An Increasing Population of Patients With Oropharyngeal Carcinoma in China is Predicted to Benefit From Proton Beam Therapy in Terms of Cost-effectiveness Consideration

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Abstract

Background: Proton beam therapy (PBT) is a new-emerging cancer treatment in China. The treatment costs are high and not yet covered by Chinese public medical insurance. The advanced form of PBT, intensity-modulated proton radiation therapy (IMPT), has been confirmed to reduce normal tissue complication probability (NTCP) compared with conventional intensity-modulated photon-radiation therapy (IMRT) in patients with oropharyngeal cancer (OPC). This study evaluated the cost-effectiveness of IMPT versus IMRT for OPC patients in China, aiming at guiding proper use of PBT.

Methods: On the basis of published data, a 7-state Markov model was designed for cost-effectiveness analysis, and an evaluation of average level was performed on a base case of 56-year-old under the hypothesis that IMPT could make a 25% NTCP-reduction concerning to long-term symptomatic dysphagia and xerostomia. Model robustness was examined using probabilistic sensitivity analysis, cohort analysis and tornado diagram. One-way sensitivity analyses were performed to identify cost-effective scenarios. IMPT was considered as cost-effective if the incremental cost-effectiveness ratio (ICER) was below the societal willingness-to-pay (WTP) threshold (3 times the gross domestic product per capita / quality-adjusted life year (QALY)).

Results: Compared with IMRT, IMPT could provide an extra 0.724 QALYs at an additional cost of 34,926.6 US dollars (\$), and made an ICER of \$48,229.8/ QALY for the base case. At current WTP level of China (\$30,828/QALY), cost-effective scenarios of IMPT existed in the following independent conditions: $\geq 57.3\%$ NTCP-reduction (IMPT compared with IMRT) in dysphagia and xerostomia; patient age ≤ 38 -year-old; or the cost of IMPT $\leq$ \$37,398.1. The estimated cost-effective population that benefit from using PBT to treat OPC increased remarkably in the past 10 years with the economic growth, and reached to 559.7 million (about 40.0% of the China's total population) in the year 2020.

Conclusions: Currently, using PBT to treat OPC could be cost-effective in considerable proportion of China's population. Considering the economic growth, the gradual increment of medical insurance coverage, as well as the proton treatment cost reduction along with more proton facility opening in the near future, it is estimated that PBT would benefit more Chinese OPC patients with respect to cost-effectiveness.

Background

The incidence of oropharyngeal cancer (OPC) has increased in the past 40 years worldwide because of the rising epidemic of human papillomavirus (HPV) infection related to sexual behavior [1]. Traditionally, China has a lower burden of HPV-positive OPC compared to the rest of the world. In the recent decade, the occurrence of OPC in China has showed an upward trend, which is probably due to the behavior changes brought by high pressure lifestyle. As reported, the age-standardized rate of incidence had increased from 2.0/100,000 per year to 2.54/100,000 per year during the year 2003–2012 [2, 3].

According to the latest treatment guidelines, radiotherapy/concurrent chemoradiotherapy has been recommended as the mainstream treatment for OPC patients with early/locally advanced stage, whether HPV-positive or HPV-negative [4, 5]. Owing to the anatomic location and a high required radical dose of this tumor type, irradiation-induced dysphagia and xerostomia become the most common late toxicities in OPC survivors. Even with the best photon irradiation technique, intensity-modulated photon-radiation therapy (IMRT), symptomatic dysphagia and xerostomia (grade 2–4) occurred with the incidences as high as 15–23% and 32–48%; and were confirmed as independent negative influential factors impacting OPC patient's long-term life quality [6–9].

Proton beam therapy (PBT) is a new-emerging particle irradiation technique with superior energy absorption distribution afforded by protons' "Bragg peaks" to protect normal tissues. In recent comparative studies, intensity-modulated proton radiation therapy (IMPT), the advanced form of PBT, was found to lower irradiation dose of normal tissues including the parotid, larynx, oral cavity, and pharyngeal constrictor muscle in OPC patients, resulting in the normal tissue complication probability (NTCP) concerning to long-term symptomatic dysphagia and xerostomia reduced by approximate 25% on average, in comparison to that of IMRT [10–13]. In previous PBT decision-making studies for OPC, such advantages of IMPT over IMRT in reducing dysphagia and xerostomia had been applied as the pivotal factor determining whether the OPC patient was appropriate to undergo PBT [14, 15].

