% vs. 32.0%, \( P < 0.001 \)) and had more phase I studies (26.7% vs. 7.6%, \( P < 0.001 \)). Unlike multiple cancer trials, NPC trials had a higher percentage of chemotherapy intervention (39.2% vs. 22.9%, \( P = 0.001 \)). Furthermore, NPC trials were more likely to be funded by other academic groups (82.8% vs. 24.2%, \( P < 0.001 \)) and had more large-scale studies (41.9% vs. 21.2%, \( P < 0.001 \)) compared to multiple cancer trials. Obviously, most of NPC trials were conducted in Asia and multiple cancer trials in US/Canada.
Table 1. Basic characteristics of the 462 trials registered with ClinicalTrials.gov up to December 30, 2016.

| Characteristics                          | Number | Percentage (%) |
|------------------------------------------|--------|----------------|
| **EBV-related trials**                   |        |                |
| Yes                                      | 47     | 10.2           |
| No                                       | 415    | 89.8           |
| **Time perspective**                     |        |                |
| Prospective                              | 447    | 96.5           |
| Retrospective                            | 15     | 3.5            |
| **Tumor stage**                          |        |                |
| Non-metastasis/recurrent                 | 187    | 40.5           |
| Metastasis/recurrent                     | 205    | 44.4           |
| Both                                     | 62     | 13.4           |
| **Health population**                    |        |                |
| 8                                        | 1.7    |                |
| **Tumor category**                       |        |                |
| NPC only                                 | 222    | 48.0           |
| Multiple *                               | 240    | 52.0           |
| **Phase**                                |        |                |
| None                                     | 77     | 16.7           |
| Phase 1                                  | 81     | 17.5           |
| Phase 1/2 or 2                           | 203    | 43.9           |
| Phase 2/3 or 3                           | 69     | 14.9           |
| Phase 4                                  | 5      | 1.1            |
| **Missing value**                        |        |                |
| 27                                       | 5.9    |                |
| **Study type**                           |        |                |
| Interventional                           | 386    | 83.5           |
| Observational                            | 76     | 16.5           |
| **Interventional phase**                 |        |                |
| None                                     | 76     | 16.5           |
| Prior to radiotherapy                    | 37     | 8.0            |
| During radiotherapy                      | 93     | 20.1           |
| After radiotherapy                       | 33     | 7.1            |
| Metastatic/recurrent disease             | 195    | 42.2           |
| Two or more phases                       | 25     | 5.4            |
| **Missing value**                        |        |                |
| 3                                        | 0.7    |                |
| **Interventional measure**               |        |                |
| None                                     | 76     | 16.5           |
| Anticancer                               | 333    | 72.0           |
| Non-anticancer *                         | 53     | 11.5           |
| **Interventional drug**                  |        |                |
| None                                     | 76     | 16.5           |
| Chemotherapy                             | 142    | 30.7           |
| Targeted therapy                         | 108    | 23.4           |
| Radiotherapy                             | 23     | 5.0            |
| Immunotherapy                            | 44     | 9.5            |
| Other *                                  | 69     | 14.9           |
| **Endpoint classification**              |        |                |
| Efficacy                                 | 93     | 20.1           |
| Safety                                   | 38     | 8.2            |
| Efficacy/safety                          | 254    | 55.0           |

(Continued)
EBV and non-EBV trials

Apparently, multiple cancer trials registered in Unite States/Canada mainly focused on other head and neck cancers and EBV was not an inclusion criteria, we therefore excluded these

| Characteristics | Number | Percentage (%) |
|-----------------|--------|----------------|
| Other \(^d\)    | 77     | 16.7           |
| Masking         |        |                |
| None            | 77     | 16.7           |
| Open label      | 348    | 75.3           |
| Blind           | 37     | 8.0            |
| Allocation      |        |                |
| None            | 77     | 16.7           |
| Randomized      | 152    | 32.9           |
| Non-randomized  | 233    | 50.4           |
| Study arm       |        |                |
| None            | 77     | 16.7           |
| One             | 229    | 49.6           |
| Two             | 139    | 30.0           |
| Three or more   | 17     | 3.7            |
| Funding source  |        |                |
| Industry        | 46     | 10.0           |
| NCI             | 174    | 37.6           |
| Other           | 242    | 52.4           |
| Study sample    |        |                |
| < 50            | 212    | 45.9           |
| 50–100          | 104    | 22.5           |
| > 100           | 144    | 31.2           |
| Missing value   | 2      | 0.4            |
| Participant age (y) |   |                |
| < 18            | 1      | 0.2            |
| ≥ 18            | 418    | 90.5           |
| Both            | 43     | 9.3            |
| Region          |        |                |
| US/Canada       | 237    | 51.3           |
| European        | 26     | 5.6            |
| Asia            | 195    | 42.2           |
| Other \(^e\)    | 4      | 0.9            |
| Centers         |        |                |
| One             | 299    | 64.7           |
| Two             | 26     | 5.6            |
| Three or more   | 137    | 29.7           |

Abbreviations: EBV = Epstein-Barr virus; NPC = nasopharyngeal carcinoma; NCI = national cancer institute; US = Unite States.

