

# Evidence on Effectiveness of Upper Neck Irradiation Versus Whole Neck Irradiation as Elective Neck Irradiation in Node-Negative Nasopharyngeal Cancer: A Meta-Analysis

review article

Jayson L. Co  
Michael Benedict A. Mejia  
Janine Margarita R. Dizon

Jayson L. Co and Michael Benedict A. Mejia, Benavides Cancer Institute, University of Santo Tomas Hospital, Espana; and Janine Margarita R. Dizon, Center for Health Research and Movement Science, University of Santo Tomas, Manila, the Philippines.

Presented, in part, as a poster presentation at the 52nd Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 3-7, 2016.

**Authors' disclosures of potential conflicts of interest and contributions are found at the end of this article.**

**Corresponding author:** Jayson L. Co, MD, Department of Radiation Oncology, Benavides Cancer Institute, University of Santo Tomas Hospital, Espana, Manila 1015, Philippines; Twitter: @JaysonCoMD; e-mail: jc\_polar@yahoo.com.

abstract

**Purpose** Nasopharyngeal carcinoma (NPC) is a central tumor with a rich lymphatic network and a propensity for bilateral cervical lymph node metastasis. There is an orderly pattern of lymph node involvement in NPC. There is no current standard for prophylactic neck irradiation in node-negative or limited retropharyngeal (RP) node-positive NPC. This study aims to synthesize the current evidence on upper neck irradiation (UNI) versus whole neck irradiation (WNI) as prophylactic neck irradiation in node-negative or limited RP node-positive NPC.

**Materials and Methods** A search of relevant articles was done from 2000 to October 2015. Critical appraisal and meta-analysis of the eligible studies were undertaken to assess the effectiveness of UNI versus WNI as prophylactic neck irradiation in node-negative or limited involved RP node NPC.

**Results** Only one randomized controlled trial investigated the use of prophylactic UNI versus WNI and showed no confirmed nodal relapse in both arms. Pooled analysis of four retrospective studies showed no significant difference in nodal recurrence, whether in-field or out-of-field recurrence. There was also no significant difference in terms of 5-year distant metastasis-free and overall survival.

**Conclusion** In node-negative or limited RP node-positive NPC, the current evidence shows the possibility of treating only the upper neck (levels II, III, and VA) without compromising nodal control, distant metastasis, and overall survival. As a result of the scarcity of data, more randomized clinical trials are warranted in this subset of patients.

J Glob Oncol 00. © 2016 by American Society of Clinical Oncology Licensed under the Creative Commons Attribution 4.0 License

## INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a prevalent malignancy in Asia, particularly southern China and Southeast Asian countries. The incidence of NPC in Asia is 1.4%, whereas in the Southeast Asian region, it is 5%.<sup>1</sup> In the Philippines, one of the countries in the Southeast Asian region, local reports of NPC data revealed an incidence of 1.2 per 100,000.<sup>2</sup> The treatment of NPC involves primary radiotherapy in early stages and concurrent chemoradiation followed by adjuvant chemotherapy for locally advanced disease.<sup>3-5</sup>

NPC is a central tumor with a rich lymphatic network and a propensity for bilateral cervical lymph node metastasis. Lymph node metastasis in NPC demonstrates an orderly pattern, and skip

metastasis is rare. A prospective study of 271 patients with NPC showed orderly progression of metastasis through clinical palpation and recommended irradiation of one nodal level further from the involved lymph node level.<sup>6</sup> Another study based on magnetic resonance imaging (MRI) showed that level II and the retropharyngeal (RP) lymph nodes were frequently involved, with orderly progression to levels III, V, and IV and the supraclavicular fossa, with only 0.5% of patients demonstrating skip metastasis.<sup>7</sup> Limiting radiation fields to the upper neck for prophylactic neck radiation may decrease the dose received by the thyroid gland, carotid artery, lung apex, larynx, trachea, and soft tissues of the neck. Because of the propensity of NPC for bilateral lymph node metastasis, current protocols in NPC suggest irradiation of

RP nodes; level II, III, IV, and V nodes; and the supraclavicular fossa regardless of nodal status.<sup>8,9</sup> There has been controversy regarding and no current standard for prophylactic neck irradiation in node-negative NPC or only RP node-positive NPC. The aim of this article is to synthesize the current evidence regarding efficacy of upper neck irradiation (UNI) versus whole neck irradiation (WNI) as prophylactic neck radiation in node-negative or limited RP node-positive NPC.

