ORIGINAL ARTICLE

# High case volume of radiation oncologists is associated with better survival of nasopharyngeal carcinoma patients treated with radiotherapy: a multifactorial cohort analysis

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**Objectives:** The relationship between physician case volume and patient outcome in patients with head and neck cancers such as nasopharyngeal carcinoma treated by radiotherapy is unknown. This study was designed to investigate the association between the case volume of radiation oncologists and the survival of patients with nasopharyngeal carcinoma.
**Design:** Retrospective cohort study.
**Setting:** Based on nationwide claims data (National Health Research Insurance Database) in the years 2002–2008.
**Participants:** Newly diagnosed patients with nasopharyngeal carcinoma receiving curative radiotherapy in the year 2003.
**Main outcome measures:** Overall survival until 2008. We used the running log-rank test to decide the optimal threshold for categorising the case volume of radiation oncologists. The characteristics of patients, their treatments and contact with health service providers were considered as co-explanatory variables. The log-rank test and Cox regression were performed. Sensitivity analyses were carried out regarding major study assumptions.
**Results:** Five hundred and sixty-two patients with nasopharyngeal carcinoma newly diagnosed in 2003 were identified as the study cohort. The 5-year overall survival was better among patients treated by high-volume (≥6 patients in year 2002) radiation oncologists than by low-volume (<6 patients in year 2002) radiation oncologists (77% *versus* 64%, $P = 0.0007$). The adjusted hazard ratio of death was 0.65 (95% confidence interval, 0.48–0.91) upon multivariate analysis. Patients aged at least 65 years also had a lower survival rate than those younger than 65 years old (adjusted hazard ratio of death: 2.81, 95% confidence interval: 1.94–4.08).The physician case volume and patient outcome effect remained the same after sensitivity analyses.
**Conclusions:** Patients with nasopharyngeal carcinoma treated by high-volume radiation oncologists have better survival compared with those treated by low-volume radiation oncologists. Further studies are needed to verify our findings with similar cancer cohorts treated by modern radiotherapy techniques or other types of radiotherapy.

The positive relationship between physician case volume and patient outcome in initial cancer treatment is well known for surgical oncology.[1,2] However, little is known about the relationship of physician case volume and patient outcome for head and neck cancer treated by radiotherapy. Taking nasopharyngeal carcinoma as an example, although radiotherapy is considered the major curative therapeutic modality except for some rare histologic types,[3] we found no relevant report among more than 1600 studies retrieved from PubMed® during the past 10 years using a strategy similar to the previous review[1] but specific to nasopharyngeal carcinoma.

The potential benefit of initial cancer care offered by high-volume health service providers was profound.[1] If such a positive case volume–patient outcome relationship could be also observed for head and neck cancer

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patients treated by radiotherapy, patient outcome would be significantly improved through providing appropriate approaches. In particular, the anatomy of the nasopharynx is quite complex, and the radiotherapy technique for nasopharyngeal carcinoma is relatively complicated. Therefore, it would be interesting to know whether the positive case volume–patient outcome relationship can be applied to nasopharyngeal carcinoma patients treated with radiotherapy. We hypothesised that nasopharyngeal carcinoma patients treated with radiotherapy by high-volume (i.e. more experienced) radiation oncologists (ROs) would have better survival compared with those treated by low-volume ROs.

## Methods

### *Study design and data source*

We conducted a nationwide retrospective cohort study using claims data from the National Health Insurance programme in Taiwan to examine the survival of newly diagnosed patients with nasopharyngeal carcinoma receiving potentially curative radiotherapy in 2003. The National Health Insurance Research Database in Taiwan was utilised. The National Health Insurance programme is a single-payer, compulsory social insurance programme that has provided insurance coverage to almost every citizen in Taiwan since 1995. By the end of 2009, more than 99% of 23 million Taiwan citizens were enrolled in this programme.[4,5] The National Health Insurance also includes a catastrophic illness programme (abbreviated as HV) to protect vulnerable beneficiaries (including cancer patients) by exempting them from co-payments for the corresponding medical services. The National Health Research Institutes maintains the data warehouse for all services reimbursed by the National Health Insurance.[6] The National Health Research Institutes created the National Health Insurance Research Database with de-identified person number, the patients' medical providers (including physicians), the corresponding medical facility identifiers and other data. The National Health Research Institutes makes the database accessible to researchers and the public in Taiwan through the process of data acquisition, approval and payment.