\(^a\) Trials includes both nasopharyngeal carcinoma and other kinds of cancer types.

\(^b\) Non-anticancer measures mainly include symptomatic treatment such as radiotherapy-induced oral mucositis.

\(^c\) Other refers to surgical treatment or drugs dealing with chemotherapy or radiotherapy-related toxicities.

\(^d\) Endpoint classifications of retrospective or prospectively observational study were considered as "other".

\(^e\) Other regions include Africa, South America, Oceania, North America other than US/Canada.

https://doi.org/10.1371/journal.pone.0196730.t001

EBV and non-EBV trials

Apparently, multiple cancer trials registered in Unite States/Canada mainly focused on other head and neck cancers and EBV was not an inclusion criteria, we therefore excluded these
### Table 2. Characteristics difference between different trials registered with ClinicalTrials.gov up to December 30, 2016.

| Characteristics                      | NPC Trials (n = 222) | Multiple Cancer Trials (n = 240) | EBV Trials (n = 41) | Non-EBV Trials (n = 181) | $P_1^a$ | $P_2^a$ |
|--------------------------------------|----------------------|----------------------------------|---------------------|--------------------------|---------|---------|
| **EBV-related trials**               |                      |                                  |                     |                          |         | -       |
| Yes                                  | 41 (18.5)            | 6 (2.5)                          | -                   | -                        | < 0.001 | -       |
| No                                   | 181 (81.5)           | 234 (97.5)                       | -                   | -                        |         | -       |
| **Time perspective**                 |                      |                                  |                     |                          | 0.246   | 0.587   |
| Prospective                          | 217 (97.7)           | 230 (95.8)                       | 41 (100)            | 176 (97.2)               |         |         |
| Retrospective                        | 5 (2.3)              | 10 (4.2)                         | 0 (0)               | 5 (2.8)                  |         |         |
| **Tumor stage**                      |                      |                                  |                     |                          | < 0.001 | < 0.001 |
| Non-metastatic/recurrent             | 122 (55.0)           | 65 (27.1)                        | 17 (41.5)           | 105 (58.0)               |         |         |
| Metastatic/recurrent                 | 73 (32.9)            | 132 (55.0)                       | 13 (31.7)           | 60 (33.1)                |         |         |
| Both                                 | 20 (9.0)             | 42 (17.5)                        | 4 (9.8)             | 16 (8.9)                 |         |         |
| **Health population**                |                      |                                  |                     |                          | 0.166   | 0.002   |
| Non-metastatic/recurrent             | 7 (3.1)              | 1 (0.4)                          | 7 (17.0)            | 0 (0)                    |         |         |
| **Phase**                            |                      |                                  |                     |                          |         |         |
| None                                 | 32 (14.4)            | 45 (18.8)                        | 12 (29.3)           | 20 (11.0)                | < 0.001 | < 0.001 |
| Phase 1                              | 17 (7.6)             | 64 (26.7)                        | 9 (21.9)            | 8 (4.4)                  |         |         |
| Phase 1/2 or 2                       | 108 (48.6)           | 95 (39.6)                        | 12 (29.3)           | 96 (53.0)                |         |         |
| Phase 2/3 or 3                       | 54 (24.3)            | 15 (6.3)                         | 8 (19.5)            | 46 (25.4)                |         |         |
| Phase 4                              | 3 (1.4)              | 2 (0.8)                          | 0 (0)               | 3 (1.7)                  |         |         |
| **Study type**                       |                      |                                  |                     |                          | 0.166   | 0.002   |
| Interventional                       | 191 (86.0)           | 195 (81.2)                       | 29 (70.7)           | 162 (89.5)               |         |         |
| Observational                       | 31 (14.0)            | 45 (18.8)                        | 12 (29.3)           | 19 (10.5)                |         |         |
| **Interventional phase**             |                      |                                  |                     |                          |         |         |
| None                                 | 31 (14.0)            | 45 (18.8)                        | 12 (29.3)           | 19 (10.5)                | < 0.001 | 0.003   |
| Prior to radiotherapy                | 32 (14.4)            | 5 (2.0)                          | 2 (4.9)             | 30 (16.6)                |         |         |
| During radiotherapy                  | 50 (22.5)            | 43 (17.9)                        | 5 (12.2)            | 45 (24.9)                |         |         |
| After radiotherapy                   | 22 (9.9)             | 11 (4.6)                         | 7 (17.1)            | 15 (8.3)                 |         |         |
| Metastatic/recurrent disease         | 70 (31.5)            | 125 (52.1)                       | 14 (34.1)           | 56 (30.9)                |         |         |
| Two or more phases                   | 15 (6.8)             | 10 (4.2)                         | 1 (2.4)             | 14 (7.7)                 |         |         |
| **Interventional measure**           |                      |                                  |                     |                          | 0.07    | < 0.001 |
| None                                 | 31 (14.0)            | 45 (18.8)                        | 12 (29.3)           | 19 (10.5)                |         |         |
| Anticancer                           | 171 (77.0)           | 162 (67.5)                       | 29 (70.7)           | 142 (78.5)               |         |         |
| Non-anticancer                       | 20 (9.0)             | 33 (13.7)                        | 0 (0)               | 20 (11.0)                |         |         |
| **Interventional drug**              |                      |                                  |                     |                          | 0.001   | < 0.001 |
| None                                 | 31 (14.0)            | 45 (18.8)                        | 12 (29.3)           | 19 (10.5)                |         |         |
| Chemotherapy                         | 87 (39.2)            | 55 (22.9)                        | 10 (24.4)           | 77 (42.5)                |         |         |
| Targeted therapy                     | 46 (20.7)            | 62 (25.8)                        | 7 (17.0)            | 39 (21.5)                |         |         |
| Radiotherapy                         | 13 (5.9)             | 10 (4.2)                         | 0 (0)               | 13 (7.2)                 |         |         |
| Immunotherapy                        | 23 (10.3)            | 21 (8.7)                         | 12 (29.3)           | 11 (6.1)                 |         |         |
| Other                                | 22 (9.9)             | 47 (19.6)                        | 0 (0)               | 22 (12.2)                |         |         |
| **Endpoint classification**          |                      |                                  |                     |                          | < 0.001 | 0.018   |
| Efficacy                             | 35 (15.8)            | 58 (24.2)                        | 5 (12.2)            | 30 (16.6)                |         |         |
| Safety                               | 11 (5.0)             | 27 (11.2)                        | 3 (7.3)             | 8 (4.4)                  |         |         |
| Efficacy/safety                       | 144 (64.8)           | 110 (45.8)                       | 21 (51.2)           | 123 (68.0)               |         |         |
| Other                                | 32 (14.4)            | 45 (18.8)                        | 12 (29.3)           | 20 (11.0)                |         |         |
| **Masking**                          |                      |                                  |                     |                          | 0.337   | 0.02    |
| None                                 | 32 (14.4)            | 45 (18.8)                        | 12 (29.3)           | 20 (11.0)                |         |         |