Nevertheless, the therapeutic benefits should still be carefully weighed against the proton's much higher treatment cost, which is 3.2 to 4.8 times that of IMRT [16]. At the mainland of China, there is only 1 operational proton center at present, the government has planned to authorize another 16 licenses for operating proton center in the major cities by the year 2020 [17]. The high treatment costs of this new-emerging cancer treatment are not yet covered by Chinese public medical insurance. Cost-effectiveness analysis (CEA) is urgently needed in guiding proper clinical decision of PBT when this treatment would become more available in the near future [18, 19]. Till present, no CEA studies was conducted to evaluate the cost-effectiveness of PBT for OPC patients in China.

On the basis of published data, we designed a 7-state Markov model to track the natural development of disease and late toxicities and simultaneously evaluate the relevant cost and effectiveness of IMPT versus IMRT in a long-term period for Chinese OPC patients. The analyses of this study aimed to identify the cost-effective scenarios and estimate the potential population that benefit from using PBT to treat OPC in China.

Methods

Model design

TreeAge Pro 2018 software (Williamstown, MA) was used for model building and analysis. A decision tree combined with two 7-state Markov models were designed to evaluate the cost-effectiveness of IMPT in comparison to that of IMRT for newly diagnosed non-metastatic OPC patients. CEA modelling was based

on two hypotheses: (1) the advantage of IMPT over IMRT would be its ability in reducing symptomatic dysphagia and xerostomia (Radiation Therapy Oncology Group, RTOG grade 2–4), defined as “NTCP-reduction” in this study, and $\text{NTCP-reduction (\%)} = [(\text{NTCP}_{\text{after IMRT}} - \text{NTCP}_{\text{after IMPT}}) / \text{NTCP}_{\text{after IMRT}}] * 100\%$; (2) all the dysphagia and xerostomia would occur within the first year after radiotherapy and late toxicities would be irreversible if occurred [20, 21].

Transition states of the Markov model were illustrated in Fig. 1. The states of “alive with cancer”, “no cancer” (including 4 sub-states of “dysphagia”, “xerostomia”, “dysphagia and xerostomia” and “no complication”) and “death” (including “cancer death” or “other death”) were used to simulate the natural process of disease and late toxicities for OPC patients after radiotherapy. A 1-year cycle length was used, and the Markov models were cycled from 1 year after radiotherapy until the estimated generalized Chinese life expectancy in 2020 (77-year-old) to evaluate the cost-effectiveness of a lifetime after radiotherapy [22]. The risk of natural non-cancer caused death was calculated based on the 2016 Life Tables of United States [23].

Base case set-up

We used a base case of 56-year-old (median age of this cancer type in China) to represent the average Chinese OPC patients [24]. Disease probabilities in the model were calibrated according to the overall survival (OS) and disease-free survival (DFS) data for OPC patients, reported by F De Felice et al. [25]. The 2 compared treatment strategies were similar except for the irradiation technique (IMPT versus IMRT), which included a radical radiotherapy and 3 cycles of concurrent chemotherapy. The NTCPs of dysphagia and xerostomia after IMRT were set according to the long-term follow-up results of OPC patients after IMRT reported by Bird T et al. and Al-Mamgani A et al., in which the probabilities of dysphagia and xerostomia ($\geq$ grade 2) were 0.19 and 0.33 respectively [5, 6]. On the basis of the published data, we assumed that IMPT could make a 25% NTCP-reduction in both dysphagia and xerostomia compared with IMRT for average OPC patients [12, 13]. Other clinical outcomes, including the survival rates, were assumed to be identical between the two strategies.