For this study, we used the following files from the 2002–2008 National Health Insurance Research Database to obtain information regarding dependent and independent variables: HV (including historical data since 1996), ambulatory care expenditures by visits, details of ambulatory care orders, details of inpatient orders, inpatient expenditures by admissions, registry for board-certified specialists, registry for contracted medical facilities and registry for beneficiaries files. The ambulatory care expenditures by visits and details of ambulatory care orders files can provide up to three International Classification of Diseases-9 (currently in use in Taiwan) diagnosis codes and one International Classification of Diseases-9 procedure code for each outpatient visit. The files also contain billing records for medical claims reimbursed by the National Health Insurance, including claims for radiotherapy. The inpatient expenditures by admissions and details of inpatient orders files provide information similar to ambulatory care expenditures by visits and details of ambulatory care orders for inpatient care.

### *Ethical considerations*

This study was exempt from Institutional Review Board review because the National Health Insurance Research Database contains de-identified person identifiers and is publicly available through the proper application process.[6,7]

### *Selection of study cohort*

We identified newly diagnosed patients with nasopharyngeal carcinoma receiving potentially curative radiotherapy in 2003, and they were followed up through 31 December 2008. Figure 1 illustrates the flow chart of study population selection and the collection of corresponding explanatory variables. First, we identified nasopharyngeal carcinoma cases based upon registration in the HV for the first time as the surrogate criterion for cancer diagnosis. A similar approach was used in another cancer study using the National Health Insurance Research Database.[8] Those National Health Insurance beneficiaries with International Classification of Diseases-9 code = 147.XX who had at least two office visits on different dates (at least 1 month apart based on our previous experience[9]) were considered as our study cohort. This is a common approach used in claim data-based cancer studies.[10] These two approaches were used to ensure data quality. Second, we used the date of the first office visit as the presumed diagnosis date (index date) and restricted our study population to those patients with nasopharyngeal carcinoma newly diagnosed in the year 2003 and having at least 5 years' follow-up. Using these criteria, we could identify whether a difference existed in survival among different groups, given that nasopharyngeal carcinoma patients' survival outcomes are relatively good. Finally, we only included those study subjects who received the allocated duration (7–13 weeks) of external beam radiotherapy, started radiotherapy within 3 months of diagnosis and were treated by the same RO; these limitations were