(Continued)
trials when analyzing the characteristic difference between EBV and non-EBV trials (Table 2). EBV trials were less likely to recruit non-metastatic/recurrent disease (41.5% vs. 58.0%, \(P < 0.001\)) and had a higher percentage of health participants (17.0% vs. 0, \(P < 0.001\)). Besides, non-EBV trials had more phase 2 or 3 (78.4% vs. 48.8%, \(P < 0.001\)) and interventional studies (89.5% vs. 70.7%, \(P = 0.002\)). Also, the intervention of non-EBV trials mainly focused on chemotheraphy (42.5% vs. 24.4%, \(P < 0.001\)) while EBV trials had an obviously higher rate of immunotherapy intervention (29.3% vs. 6.1%, \(P < 0.001\)). Furthermore, non-EBV trials were more likely to receive funding from industry (13.8% vs. 0, \(P < 0.001\)) and registered in Asia (82.9% vs. 63.5%, \(P = 0.006\)).

**Metastatic/Recurrent and Non-metastatic/Recurrent trials**

As prognosis of non-metastatic/recurrent nasopharyngeal carcinoma is much better than that of metastatic/recurrent disease, we therefore further compared the characteristics difference between trials recruiting non-metastatic/recurrent and metastatic/recurrent patients (Table 3).