Cost and utilities

The costs of treatment were calculated based on casual clinical prescriptions to reflect similar costs as that of daily practice in a Chinese hospital. All costs were adjusted to US dollars (\$), using a Sino-US exchange rate of \$1 = 6.93 RMB (January 23, 2020). The cost of IMPT and IMRT were estimated as being \$50,000 and \$12,000 respectively for simulating a 32-fraction to a total dose of 70 Gy. The cost of concurrent chemotherapy was assumed as \$5,000 (simulating 3 cycles of 80100 mg/m² cisplatin bolus injection delivered on day-1, -21 and - 42 of the radiotherapy). The follow-up cost per year was assumed as \$1,000 (including hematologic and biochemistry profiles, nasopharyngeal fiberoptic endoscope examination, magnetic resonance imaging of head and neck, chest radiography and abdominal ultrasonography); the cost of palliative therapy per year was assumed as \$5,000 (simulating 8 cycles of oral palliative chemotherapy with 5-fluorouracil). The treatment cost for dysphagia per year was

estimated to be \$3,000; simulating long-term use of nasal feeding tube or percutaneous gastrostomy tube. The treatment cost for xerostomia per year was estimated to be \$2,000; simulating the consumption of traditional Chinese medicine or artificial saliva. For patients in the “no cancer” state, the incremental cost per year was the follow-up cost $\pm$ the treatment cost for dysphagia and/or xerostomia. For patients in the “alive with cancer” state (recurrence, metastasis, or residue), the incremental cost per year included the follow-up cost and the cost of palliative chemotherapy.

The utilities were adjusted to QALYs using health state utility values (HSUV) derived from previously published studies for head and neck cancer. HSUV can be interpreted as the strength of preference for a given health state on a cardinal scale anchored at 0 (“death”) and 1 (“full health”). In this model, the HSUV of “alive with cancer” was assumed as 0.57 to represent a progressive disease with the disutility caused by anticancer treatment [26]. The HSUVs for the states of “dysphagia”, “xerostomia” and “dysphagia and xerostomia” ($\geq$ grade 2) were standardized as 0.803, 0.846 and 0.763, according to the report of Ramaekers et al. [9]. The HSUVs for the states of “no complication” and “death” were set as 1 and 0. Costs and quality-adjusted life-years (QALYs) were discounted at an annual rate of 3% [27].

Outcomes measurement

OS was defined as time interval between the end of the radiotherapy and death from any cause. DFS was defined as the time interval between the end of the radiotherapy and first cancer progression or death from any cause. The outcome measure of the model was the incremental cost-effectiveness ratio (ICER) which represented the ratio of the difference in costs to the difference in effectiveness (incremental cost / incremental effectiveness) between IMPT and IMRT. A strategy is deemed cost-effective by comparing the ICER with an established societal willingness-to-pay (WTP). According to the World Health Organization guidelines, a strategy is defined as cost-effective if the ICER value is below 3 times the gross domestic product (GDP) per capita. In this study, \$30,828 / QALY (3 times the Chinese GDP per capita in 2019) was applied as the current WTP level of China [28, 29].

Sensitivity analysis and Monte Carlo simulation

Probabilistic sensitivity analysis was applied to illustrate the robustness of the model in light of a joint uncertainty for model parameters by running over 50,000 iteration trials, and the 90% confidence interval of the model parameters were identified. Tornado diagram was used to evaluate the influences of the parameters on the ICER over the variation of their 90% confidence interval. One-way sensitivity analyses were performed to identify the cost-effective scenarios of IMPT. Monte Carlo simulation (50,000 trials) was applied to show trials distribution of the two strategies and determine which would be the recommended strategy from the perspective of net benefit.

Estimation of cost-effective population

The population with a WTP level beyond the ICER value was estimated as cost-effective population in China in this study. All the 397 administrative regions (cities) at the mainland of China were ranked according to their GDP per capita level. The forefront regions in the ranking, with accumulated total GDP

and total population that corresponded an average GDP per capita that made a WTP threshold value (3 times the GDP per capita) beyond the ICER value, were delineated as the cost-effective regions; and the total population in these forefront regions were estimated as the cost-effective population in China. All GDP and population data were collected from the official website of Chinese National Bureau of Statistics [30].

Results

Model robustness verification

The model input information and probabilistic sensitivity analyses for the model parameters are summarized in **Table 1**. The model robustness verification was performed using the base case set-up. Markov cohort analyses for both IMPT strategy and IMRT strategy are shown in **Additional file 1: Figure S1**. The CEA model predicted the 1-, 3-, 5- and 10-year OS rates of 90.0%, 85.5%, 80.0% and 68.7%; and the 1-, 3-, 5- and 10-year DFS rates of 85.0%, 78.8%, 72.9% and 67.1% for average OPC patients. Such survival data were very similar with the previous outcomes reported by [F De Felice et al. \[25\]](#) (detailed in **Additional file 2: Figure S2**).