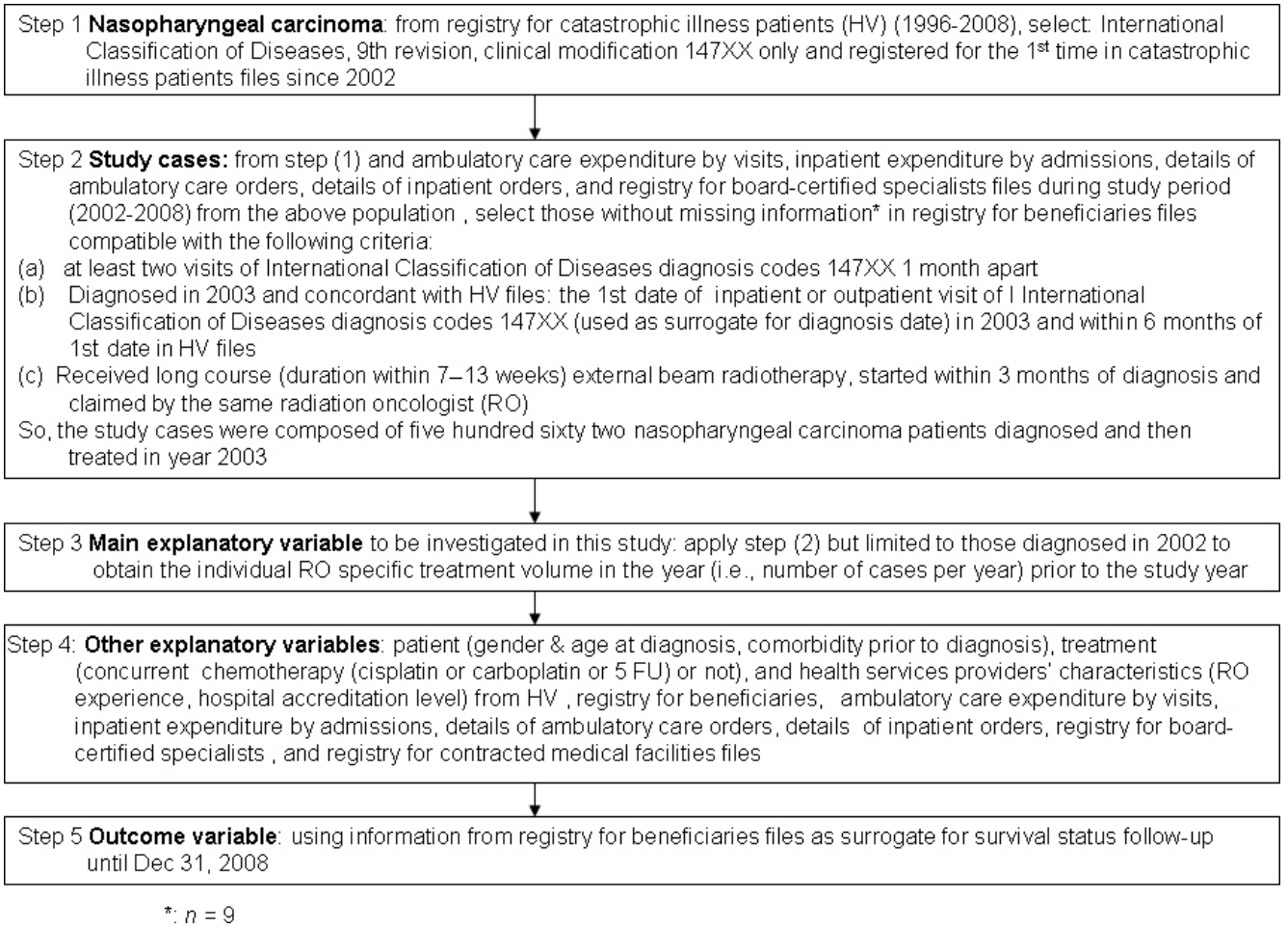


**Fig. 1.** Selection of study population and collection of corresponding explanatory and outcome variables.

used as the surrogate criteria to identify those who were receiving curative radiotherapy. These time points were selected based on clinical experiences and the National Comprehensive Cancer Network guideline,[11] which is commonly employed in Taiwan. Furthermore, such an interval was intended to exclude patients with distant metastases and those receiving a short course of palliative radiotherapy in general. The first date of radiotherapy claims was recognised as the beginning date of radiotherapy, and the last 'treatment-end-date' (a required variable for National Health Insurance radiotherapy claims, usually on a monthly basis) within 9 months of diagnosis was recognised as the end date of radiotherapy.