---

**Table 2. (Continued)**

| Characteristics | NPC Trials (n = 222) | Multiple Cancer Trials (n = 240) | EBV Trials (n = 41) | Non-EBV Trials (n = 181) |
|-----------------|----------------------|-------------------------------|-------------------|-------------------------|
| **Open label**  | No. (%)              | No. (%)                       | No. (%)           | No. (%)                 |
| Open label      | 174 (78.4)           | 174 (72.5)                    | 27 (65.8)         | 147 (81.3)              |
| Blind           | 16 (7.2)             | 21 (8.7)                      | 2 (4.9)           | 14 (7.7)                |
| **Allocation**  | < 0.001              |                               | 0.008             |                         |
| None            | 32 (14.4)            | 45 (18.8)                     | 12 (29.3)         | 20 (11.0)               |
| Randomized      | 105 (47.3)           | 47 (19.6)                     | 14 (34.1)         | 91 (50.3)               |
| Non-randomized  | 85 (38.3)            | 148 (61.6)                    | 15 (36.6)         | 70 (38.7)               |
| **Study arm**   | < 0.001              |                               | 0.01              |                         |
| None            | 32 (14.4)            | 45 (18.8)                     | 12 (29.3)         | 20 (11.0)               |
| One             | 83 (37.4)            | 146 (60.8)                    | 15 (36.6)         | 68 (37.6)               |
| Two             | 96 (43.2)            | 43 (17.9)                     | 12 (29.3)         | 84 (46.4)               |
| Three or more   | 11 (5.0)             | 6 (2.5)                       | 2 (4.8)           | 9 (5.0)                 |
| **Funding source** | < 0.001              |                               | 0.006             |                         |
| Industry        | 25 (11.3)            | 21 (8.7)                      | 0 (0)             | 25 (13.8)               |
| NCI             | 13 (5.9)             | 161 (67.1)                    | 6 (14.6)          | 7 (3.9)                 |
| Other           | 184 (82.8)           | 58 (24.2)                     | 35 (85.4)         | 149 (82.3)              |
| **Study sample** | < 0.001              |                               | 0.01              |                         |
| < 50            | 72 (32.4)            | 140 (58.3)                    | 18 (43.9)         | 54 (29.8)               |
| 50–100          | 57 (25.7)            | 47 (19.6)                     | 3 (7.3)           | 54 (29.8)               |
| >100            | 93 (41.9)            | 51 (21.2)                     | 20 (48.8)         | 73 (40.4)               |
| **Region**      | < 0.001              |                               | 0.006             |                         |
| US/Canada       | 34 (15.3)            | 203 (84.6)                    | 14 (34.1)         | 20 (11.0)               |
| European        | 10 (4.5)             | 16 (6.7)                      | 1 (2.4)           | 9 (5.0)                 |
| Asia            | 176 (79.3)           | 19 (7.9)                      | 26 (63.5)         | 150 (82.9)              |
| Other           | 2 (0.9)              | 2 (0.8)                       | 0 (0)             | 2 (1.1)                 |

Abbreviations: NPC = nasopharyngeal carcinoma; EBV = Epstein-Barr virus; NCI = national cancer institute; US = United States.

\(a\) P-Values were calculated using Pearson Chi-Square test or Fisher’s exact test if indicated.

\(b\) 8 trials in the NPC trials arm and 19 trials in the multiple cancer trials arm were missing; 8 trials in Non-EBV trials arm were missing.

\(c\) 2 trials in the NPC trials arm and 1 trial in multiple cancer trials arm were missing; 2 trials in Non-EBV trials arm were missing.

\(d\) 2 trials in multiple cancer trials arm were missing.

https://doi.org/10.1371/journal.pone.0196730.002
| Characteristics        | Metastatic/recurrent Trials (n = 205) | Non-metastatic/recurrent Trials (n = 187) | P  
|------------------------|---------------------------------------|-------------------------------------------|------
| Time perspective       |                                       |                                           | 0.032
| Prospective            | 198 (96.6)                            | 186 (99.5)                                |     
| Retrospective          | 7 (3.4)                               | 1 (0.5)                                   |     
| Phase a                 |                                       |                                           | < 0.001
| None                   | 11 (5.4)                              | 27 (14.4)                                 |     
| Phase 1                | 59 (28.8)                             | 12 (6.4)                                  |     
| Phase 1/2 or 2         | 122 (59.5)                            | 71 (38.0)                                 |     
| Phase 2/3 or 3         | 10 (4.9)                              | 55 (29.4)                                 |     
| Phase 4                | 0 (0)                                 | 3 (1.6)                                   |     
| Study type             |                                       |                                           | 0.001
| Interventional         | 195 (95.1)                            | 160 (85.6)                                |     
| Observational          | 10 (4.9)                              | 27 (14.4)                                 |     
| Interventional measure |                                       |                                           | < 0.001
| None                   | 10 (4.9)                              | 27 (14.4)                                 |     
| Anticancer             | 194 (94.6)                            | 119 (63.6)                                |     
| Non-anticancer         | 1 (0.5)                               | 41 (22.0)                                 |     
| Interventional drug    |                                       |                                           | < 0.001
| None                   | 10 (4.9)                              | 27 (14.4)                                 |     
| Chemotherapy           | 65 (31.7)                             | 70 (37.4)                                 |     
| Targeted therapy       | 73 (35.6)                             | 30 (16.0)                                 |     
| Radiotherapy           | 6 (2.9)                               | 15 (8.0)                                  |     
| Immunotherapy          | 37 (18.1)                             | 4 (2.2)                                   |     
| Other                  | 14 (6.8)                              | 41 (22.0)                                 |     
| Endpoint classification |                                       |                                           | < 0.001
| Efficacy               | 35 (17.1)                             | 52 (27.8)                                 |     
| Safety                 | 24 (11.7)                             | 5 (2.7)                                   |     
| Efficacy/safety        | 136 (66.3)                            | 102 (54.5)                                |     
| Other                  | 10 (4.9)                              | 28 (15.0)                                 |     
| Masking                |                                       |                                           | < 0.001
| None                   | 11 (5.4)                              | 27 (14.4)                                 |     
| Open label             | 189 (92.2)                            | 130 (69.6)                                |     
| Blind                  | 5 (2.4)                               | 30 (16.0)                                 |     
| Allocation             |                                       |                                           | < 0.001
| None                   | 11 (5.4)                              | 27 (14.4)                                 |     
| Randomized             | 34 (16.6)                             | 109 (58.3)                                |     
| Non-randomized         | 160 (78.0)                            | 51 (27.3)                                 |     
| Funding source         |                                       |                                           | < 0.001
| Industry               | 29 (14.2)                             | 12 (6.4)                                  |     
| NCI                    | 103 (50.2)                            | 43 (23.0)                                 |     
| Other                  | 73 (35.6)                             | 132 (70.6)                                |     
| Study sample           |                                       |                                           | < 0.001
| < 50                   | 129 (62.9)                            | 59 (31.6)                                 |     
| 50–100                 | 47 (22.9)                             | 43 (23.0)                                 |     
| >100                   | 29 (14.2)                             | 85 (45.4)                                 |     
| Region                 |                                       |                                           | < 0.001