The tornado diagram identified the top 5 parameters influencing the ICER as the NTCP of dysphagia after IMPT, the cost of IMPT, the NTCP of xerostomia after IMPT, the NTCP of dysphagia after IMRT and the NTCP of xerostomia after IMRT; and the other parameters had only a minor impact on the ICER (**Fig. 2**).

Cost-effectiveness of the base case

By model calculation, IMPT (compared with IMRT) provided the base case an additional 0.724 QALYs at an additional cost of \$34,926.6, and the ICER was \$48,229.8/QALY. Thus, IMPT was not cost-effective for the base case at the current WTP level of China (\$30,828/QALY). IMPT was the recommended strategy in 34.0% of trials from the perspective of net benefit in Monte Carlo simulations, as showed in **Additional file 3: Figure S3**.

Cost-effective scenarios of proton beam therapy

One-way sensitivity analyses identified the potential cost-effective scenarios of IMPT with base case set-up, using 3 different WTP thresholds (\$30,828 / QALY, \$50,000 / QALY and \$100,000 / QALY) (**Table 2**). At the current WTP level of China (\$30,828 / QALY), the cost-effective scenarios of IMPT existed in the following independent conditions: $\geq 57.3\%$ NTCP-reduction (IMPT compared with IMRT) in dysphagia and xerostomia; patient age ≤ 38 -year-old; or the cost of IMPT $\leq$ \$37,398.1.

Cost-effective population in China benefit from proton beam therapy

The cost-effective population that benefit from using PBT to treat OPC in China was estimated for the years from 2010 to 2020, summarized in **Additional file 4: Table S1**. The estimated cost-effective population increased remarkably in the past 10 years with the growth of GDP per capita in China; and

such population reached to 559.7 million, about 40.0% of the China's total population in the year 2020, as shown in **Fig. 3** and **Additional file 5: Table S2**.

Discussion

In this study, a reliable and robust 7-state Markov model was designed to evaluate the cost-effectiveness of IMPT versus IMRT for OPC, a fast-growing malignancy in China. On the basis of published data, the cost-effective scenarios of IMPT at the current WTP level of China were identified as the following independent conditions: $\geq 57.3\%$ NTCP-reduction (IMPT compared with IMRT) in dysphagia and xerostomia; patient age ≤ 38 -year-old; or the cost of IMPT $\leq \$37,398.1$. The cost-effective population in China that benefit from using PBT to treat OPC increased remarkably in the past 10 years with the growth of GDP per capita. It was estimated that such cost-effective population would be about 40.0% of the China's total population in the year 2020.

Cost-effectiveness of PBT has been poorly evaluated worldwide, and has been referred as the proton's "economic controversy" [18, 31]. The only documented CEA study of PBT for OPC patients was reported by Sher DJ et al., a 6-state Markov model was designed for a 65-year-old OPC patient based on a hypothesis that IMPT could make a 25% reduction of xerostomia, dysgeusia and the need for gastrostomy tube, with the model set-up reflecting the practice in American hospitals [32]. But the 6-state Markov model in that study was found not applicable for Chinese OPC patients in certain regards, such as Chinese patients' unwillingness to undergo invasive surgery like percutaneous gastrostomy tube for treating the eating difficulty, and the extensive use of traditional Chinese medicine in dealing with xerostomia.

Markov model design is a key step of CEA modelling for PBT. In our previous CEA modelling for paranasal sinus and nasal cavity cancer, a reliable 3-state Markov model was designed to simulate the tumor development and evaluate the cost-effectiveness of IMPT in comparison to IMRT in terms of tumor control improvement [33]. Unlike paranasal sinus and nasal cavity cancer, the advantages of IMPT over IMRT for OPC patients lied in reducing late toxicities while not in improving tumor control or survival rates [34, 35]. In this CEA modelling for OPC, we also used 3 main states including "alive with cancer", "no cancer" and "death" to simulate the tumor development of OPC, but the survival probabilities were set identical between IMPT strategy and IMRT strategy. The model-predicted OS and DFS were found correspond to the previous long-term survival outcomes [25], which demonstrated that the CEA modelling did abide with the natural disease process of OPC.