### *Definition of study variables*

We used registration status in the National Health Insurance programme as the surrogate for survival status (all-cause mortality). The National Health Insurance registration status is not likely to be correlated with treatment site and is a good proxy for a patient's survival.[12] The censor date is therefore the ending date of registration in National Health Insurance or the last date of our data (31 December 2008). Additionally, we identified the optimal threshold of physician case volume using the running log-rank statistic,[13,14] according to the study cohort survival, for the case number of newly diagnosed patients with nasopharyngeal carcinoma receiving potentially curative radiotherapy in 2002 to reflect the very recent (around 1 year's period) experience of the treating ROs. In addition to this main explanatory variable, we also obtained the characteristics of patients, their treatments, and their health service providers as co-explanatory variables (Fig. 1). In this analysis, age was coded as a binary variable (at least or <65 years old) to reflect aged or not as commonly considered in geriatric oncological literature[15] as well as in previous studies.[9,16] Patients' residency region obtained from the registry for beneficiaries files was coded as north *versus* non-north based upon the consensus of clinical experiences. The

patient's pre-diagnostic comorbidity (1 year before the index date) was identified based on the Klabunde *et al.* algorithm,[17] which has been applied in other National Health Insurance claim data.[18] The comorbidity status was coded as a binary variable (with or without comorbidity). As for the treatment-related co-explanatory variables, the study cohort was categorised as receiving concurrent chemoradiotherapy or not by recognising whether they received cisplatin, carboplatin or 5-fluorouracil based on clinical experience and the National Comprehensive Cancer Network guideline.[11] The ROs' experience was categorised as senior (more than 10 years' experience after board certification) or junior (<10 years' experience). The hospital accreditation level was coded as a binary variable (medical centre (the highest hospital level in Taiwan) *versus* non-medical centre).

### *Sensitivity analysis and statistical analysis*

To avoid potential interpretation bias, sensitivity analyses were performed to scrutinise the potential impact on the findings of the major study assumptions. First, we examined the impact of different surrogate definitions in identifying potentially curative radiotherapy by limiting the irradiated duration to within 7–9 weeks, which is a more idealistic scenario for curative radiotherapy. Second, we examined the impact of different surrogate definitions in identifying survival status by using medical visits (theoretically more accurate than registration). Finally, we examined the impact of more treatment-related factors such as neoadjuvant or adjuvant chemotherapy (i.e. chemotherapy was used within 9 months of diagnosis, but not during concurrent chemoradiotherapy). Although this is not a high-level recommendation (category 3 in the National Comprehensive Cancer Network guideline[11]), it has become a common practice for patients with nasopharyngeal carcinoma in Taiwan.[19,20] We used the Kaplan–Meier method to calculate the overall survival (OS) rate. The log-rank test and Cox regression were performed to explore the impact of explanatory variables on survival rate. Statistical significance was defined as two-sided, $P < 0.05$. We used SAS version 9.0 (SAS Institute, Cary, NC, USA) for data management and STATA/IC version 11.1 (Stata Corporation, College Station, TX, USA) for statistical analyses.

## Results

### *Patient characteristics of the study cohort*

Five hundred and sixty-two newly diagnosed patients with nasopharyngeal carcinoma receiving potentially curative radiotherapy in 2003 were identified as the study cohort. Their characteristics are described in Table 1. Most patients were of middle age (median age, 47 years), were men (75%), lived in the regions outside northern Taiwan (54%) and had no pre-diagnostic comorbidity.

**Table 1.** Patient characteristics of our study cohort ($n$ = 562)

| Characteristic | Number (rounded%), or median | Range if applicable |
|---|---|---|
| Age at diagnosis (year) | 47 | 14–87 (inter-quartile range: 40–56) |
| <65 | 489 (87) | – |
| ≥65 | 73 (13) | – |
| Gender, male | 424 (75) | – |
| Residency region: north | 259 (46) | – |
| Pre-diagnostic Carlson Comorbidity score* | 0 | 0–4 |
| 0 | 391 (70) | – |
| 1 | 112 (20) | – |
| 2 | 41 (7) | – |
| 3 | 15 (3) | – |
| 4 | 3 (1) | – |
| Concurrent chemoradiotherapy | 343 (61) | – |
| Treating RO's years of practising | 10 | 1–15 (inter-quartile range: 7–13) |
| Radiotherapy facility in medical centre | 354 (63) | – |

RO, radiation oncologist.
*The sum of the weighted comorbidities and accounts for the number and seriousness of the conditions; score 0: no cormobidity; score 1–2 and score 3–4 largely corresponding to mild and moderate comorbidity, respectively.