(Continued)
Obviously, more phase 2/3 or 3 trials were conducted in patients with non-metastatic/recurrent disease (29.4% vs. 4.9%, \( P < 0.001 \)); however, metastatic/recurrent trials were more likely to be anticancer (94.6% vs. 63.6%, \( P < 0.001 \)). Moreover, metastatic/recurrent trials had a higher percentage of targeted therapy (35.6% vs. 16.0%, \( P < 0.001 \)) and immunotherapy (18.1% vs. 2.2%, \( P < 0.001 \)) interventions compared with non-metastatic/recurrent trials. In addition, non-metastatic/recurrent trials intended to be funded by other academic groups (70.6% vs. 35.6%, \( P < 0.001 \)), be conducted in Asia (58.3% vs. 29.8%, \( P < 0.001 \)) and have large-scale samples of more than 100 (45.4% vs. 14.2%, \( P < 0.001 \)).

Discussion

Clinical trials have play an irreplaceable role in changing clinical practice and decision making in medicine, especially for well-designed randomized clinical trials. NPC, known as a cancer rising from nasopharynx epithelium, is mainly prevalent in Southeast Asia, the Middle East and North Africa [10–12]. Therefore, given the overall low incidence rate worldwide, NPC does not attract the attention of most researches and little is known about the current status of clinical trials regarding NPC. To the best of our knowledge, our study is the first one to report the landscape of NPC-related trials and assess the characteristics of these trials. Our findings suggested that NPC-related trials were predominantly early-phase trials with small samples less than 100 and mainly focused on chemotherapy and targeted therapy intervention. Surprisingly, metastatic/recurrent disease even occupied a greater part in these trials. Obviously, NPC trials were more likely to be performed in Asia while multiple cancer trials were mainly conducted in US/Canada.

Although multiple cancer trials recruited patients with NPC, the information of managing NPC they provided may be very limited because most of these trials were conducted in US/Canada where the incidence of NPC is extremely low and mainly focused on other head and neck cancers. Actually, there are few publications regarding NPC from this region. Notably, compared with NPC trials, the multiple cancer trials had a higher percentage of phase 1 (26.7% vs. 6.7%) studies and patients with metastatic/recurrent disease (72.5% vs. 41.9%). One reasonable explanation is that these trials were conducted to test new drugs or new treatment modalities in patients with metastatic/recurrent who failed standard therapy. Hence, these trials were more likely to have small samples of less than 50 (58.3% vs. 32.4%) and to be single arm (60.8% vs. 37.4%) and non-randomized (61.6% vs. 38.3%).