To evaluate long-term differences in effectiveness and cost between the two strategies, the state of "no cancer", referring to OPC survivor after radiotherapy, was further divided into 4 sub-states of "dysphagia", "xerostomia", "dysphagia and xerostomia" and "no complication", the initial state probabilities of the 4 sub-states were set according to the NTCPs of dysphagia and xerostomia. For each cycle, the HSUVs for states of "dysphagia", "xerostomia", "dysphagia and xerostomia" and "no complication" were set as 0.803, 0.846, 0.763 and 1, respectively; meanwhile, the annual costs for dealing with these toxicities were

added as the accumulated incremental costs. Therefore, NTCP-reductions of dysphagia and xerostomia (IMPT compared with IMRT) became the original motivations of differences in effectiveness and cost between the two strategies. The robustness of this model design was confirmed by tornado diagram analysis, which demonstrated that only the NTCPs and the cost of IMPT had major impacts on ICER value.

In this study, the cost-effective scenarios of PBT were identified as 3 independent conditions for Chinese OPC patients: $\geq 57.3\%$ NTCP-reduction, patient age ≤ 38 -year-old, or the cost of IMPT $\leq \$37,398.1$. In previous PBT decision-making studies for OPC patients, the superiority of IMPT over IMRT in reducing dysphagia and xerostomia (NTCP-reductions) has been applied as the determining factor for treatment decision making between IMPT and IMRT, and NTCP models were applied to estimate NTCP-reductions using dosimetric information in IMPT and IMRT treatment plans, such as the approaches developed by Langendijk JA et al. and Brodin et al. [14, 15]. However, the threshold of NTCP-reduction, above which an OPC patient could be considered as appropriate for PBT, had not been defined in the previous studies. Here, we first defined a threshold for NTCP-reduction based on the criterion of cost-effectiveness. In our CEA modelling, we also found that younger patient who had a longer survival time could benefit more from PBT from the cost-effectiveness consideration. Thus, patient age should be another main consideration in the clinical decision making of prescribing PBT. In addition, proton treatment cost was identified as one of the major influential factors to the cost-effectiveness, and the current proton treatment cost was found high at current WTP level of China. But we estimated that such treatment cost will probably be reduced in the near future due to the market competition and technology upgrade along with more proton centers open in China [36].

Of note, at current stage without public medical insurance coverage, the level of ability-to-pay (WTP level) should also be weighed in clinical decision of using PBT. Regional difference of WTP level in China is obvious. For example, the GDP per capita in Shenzhen City of China (the second highest) are as high as \$28,931 in the year 2019, corresponded a WTP of \$86,793/QALY (2.8 times the current WTP of China). In order to evaluate the acceptance of using PBT to treat OPC in whole population of China, we delineated the population of a higher level of GDP level that corresponded a WTP level beyond the ICER value (\$48,229.8/QALY) as an estimated cost-effective population in this study. Such cost-effective population was found increased remarkably in the 10 past years with the growth of GDP per capita, and reached to 559.7 million (about 40.0% of the China's total population) in the year 2020. This finding indicated the great market potential and future trend of PBT in Chinese society, even though such estimation might not be accurate due to the uneven distribution of social wealth.

There are two main limitations in this study. First, our CEA modelling was hypothesis-based. We assumed that all the symptomatic dysphagia and xerostomia would occur within the first year after radiotherapy and late toxicities would be irreversible if occurred. This assumption was based on the previously observed studies, which showed that the changes of two late toxicities would be tiny and negligible after 1 year [37, 38]. The Markov models were cycled from 1 year after radiotherapy, and the potential differences in irradiation-induced adverse events within the first year after radiotherapy, including the

acute toxicities and hospital admission rates, were not taken into account in CEA. Hence, these hypothesis-related problems may hamper the interpretation of the results. Second, the CEA modelling in this study was performed with the base case set-up (a 25% NTCP-reduction, 56-year-old, and the current WTP of China) to represent Chinese OPC patients of an average level. However, the clinical decision making of prescribing PBT to a specific OPC patient should base on CEA modelling with individualized set-up, which enables to take patient's age, tumor stage and economic situation into account. So, the next step, we plan to conduct individualized CEA modelling for treatment decision making (IMPT versus IMRT).