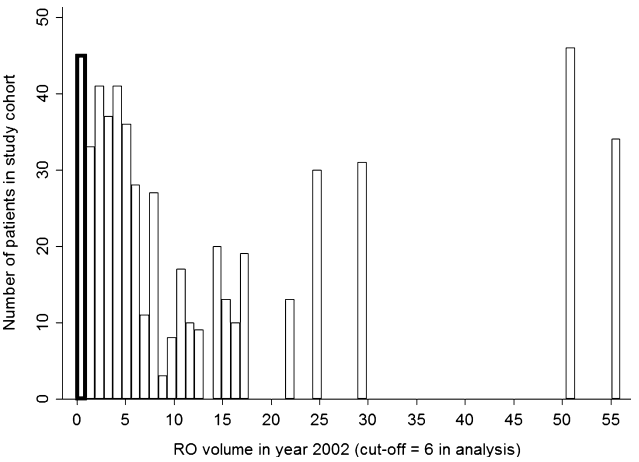


**Fig. 2.** The relationship of numbers in the study cohort and their ROs' case volume in the year 2002. RO: radiation oncologist.

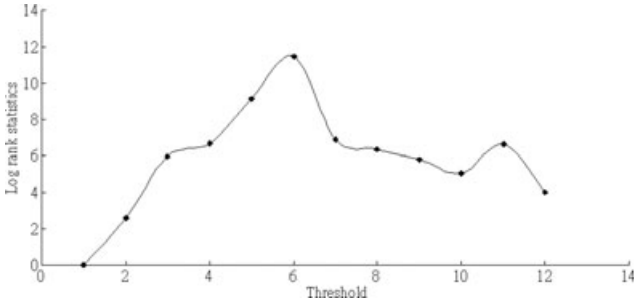


**Fig. 3.** Running log-rank statistic for different radiation oncologist volume cut-off points.

Most received concurrent chemoradiotherapy (61%) and were treated in medical centres (63%). The median practice experience of the ROs in charge was 10 years (range: 1–15).

### *Case volume threshold for the ROs*

The identified newly diagnosed patients with nasopharyngeal carcinoma were treated by 83 ROs. Figure 2 describes the case volume for these ROs in the year 2002. For example, 45 patients in our study cohort were treated by ROs who treated no patients with nasopharyngeal carcinoma curatively in the year 2002 (the leftmost bar in Fig. 2), whereas 34 patients were treated by ROs who treated 56 patients with nasopharyngeal carcinoma curatively in the year 2002 (the rightmost bar in Fig. 2). For patients treated in 2003, the difference in survival between those treated by the low- and high-volume ROs was statistically most significant at the cut-point (i.e. ≥6 per year, $P = 0.0007$) of case volume according to the running log-rank statistic (Fig. 3). Using this definition, 59% of the study cohort was treated by these twenty-seven high-volume ROs.

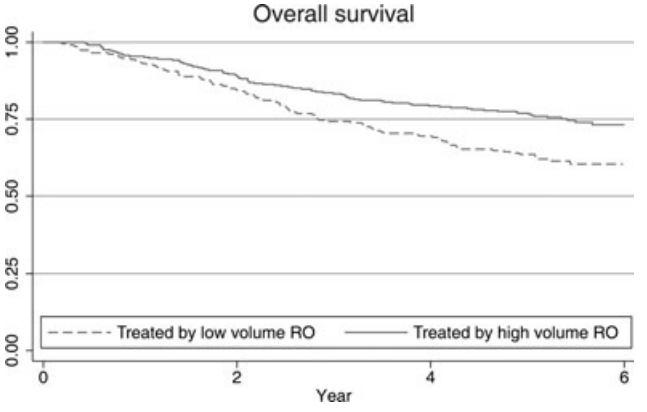


**Fig. 4.** Survival differences according to high and low RO volume (≥6 in year 2002 *versus* <6 in year 2002). RO: radiation oncologist.