NPC has been established as an EBV-associated cancer for a long time [13–15]. Subsequently, the prognostic value of plasma EBV DNA has been widely proven both in non-disseminated [9, 16–23] and metastatic/recurrent disease [24, 25]. Moreover, plasma EBV DNA...
could also stratify patients into different risk groups and guide individualized treatment [26–28]. Therefore, plasma EBV DNA could be a reliable biomarker and should play an important role when designing clinical trials. However, results of our study reveal only 10.2% of the trials are EBV-related, and the distribution of these trials (Fig 3) remind us that the number increased only after 2014 but was still small. One of the main reasons is that there is no uniform standard in detecting the plasma EBV DNA level worldwide and hospitals would get different results if different test reagents are used, which makes it hard to perform multicenter collaborations. Therefore, EBV trials has a lower percentage of phase 2/3 (48.8% vs. 78.4%) and interventional (70.7% vs. 89.5%) studies. Future trials are urgently warranted to focus on the standardization of detecting plasma EBV DNA.

Although primary metastasis at initial diagnosis accounts for only 4.4% to 6% of all NPC patients [29–31] and excellent therapeutic outcomes have been achieved for advanced NPC, distant metastasis and recurrence after radiotherapy still remain a huge challenge. Our study showed that 205 trials regarding metastatic/recurrent disease were performed; however, most of these trials were conducted in US/Canada and were multiple cancer trials mainly focusing on other head and neck cancers. Furthermore, these trials were more likely to be early-phase, non-randomized and small-scale (< 50) compared with trials recruiting non-metastatic/recurrent patients. Therefore, we still lack high-level evidence of managing metastatic/recurrent disease. Actually, a recent study carried out by Zhang et al. [32] is the only phase 3 randomized trial focusing on metastatic/recurrent disease in endemic era. Hence, more attention should be paid to this subpopulation to optimize clinical practice.
Limitations of this study should also be acknowledged. First, ClinicalTrials.gov database does not include all clinical trials because investigators and sponsors may register their studies at other registrations. This may be embedded in the small number of trials from European. Second, some investigators or sponsors may input unconsciously wrong information in this database which would complicate our conclusions as the NLM cannot verify the trial information sponsors provided on ClinicalTrials.gov. Moreover, we did not assess the final results of these trials because part of these trials are still ongoing or not reporting the results.

Conclusions

Overall, our study firstly provides a best-possible overview of current clinical trials regarding NPC and demonstrated that the number is still insufficient especially for high-level, randomized phase 3 trials. The role of plasma EBV DNA in clinical trials is far from its value in clinical practice although numerous studies have established its value in prognosis prediction, risk stratification and decision making. Moreover, more randomized clinical trials should be performed for patients with metastatic/recurrent disease because we still lack high-level evidence in treating these patients.

Supporting information

S1 File. Summary of the 462 included clinical trials.
(XLSX)

Acknowledgments

We sincerely thanked the Sun Yat-sen University Cancer Center for providing the Research Data Deposit site for storing the data of current study (RDDA2017000152).

Author Contributions

Conceptualization: Hao Peng, Lei Chen, Jun Ma.
Data curation: Hao Peng, Lei Chen, Yu-Pei Chen.
Formal analysis: Hao Peng, Yu-Pei Chen, Wen-Fei Li, Ling-Long Tang, Ai-Hua Lin.
Funding acquisition: Jun Ma.
Methodology: Lei Chen, Yu-Pei Chen.
Project administration: Wen-Fei Li.
Software: Hao Peng, Yu-Pei Chen, Wen-Fei Li, Ai-Hua Lin.
Supervision: Jun Ma.
Validation: Hao Peng, Ling-Long Tang, Ying Sun, Jun Ma.
Visualization: Ying Sun, Jun Ma.
Writing – original draft: Hao Peng, Ling-Long Tang.
Writing – review & editing: Ling-Long Tang, Ying Sun, Jun Ma.

References

1. Razak AR, Siu LL, Liu FF, Ito E, O'Sullivan B, Chan K. Nasopharyngeal carcinoma: the next challenges. Eur J Cancer. 2010; 46:1967–1978. https://doi.org/10.1016/j.ejca.2010.04.004 PMID: 20451372.
2. Sun X, Su S, Chen C, Han F, Zhao C, Xiao W, et al. Long-term outcomes of intensity-modulated radiotherapy for 868 patients with nasopharyngeal carcinoma: an analysis of survival and treatment toxicities. Radiother Oncol. 2014; 110:398–403. https://doi.org/10.1016/j.radonc.2013.10.020 PMID: 24231245.

3. Yang L, Hong S, Wang Y, Chen H, Liang S, Peng P, et al. Development and External Validation of Nomograms for Predicting Survival in Nasopharyngeal Carcinoma Patients after Definitive Radiotherapy. Sci Rep. 2015; 5:15638. https://doi.org/10.1038/srep15638 PMID: 26497224.

4. Zhang MX, Li J, Shen GP, Zou X, Xu JJ, Jiang R, et al. Intensity-modulated radiotherapy prolongs the survival of patients with nasopharyngeal carcinoma compared with conventional two-dimensional radiotherapy: A 10-year experience with a large cohort and long follow-up. Eur J Cancer. 2015; 51:2587–2595. https://doi.org/10.1016/j.ejca.2015.08.006 PMID: 26318726.