Conclusions

On the basis of published data and hypothesis-based CEA modelling, the results in this study demonstrated that the cost-effective scenarios of PBT did exist in Chinese OPC patients; and using PBT to treat OPC could be cost-effective in considerable proportion of China's population at current stage. Considering future changes including the economic growth, the gradual increment of medical insurance coverage and the proton treatment cost reduction, it is predicted that PBT would benefit more Chinese OPC patients with respect to cost-effectiveness.

Abbreviations

PBT: Proton beam therapy; IMPT: Intensity-modulated proton radiation therapy; IMRT: Intensity-modulated photon-radiation therapy; OPC: Oropharyngeal cancer; NTCP: Normal tissue complication probability; PSA: Probabilistic sensitivity analysis; ICER: Incremental cost-effectiveness ratio; WTP: Willingness-to-pay; HPV: Human papillomavirus; CEA: Cost-effectiveness analysis; RTOG: Radiation Therapy Oncology Group; OS: Overall survival; DFS: Disease-free survival; GDP: Gross domestic product; \$: US dollars; QALY: Quality-adjusted life year; SPHIC: Shanghai proton and heavy Ion Center; SYSUCC: Sun Yat-sen University Cancer Center; HSUV: Health state utility value.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

CNQ and GL were responsible for the concept and design of the analysis. JG, CNQ and YXH collected data for analysis. GL, DO, YXH, PYB and BQ performed the analysis and interpretation of results. GL and CNQ prepared a first draft of the manuscript. JD, KB, BQ and YFX provided critical revision to the first and subsequent drafts of the manuscript. All authors contributed to and have reviewed and approved the final version of the manuscript. CNQ is the guarantor of the manuscript.

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Authors' Information

Details in authors' names and affiliations in Title Page part.

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Tables

Table 1 Model information and probabilistic sensitivity analysis for the parameters

Parameters	Input information	90% CI in PSA ^a	Distribution ^b	Source
Target Cancer	OPC			
Evaluated treatment strategies	IMPT vs. IMRT			
Base case set-up				
Patient age ^c	56-year-old ^d			
Disease probabilities				
DFS (1-year)	0.85			F De Felice et al. [25]
OS (1-year)	0.9			F De Felice et al. [25]
“no cancer” to “alive with cancer”	0.03(2 nd -5 rd year); 0 (6 th -10 th year)			F De Felice et al. [25]
“alive with cancer” to “cancer death”	0.3			F De Felice et al. [25]
Long-term toxicities probabilities				
NTCP of dysphagia after IMRT	0.19	0.129 - 0.256	Beta	Bird T et al. [5]
NTCP of xerostomia after IMRT	0.33	0.266 - 0.394	Beta	Al-Mamgani A et al. [6]
NTCP of dysphagia after IMPT	0.143	0.0369 - 0.276	Beta	Meijer TWH et al. [12]
NTCP of xerostomia after IMPT	0.248	0.128 - 0.377	Beta	Meijer TWH et al. [12]
Utilities (QALYs)				
No complication	1			
Dysphagia	0.803	0.671 - 0.918	Beta	Ramaekers BL et al. [9]
Xerostomia	0.846	0.714 - 0.955	Beta	Ramaekers BL et al. [9]
Dysphagia and xerostomia	0.763	0.631 - 0.881	Beta	Ramaekers BL et al. [9]

Alive with cancer	0.57	0.442 - 0.696	Beta	de Almeida JR et al. [26]
Death (cancer death or other death)	0			
Cost (\$)				
IMPT	50,000	37,134.7 - 62,882.3	Normal	SPHIC
IMRT	12,000	10,737.4 - 13,282.5	Normal	SYSUCC
Concurrent chemotherapy	5,000	3,728.8 - 6,297.3	Normal	SYSUCC
Follow-up / year	1,000	869.7 - 1,128.0	Normal	SYSUCC
Treatment for dysphagia / year	3,000	1,716.6 - 4,273.0	Normal	SYSUCC
Treatment for xerostomia / year	2,000	1,362.6 - 2,641.6	Normal	SYSUCC
Palliative therapy / year	5,000	2,411.2 - 7,567.2	Normal	SYSUCC
Markov model set-up				
Cycle length	1-year			
Number of cycles	77 ^e - patient age			
Discount rate / year	3%			