### *Relationship between physician case volume and patient outcome*

In the unadjusted analysis, treatment of patients with nasopharyngeal carcinoma by high-volume ROs was associated with better survival when compared with treatment by low-volume ROs [5-year OS: 77% *versus* 64%, $P = 0.0007$ (Fig. 4)]. The test of the proportional-hazard assumption using the STATA 'estat phtest' command revealed no violation ($P = 0.67$). Table 2 summarises the results of the univariate and multivariate analyses. Patients receiving radiotherapy who were treated by high-volume ROs had better survival than those treated by low-volume ROs (adjusted hazard ratio for death: 0.65, 95% confidence interval: 0.48–0.89). In contrast, patients aged at least 65 years had a lower survival rate than those younger than 65 years (adjusted hazard ratio: 2.81; 95% confidence interval: 1.94–4.08), whereas other factors (i.e. gender, residency region, pre-diagnostic comorbidity, concurrent chemoradiotherapy, ROs' years of practice and hospital accreditation level) were not significantly related to survival.

### *Sensitivity analyses*

In the first sensitivity analysis, which addressed the impact of different surrogate definitions of curative radiotherapy, the finding was the same [i.e. high-volume ROs were associated with better survival ($P = 0.035$)]. In the second sensitivity analysis, which addressed identifying survival status, the result was not changed ($P = 0.013$ for the pattern of survival rate difference). In the final analysis, which concerned the impact of neoadjuvant or adjuvant chemotherapy, the finding was also the same ($P = 0.012$ for pattern of survival rate difference).

## Discussion

### *Synopsis of key findings*

This study is the pioneer nationwide cohort study to explore the impact of ROs' case volume on OS. We demonstrate that high-volume ROs are associated with better patient survival. This finding is robust in the sensitivity analyses.

### *Clinical applicability and interpretation of the study*

Our study suggests that quality-of-care strategies (e.g. service centralisation and standardisation initiatives) should be set up to facilitate the improvement of radiotherapy service and to enhance the efficiency of patient care.

**Table 2.** Association between explanatory variables and survival

| Explanatory variables | Reference group | Univariate hazard ratio | Multivariate hazard ratio | Multivariate hazard ratio | |
|---|---|---|---|---|---|
| | | | | Lower range† | Upper range† |
| Physician volume | <6 in year 2002 | 0.6* | 0.65* | 0.48 | 0.89 |
| Age | <65 years old | 2.91* | 2.81* | 1.94 | 4.08 |
| Gender | Female | 1.5 | 1.4 | 0.95 | 2.06 |
| Residency region | Outside north Taiwan | 0.87 | 0.97 | 0.71 | 1.32 |
| Prediagnostic comorbidity | Without comorbidity | 1.4* | 1.11 | 0.8 | 1.54 |
| Concurrent chemo radiotherapy | No concurrent chemoradiotherapy | 1.06 | 1.18 | 0.86 | 1.62 |
| Treating RO's years of practising | ≥10 years | 0.99 | 1.14 | 0.84 | 1.55 |
| Hospital accreditation level | Non-medical centre | 0.92 | 0.91 | 0.67 | 1.24 |

RO, radiation oncologist.
*$P < 0.05$.
†95% confidence interval.