## MATERIALS AND METHODS

Both published and unpublished English-language studies from 2000 to October 2015 were sought using the search terms “nasopharyngeal carcinoma,” “node negative,” and “neck radiation,” in MEDLINE Complete, CINAHL Plus, ProQuest Health and Medical Complete, Academic Search Complete, Biomedical Reference Collection Basic, and PubMed. Five studies were published in English, whereas for one study, only the abstract is in English. The reference lists of all identified publications (both included and excluded) were searched for additional studies. A Google Scholar search was also done. Two additional studies were included. Content experts were contacted to obtain additional references and unpublished trials. E-mails were also sent to try to obtain any unavailable data.

### Criteria for Considering Studies in This Review

**Types of participants.** This review included studies of node-negative NPC determined by either computed tomography (CT) or MRI in accordance with the sixth edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (2002), published in cooperation with the International Union Against Cancer (AJCC/UICC). Studies that included NPC with RP nodal involvement were included, because this was considered as node-negative disease in the sixth edition of the AJCC/UICC staging system. Studies that used mere clinical palpation without imaging for the nodal staging were excluded. All studies had patients receiving radiotherapy to both primary and neck sites, with or without chemotherapy and with or without tumor boost.

**Types of interventions.** The intervention included the use of either UNI or WNI as part of the elective neck irradiation (ENI). UNI included at least cervical levels II, III, and VA, whereas WNI included the addition of level IV and/or supraclavicular fields. The line of delineation was the cricoid cartilage. The dose received to this prophylactic area should be at least 50 Gy.

**Types of outcome.** Studies with main outcome measures of nodal relapse, distant metastasis,

and overall survival were included. Oncologic outcomes were measured using standardized reports of nodal relapse, distant metastasis, and overall survival. Nodal relapse was defined as absence of clinical or radiographic recurrence in the regional nodes. Distant metastasis-free survival was defined as the number of patients free of distant metastasis after 5 years, whereas overall survival was defined as the number of patients alive after 5 years from the date of treatment.

**Types of studies.** This review included randomized controlled trials and retrospective comparative studies, which, because of the scarcity of evidence, were required to be able to obtain at least level 3 evidence. This is in consonance with the Oxford Centre for Evidence-Based Medicine, wherein retrospective cohorts are considered as level 3 evidence.<sup>10</sup>

**Assessment of methodologic quality.** Two reviewers (J.L.C. and M.B.A.M.) conducted an independent critical appraisal of the eligible studies using a standardized critical appraisal form, the McMaster Critical Review Form—Quantitative Studies. There was no disagreement on the decision to include or exclude a study.