5. Yi JL, Gao L, Huang XD, Li SY, Luo JW, Cai WM, et al. Nasopharyngeal carcinoma treated by radical radiotherapy alone: Ten-year experience of a single institution. Int J Radiat Oncol Biol Phys. 2006; 65:161–168. https://doi.org/10.1016/j.ijrobp.2005.12.003 PMID: 16542792.

6. Wei WI, Sham JS. Nasopharyngeal carcinoma. Lancet. 2005; 365:2041–2054. https://doi.org/10.1016/S0140-6736(05)66698-6 PMID: 15950718.

7. De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. N Engl J Med. 2004; 351:1250–1251. https://doi.org/10.1056/NEJMe046225 PMID: 15356289.

8. Anderson ML, Chiswell K, Petersen ED, Tasneem A, Topping J, Califf RM. Compliance with results reporting at ClinicalTrials.gov. N Engl J Med. 2015; 372:1031–1039. https://doi.org/10.1056/NEJMs0140936 PMID: 25760355.

9. Lin JC, Wang WY, Chen KY, Wei YH, Liang WM, Jan JS, et al. Quantification of plasma Epstein-Barr virus DNA in patients with advanced nasopharyngeal carcinoma. N Engl J Med. 2004; 350:2461–2470. https://doi.org/10.1056/NEJMa032260 PMID: 15190138.

10. Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. Cancer Epidemiol Biomarkers Prev. 2006; 15:1765–1777. https://doi.org/10.1158/1055-9965.EPI-06-0353 PMID: 17035381.

11. Shanmugaratnam K, Chan SH, de-The G, Goh JE, Khor TH, Simons MJ, et al. Histopathology of nasopharyngeal carcinoma: correlations with epidemiology, survival rates and other biological characteristics. Cancer. 1979; 44:1029 –1044. PMID: 225002.

12. Yu MC, Yuan JM. Epidemiology of nasopharyngeal carcinoma. Semin Cancer Biol. 2002; 12:421–429. PMID: 12450728.

13. Chang YS, Tyan YS, Liu ST, Tsai MS, Pao CC. Detection of Epstein-Barr virus DNA sequences in nasopharyngeal carcinoma cells by enzymatic DNA amplification. J Clin Microbiol. 1990; 28:2398–2402. PMID: 2174898.

14. Chen CL, Wen WN, Chen JY, Hsu MM, Hsu HC. Detection of Epstein-Barr virus genome in nasopharyngeal carcinoma by in situ DNA hybridization. Intervirology. 1993; 36:91–98. https://doi.org/10.1159/000150327 PMID: 8294187.

15. Tsai ST, Jin YT, Su IJ. Expression of EBER1 in primary and metastatic nasopharyngeal carcinoma tissues using in situ hybridization. A correlation with WHO histologic subtypes. Cancer. 1996; 77:231–236. https://doi.org/10.1002/(SICI)1097-0144(19960115)77:2<231::AID-CNCR2>3.0.CO;2-P PMID: 8625228.

16. Chan AT, Lo YM, Zee B, Chan LY, Ma BB, Leung SF, et al. Plasma Epstein-Barr virus DNA and residual disease after radiotherapy for undifferentiated nasopharyngeal carcinoma. J Natl Cancer Inst. 2002; 94:1614–1619. PMID: 12419787.

17. Leung SF, Chan AT, Zee B, Ma B, Chan LY, Johnson PJ, et al. Pretherapy quantitative measurement of circulating Epstein-Barr virus DNA is predictive of posttherapy distant failure in patients with early-stage nasopharyngeal carcinoma of undifferentiated type. Cancer. 2003; 98:288–291. https://doi.org/10.1002/cncr.11496 PMID: 12872347.

18. Leung SF, Chan KC, Ma BB, Hui EP, Mo F, Chow KC, et al. Plasma Epstein-Barr viral DNA load at midpoint of radiotherapy course predicts outcome in advanced-stage nasopharyngeal carcinoma. Ann Oncol. 2014; 25:1204–1208. https://doi.org/10.1093/annonc/mdu117 PMID: 24638904.

19. Leung SF, Zee B, Ma BB, Hui EP, Mo F, Lai M, et al. Plasma Epstein-Barr viral deoxyribonucleic acid quantitation complements tumor-node-metastasis staging prognostication in nasopharyngeal carcinoma. J Clin Oncol. 2006; 24:5414–5419. https://doi.org/10.1200/JCO.2006.07.7892 PMID: 17135642.