We also found that elderly patients are associated with inferior outcome, which is compatible with other epidemiological and clinical studies.[16,21,22] In an epidemiology study, the 5-year survival rate for the youngest age group (15–45 years) and the eldest age group (more than 75 years) were 56% and 6%, respectively.[21] In a clinical study from Europe, the 3-year survival rate for those <45 years old, 45–65 years old and over 65 years old were 100%, 84% and 43%, respectively.[16] Similar trends were noted in another clinical study from Asia as well.[22] The optimal management for these aged patients with nasopharyngeal carcinoma deserved further studies in the future.

The volume–outcome relationship can be interpreted from many perspectives. The major concern is about the quality of radiotherapy planning. Although adherence to treatment guidelines is a major predictor of head and neck cancer patients' survival,[23] our study demonstrated another finding: that radiotherapy treatment provided by high-volume ROs is also a factor associated with patient survival. This could be attributed to the complexity of the anatomy and the radiotherapy planning for nasopharyngeal carcinoma.

### *Comparisons with other studies*

Most of the published volume–outcome studies focused on surgeon or treatment-centre volume.[1,2] Some recent studies also extended the outcome from survival to intermediate process indicators.[18]

When compared with other strategies to improve patient outcome, our study indicates that the potential benefit of initial cancer care provided by high case volume providers might be significant.[1] The survival difference between two patient groups treated by physicians with varying case volumes was 13% (77% *versus* 64%). This value was comparable to the synergistic effects because of a combination of radiotherapy and systematic therapy for advanced head and neck cancer.[24]

### *Strengths and weaknesses of the study*

There are four major limitations of this study. First, although the accuracy of the National Health Insurance Research Database has been validated for some other diseases (e.g. diabetes and stroke),[6] there is limited information about cancer. To minimise interpretation bias, the major assumptions regarding case identification or variable definitions utilised in some other studies[8,10,12] were examined via sensitivity analyses. Taking cancer diagnosis as an example, it might be more accurate if data linkage with a cancer registry were available. However, this was not routinely available at the time of our research. On the other hand, we used information from HV registration, an approach with high accuracy in previous National Health Insurance Research Database studies.[8,9,18] Future studies may also rely on the upcoming National Health Informatics Project initiated by the Department of Health in Taiwan to obtain more accurate cancer diagnosis information. Second, it is not possible to retrieve data related to the impact of modern radiotherapy techniques (i.e. intensity modulated radiotherapy) from the National Health Insurance Research Database. In fact, one published randomised study revealed that patients with nasopharyngeal carcinoma treated by intensity modulated radiotherapy experienced decreased late complications, but local control and OS were comparable to those of patients treated with conventional radiotherapy.[25] Third,

cancer-staging information was not available in the National Health Insurance Research Database. However, bias was minimised by restricting the selection criteria for the study cohort. For example, counting concurrent chemoradiotherapy records could partially supplement the staging information because concurrent chemoradiotherapy is mainly suggested for those beyond stage I.[11] Finally, this study was an observational study, not an interventional one. Thus, our study is just the starting point, and further detailed retrospective or prospective studies would be the next step to investigate other issues regarding the case volume–patient outcome relationship. Future studies focusing on relative (cancer-specific) survival might be helpful to understand the excess mortality associated with the disease.

## Conclusions

Patients with nasopharyngeal carcinoma treated by high-volume ROs had better survival than those treated by low-volume ROs. It is not possible to determine whether treatment by high-volume ROs is causally associated with better survival or whether this difference may result from differences in case mix. This is an area that requires further research. Further studies are needed to confirm the generalisability of this finding to the same cancer cohort treated by modern radiotherapy techniques or in other applications of radiotherapy.

### Keypoints

- Nasopharyngeal carcinoma patients treated by high-volume radiation oncologists had better survival than those treated by low-volume radiation oncologists.
- This empirical evidence supported that case volume – patient outcome effect might be extended from surgical oncology to radiation oncology as well.

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## Conflict of interest

The author(s) declare that they have no competing interests.

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