### Data Collection and Synthesis

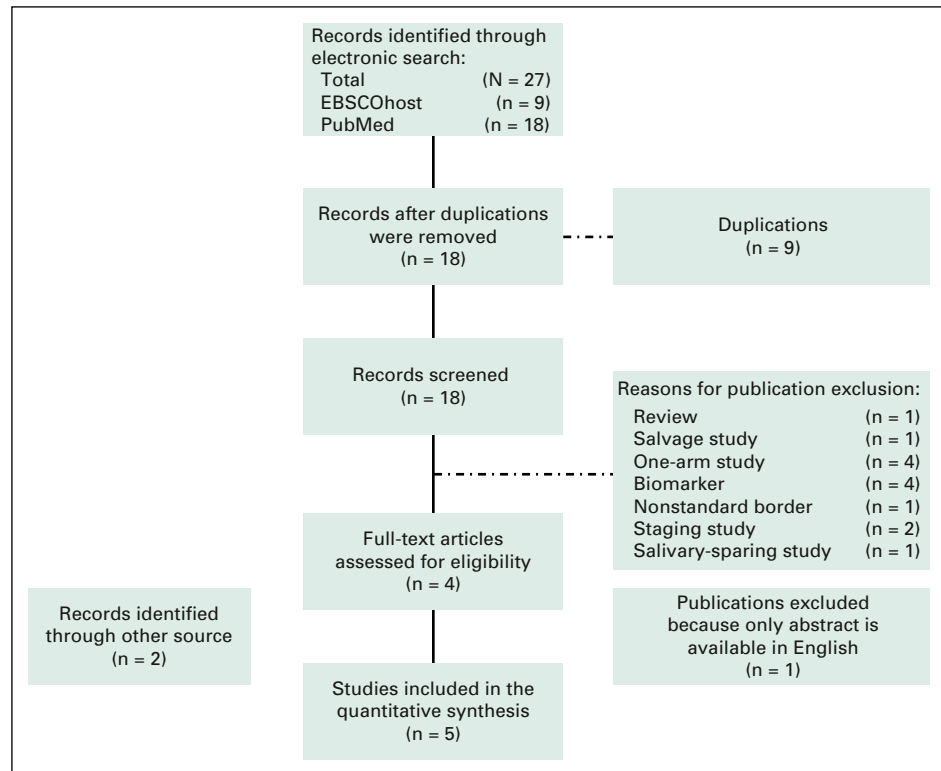
Data were extracted independently by the two reviewers using a purpose-built Microsoft Excel spreadsheet (Microsoft, Redmond, WA). Data extraction included author, year, title, study design, sample size, study population, intervention, control, outcomes, and results. Statistical pooling was done for similar outcome using Review Manager Software 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Heterogeneity was assessed using  $\chi^2$  analysis. In the presence of significant heterogeneity, a random-effects meta-analysis was used. Other data with dissimilar variables were collated using a narrative synthesis. An overall summary of recommendations was developed using the Australian National Health and Medical Research Council body of evidence framework. This framework has five components (evidence base, consistency, clinical impact, generalizability, and applicability) and an overall body of recommendation.<sup>11</sup>

## RESULTS

### Search Result

This review initially yielded 27 abstracts (Fig 1). Twenty-three studies were excluded for the following reasons: duplication (n = 9), review study (n = 1), salvage study (n = 1), one-arm treatment (n = 4),

**Fig 1 –**  
Preferred Reporting Items  
for Systematic Reviews and  
Meta-Analyses (PRISMA).



biomarkers (n = 4), nonstandard border (n = 1), staging study (n = 2), and salivary-sparing study (n = 1). An additional two studies were included from the search of the reference lists of the included studies. Full texts of the six studies were then reviewed for eligibility. Of the six studies, one study was excluded because only the abstract form was available in English and thus critical appraisal of the methods would not be possible.<sup>12</sup> A total of five trials were included in the qualitative analysis.<sup>13-17</sup>

### Critical Appraisal

The five studies included in this review were of sound methodologic quality (Table 1). All studies had a clear purpose, relevant background, and justification for conducting the study. One study was a randomized controlled trial,<sup>13</sup> and the other four were retrospective two-arm studies.<sup>14-17</sup> The randomized controlled trial had an adequate sample, and contamination and co-interventions were controlled, which would be difficult in a retrospective study. All studies had measurable outcomes with clinically significant results. All of the studies reported on dropout rates, but only three studies provided the reasons for dropout.

### Main Result

**Data from randomized controlled trial.** Only one randomized controlled trial investigated the use

of prophylactic UNI versus WNI in node-negative disease.<sup>13</sup> The study randomly assigned node-negative patients using the sixth edition of AJCC/UICC staging system to either UNI, including levels II, III, and VA with 54 Gy, or WNI, with the addition of 50 Gy to the low anterior neck field. One hundred forty-eight patients were randomly assigned to UNI, whereas 153 patients were assigned to WNI, with a median follow-up time of 39 months. There were no confirmed nodal relapses in either arm, but two patients had suspicious nodes, one of 5 mm in the UNI arm and one of 4 mm in the WNI arm. The former occurred in level II, whereas the latter occurred in the supraclavicular fossa. The latter patient died of distant metastasis. The rates for 3-year overall survival and metastasis-free survival in the UNI versus WNI arms were 89.5% v 87.4% and 91.7% v 90.9%, respectively.