CI confidence interval, *PSA* probabilistic sensitivity analysis, *OPC* oropharyngeal cancer, *IMPT* intensity modulated proton therapy, *IMRT* intensity modulated radiation therapy, *OS* overall survival, *DFS* disease-free survival, *NTCP* normal tissue complication probability, *QALY* quality adjusted life year, \$ US dollars, *SPHIC* Shanghai Proton and Heavy Ion Center, *SYSUCC* Sun Yat-sen University Cancer Center, *CEA* cost-effectiveness analysis

^aProbabilistic sensitivity analysis (PSA) was performed to determine 90% CI for model parameters by running over 50,000 iteration trials.

^bThe utilities and probabilities were tested using beta distribution and the costs were tested using uniform distribution.

^cThe patient age when preparing for radiotherapy.

^dMedian age of OPC patients in China.

^eThe estimated Chinese life expectancy. For the base case, Markov models were to be cycled 21 times to evaluate the outcomes over a time-period from 1 year after radiotherapy to the end of the estimated Chinese life expectancy.

Table 2 One-way sensitivity analysis identifying cost-effective scenarios of proton beam therapy with different willingness-to-pay thresholds

Parameters	Base Case Set-up	Expected Value	Cost-effective Threshold Value		
			\$30,828 / QALY ^b	\$50,000 / QALY	\$100,000 / QALY
NTCP-reduction ^a	25%	Minimum	57.3%	22.6%	1.4%
Patient age (year-old)	56	Maximum	38	56	68
The cost of IMPT (\$)	50,000	Maximum	37,398.1	51,281.9	87,490.4

NTCP normal tissue complication probability, *IMPT* intensity modulated proton radiation therapy, \$ US dollars, *QALY* quality-adjusted life-year

^aNTCP-reduction referred to the advantage of IMPT over IMRT in reducing symptomatic dysphagia and xerostomia, and calculated with the formula: $\text{NTCP-reduction (\%)} = [(\text{NTCP}_{\text{after IMRT}} - \text{NTCP}_{\text{after IMPT}}) / \text{NTCP}_{\text{after IMRT}}] * 100\%$.

^bThe willingness-to-pay threshold of China.

Figures

Figure 1

Transition states of Markov model Legend: 3 main Markov states of “no cancer”, “alive with cancer” and “death” were used to simulate the disease process of oropharyngeal cancer. The state of “no cancer” included four sub-states “dysphagia”, “xerostomia”, “dysphagia and xerostomia” and “no complication”; and their initial state probabilities were set according to NTCPs. For each cycle, if the patient was in the state of “no cancer”, s/he might stay in the state of “no cancer”, develop into the state of “alive with cancer” or develop into the state of “death” (“other death”); If the patient was in the state of “alive with cancer”, s/he might stay in the state of “alive with cancer” or develop into the state of “death” (“cancer death” or “other death”); If the patient was in the absorbing state “death”, the loop operation would be terminated. 1-year cycle length was used, and the Markov model will be cycled from 1 year after radiotherapy until the patient’s 77-year-old (Chinese life expectancy).

Figure 2

Tornado diagram analyzing of influential parameters affecting the incremental cost-effectiveness ratio

Legend: The tornado diagram demonstrated the range of incremental cost-effectiveness ratio (ICER) when varying each parameter individually. Influential parameters were listed in descending order according to their abilities of affecting the ICER over the variation of their 90% confidence interval. IMPT, intensity modulated proton radiation therapy; IMRT, intensity modulated photon-radiation therapy; NTCP, normal tissue complication probability; EV, expected value; QALY, quality adjusted life year; \$, US dollars.

Figure 3

The estimated cost-effective population that benefit from proton beam therapy in China in the past 10 years Legend: The population with a WTP level (3 times the GDP per capita / QALY) beyond the ICER value (\$48,229.8/ QALY) was estimated as cost-effective population in China. \$, US dollars; GDP, gross domestic product; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.

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