20. Lin JC, Chen KY, Wang WY, Jan JS, Liang WM, Tsai CS, et al. Detection of Epstein-Barr virus DNA in the peripheral-blood cells of patients with nasopharyngeal carcinoma: relationship to distant metastasis.
and survival. J Clin Oncol. 2001; 19:2607–2615. https://doi.org/10.1200/JCO.2001.19.10.2607 PMID: 11352952.

21. Lin JC, Wang WY, Liang WM, Chou HY, Jan JS, Jiang RS, et al. Long-term prognostic effects of plasma Epstein-barr virus DNA by minor groove binder-probe real-time quantitative PCR on nasopharyngeal carcinoma patients receiving concurrent chemoradiotherapy. Int J Radiat Oncol Biol Phys. 2007; 68:1342–1348. https://doi.org/10.1016/j.ijrobp.2007.02.012 PMID: 17449194.

22. Ma BB, King A, Lo YM, Yau YY, Zee B, Hui EP, et al. Relationship between pretreatment level of plasma Epstein-Barr virus DNA, tumor burden, and metabolic activity in advanced nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys. 2006; 66:714–720. https://doi.org/10.1016/j.ijrobp.2006.05.064 PMID: 17011447.

23. Peng H, Guo R, Chen L, Zhang Y, Li WF, Mao YP, et al. Prognostic Impact of Plasma Epstein-Barr Virus DNA in Patients with Nasopharyngeal Carcinoma Treated using Intensity-Modulated Radiation Therapy. Sci Rep. 2016; 6:22000. https://doi.org/10.1038/srep22000 PMID: 26924234.

24. An X, Wang FH, Ding PR, Deng L, Jiang WQ, Zhang L, et al. Plasma Epstein-Barr virus DNA level strongly predicts survival in metastatic/recurrent nasopharyngeal carcinoma treated with palliative chemotherapy. Cancer. 2011; 117:3750–3757. https://doi.org/10.1002/cncr.25932 PMID: 21319149.

25. Jin Y, Cai XY, Cai YC, Cao Y, Xia Q, Tan YT, et al. To build a prognostic score model containing indispensible tumour markers for metastatic nasopharyngeal carcinoma in an epidemic area. Eur J Cancer. 2012; 48:882–888. https://doi.org/10.1016/j.ejca.2011.09.004 PMID: 22030451.

26. Du XJ, Tang LL, Chen L, Mao YP, Guo R, Liu X, et al. Neoadjuvant chemotherapy in locally advanced nasopharyngeal carcinoma: Defining high-risk patients who may benefit before concurrent chemotherapy combined with intensity-modulated radiotherapy. Sci Rep. 2015; 5:16664. https://doi.org/10.1038/srep16664 PMID: 26564805.

27. Peng H, Chen L, Li WF, Guo R, Zhang Y, Zhang F, et al. Prognostic Value of Neoadjuvant Chemotherapy in Locoregionally Advanced Nasopharyngeal Carcinoma with Low Pre-treatment Epstein-Barr Virus DNA: a Propensity-matched Analysis. J Cancer. 2016; 7:1465–1471. https://doi.org/10.7150/jca.15736 PMID: 27471562.

28. Twu CW, Wang WY, Chen CC, Liang KL, Jiang RS, Wu CT, et al. Metronomic adjuvant chemotherapy improves treatment outcome in nasopharyngeal carcinoma patients with postradiation persistently detectable plasma Epstein-Barr virus deoxyribonucleic acid. Int J Radiat Oncol Biol Phys. 2014; 89:21–29. https://doi.org/10.1016/j.ijrobp.2014.01.052 PMID: 24725686.

29. Lee AW, Poon YF, Foo W, Law SC, Cheung FK, Chan DK, et al. Retrospective analysis of 5037 patients with nasopharyngeal carcinoma treated during 1976–1985: overall survival and patterns of failure. Int J Radiat Oncol Biol Phys. 1992; 23:261–270. PMID: 1587745.

30. Sham JS, Choy D, Choi PH. Nasopharyngeal carcinoma: the significance of neck node involvement in relation to the pattern of distant failure. Br J Radiol. 1990; 63:108–113. https://doi.org/10.1259/0007-1285-63-746-108 PMID: 2310902.

31. Teo PM, Kwan WH, Lee WY, Leung SF, Johnson PJ. Prognosticators determining survival subsequent to distant metastasis from nasopharyngeal carcinoma. Cancer. 1996; 77:2423–2431. https://doi.org/10.1002/(SICI)1097-0142(19960615)77:12<2423::AID-CNCR2>3.0.CO;2-N PMID: 8640688.

32. Zhang L, Huang Y, Hong S, Yang Y, Yu G, Jia J, et al. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. Lancet. 2016; 388:1883–1892. https://doi.org/10.1016/S0140-6736(16)31388-5 PMID: 27567279.