**Pooled data from retrospective studies.** Pooled analysis on nodal recurrence, whether in-field or out-of-field recurrence, showed no significant difference when UNI versus WNI was used (risk ratio, 1.24; 95% CI, 0.48 to 3.19; Fig 2). Only three studies reported on the rates of 5-year overall survival and distant metastasis-free survival; they showed no significant difference in risk of developing distant metastasis and overall survival at 5 years with risk ratios of 1.01 (95% CI,

**Table 1** – Critical Appraisal of the Included Studies

Study Characteristic	Study				
	Li et al <sup>13</sup>	Xie et al <sup>17</sup>	Sun et al <sup>16</sup>	Ou et al <sup>15</sup>	Zeng et al <sup>14</sup>
Study purpose					
Was the purpose stated clearly?	Yes	Yes	Yes	Yes	Yes
Outline the purpose of the study. How does the study apply to your research question?	To verify the hypothesis that omitting the lower neck during prophylactic node irradiation will not significantly increase the rate of lower neck nodal relapse	To analyze the clinical data of patients with stage NO NPC confirmed on diagnostic imaging, investigate the method of cervical radiotherapy, and analyze patterns of treatment failure and factors of prognosis	To evaluate the therapeutic outcomes of patients with NO NPC treated primarily with external-beam radiation for improving the current NO NPC treatment strategies	To identify the outcome and patterns of treatment failure of patients with RLN involvement only and figure out whether elective neck irradiation is appropriate for them	To investigate the prophylactic irradiation volume to neck drainage areas for patients with neck lymph node–negative NPC treated by IMRT
Literature					
Was relevant background literature reviewed?	Yes	Yes	Yes	Yes	Yes
Design					
Describe the study design. Was the study design appropriate for the study question (eg, for the knowledge level about this issue, outcome, ethical issues)?	Randomized controlled trial	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective
Specify any biases that may have been operating and the direction of their influence on the results	Blinding not mentioned	Retrospective	Retrospective	Retrospective	Retrospective
Sample					
No. of patients					
Total	301	205	610	119	270
UNI	153	88	542	89	171
WNI	148	117	68	30	99
Was the sample described in detail?	Yes	Yes	No mention	Yes	Yes
Was sample size justified?	Yes	No mention	No mention	No mention	No mention
Sampling (Who? Characteristics? How many? How was sampling done?) If more than one group, were there similarities between groups?	Patients with NPC with no regional nodal metastases based on MRI or CT scans	Patients with NPC with no regional nodal metastases based on MRI or CT scans	Patients with NPC with no regional nodal metastases based on MRI or CT scans	Patients with NPC with MRI that confirmed that no other cervical lymph node was metastatic except RP	Patients with NPC with no regional nodal metastases based on MRI or CT scans

(Continued on following page)

**Table 1** – Critical Appraisal of the Included Studies (Continued)

Study Characteristic	Study				
	Li et al <sup>13</sup>	Xie et al <sup>17</sup>	Sun et al <sup>16</sup>	Ou et al <sup>15</sup>	Zeng et al <sup>14</sup>
Describe ethics procedure. Was informed consent obtained?	This study was approved by the ethics committee, and informed consent was obtained	No mention	No mention	No mention	No mention
Outcomes					
Were the outcome measures reliable?	Yes	Yes	Yes	Yes	Yes
Were the outcome measures valid?	Yes, intention to treat	Yes	Yes	Yes	Yes
Specify the frequency of outcome measurement	Every 3 months for the first 3 years, every 6 months for the next 2 years, and yearly thereafter	368 months, with a median follow-up of 44 months	Every 3 months during the first 2 years, then every 6 months for the subsequent 3 years, and then once every year thereafter	Every 3 months in the first year, then every 3-6 months in the second to fourth year, and yearly thereafter	Every 1-3 months during the first 2 years, every 6 months in years 2-5, and annually thereafter
Outcome areas; list measures used	Local relapse, regional relapse, distant metastases, overall survival	Overall survival, disease-free survival, local recurrence, distant metastasis	Local control, regional control, overall survival, distant metastasis	Local recurrence-free survival, nodal recurrence-free survival, distant metastasis free survival, overall survival	Distant metastasis-free survival, disease-free survival, nodal recurrence, overall survival
Intervention	UNI v WNI	UNI v WNI	UNI v WNI	UNI v WNI	UNI v WNI
Intervention was described in detail	Yes	Yes	Yes	Yes	Yes
Contamination was avoided	Yes	No mention	No mention	No mention	No
Co-intervention was avoided	Yes	No mention	No mention	No mention	No mention
Provide a short description of the intervention (focus, who delivered it, how often, setting). Could the intervention be replicated in practice?	For patients in both groups, the primary tumor, the potentially involved surrounding tissues, and the upper neck lymph drainage areas were irradiated. The total doses were 69 Gy to the primary tumor, 60 Gy to high-risk involved tissues and suspicious node drainage area, and 54 Gy to the low-risk regions and level II, III, and VA nodes in 30 daily fractions. For patients in the WNI group, a lower neck anterior field delivered by a 6-MV photon with a 3-cm central block was used to give a total	Radiotherapy of the upper neck included lymph nodes in levels II, III, and VA and radiotherapy of the lower neck included lymph nodes in levels II, III, IV, and V. The radiation dose to the primary nasopharyngeal tumor was 60-80 Gy, with a median dose of 70 Gy. The cervical therapeutic dose was 46 Gy, with a median dose of 50 Gy.	The prescribed dose of IMRT was 70.4 Gy to nasopharynx and 60 Gy to upper neck (including levels II, III, and VA) in 32 fractions, whereas dose to entire neck was as recommended by the attending physicians.	In some patients, only the upper neck was treated, including levels II, III, and VA. In others, the whole neck received radiation, including levels II, III, IV, and V, according to the EORTC and RTOG consensus guideline.	WNI included lower neck and the supraclavicular area via anterior semifield radiation with midline shield to 50 Gy.

(Continued on following page)

**Table 1** – Critical Appraisal of the Included Studies (Continued)

Study Characteristic	Study				
	Li et al <sup>13</sup>	Xie et al <sup>17</sup>	Sun et al <sup>16</sup>	Ou et al <sup>15</sup>	Zeng et al <sup>14</sup>
	dose of 50 Gy, regardless of the radiotherapy technique used. The junction point to lower neck was set at the lower margin of the cricoid bone.				
Results					
Results were reported in terms of statistical significance?	Yes	Yes	Yes	Yes	Yes
Were the analysis methods appropriate?	Yes	Yes	Yes	Yes	Yes
What were the results? Were they statistically significant ( $P < .05$ )? If not statistically significant, was the study big enough to show an important difference if it should occur? If there were multiple outcomes, was that taken into account for the statistical analysis?	No	No	No	Yes	No
Was clinical importance reported?	Yes	Yes	Yes	Yes	Yes
What was the clinical importance of the results? Were differences between groups clinically meaningful (if applicable)?	Yes	Yes	Yes	Yes	Yes
Were dropouts reported?	Yes	Yes	No mention	Yes	Yes
Did any participants drop out from the study? Why? (Were reasons given, and were dropouts handled appropriately?)	Yes, intention to treat	Dropout reasons were not mentioned	No mention	Yes	Yes

(Continued on following page)

**Table 1 – Critical Appraisal of the Included Studies (Continued)**

Study Characteristic	Study				
	Li et al <sup>13</sup>	Xie et al <sup>17</sup>	Sun et al <sup>16</sup>	Ou et al <sup>15</sup>	Zeng et al <sup>14</sup>
Conclusion and implications					
Conclusions were appropriate given the study methods and results	Yes	Yes	Yes	Yes	Yes
What did the study conclude?	Prophylactic UNI is sufficient for patients with node-negative NPC	Prophylactic irradiation to the upper neck does not influence regional failure or long-term survival in patients with stage NO NPC; radiotherapy to the upper neck (levels II, III, and VA) is recommended for patients with stage NO NPC	Prophylactic irradiation to the upper neck does not influence regional failure or long-term survival in patients with stage NO NPC; radiotherapy to the upper neck (levels II, III, and VA) is recommended for patients with stage NO NPC	Elective irradiation to levels II, III, and VA was not inferior to WNI for patients with NPC with RLN metastasis only; however, more evidence is needed to confirm the result	Prophylactic irradiation to the upper neck may be feasible for patients with neck lymph node–negative NPC
What are the implications of these results for practice? What were the limitations or biases in the study?	Slow enrollment of patients; thus, long period of accrual		Retrospective	Retrospective	Retrospective

Abbreviations: CT, computed tomography; EORTC, European Organisation for Research and Treatment of Cancer; IMRT, intensity-modulated radiotherapy; MRI, magnetic resonance imaging; NPC, nasopharyngeal carcinoma; RLN, retropharyngeal lymph node; RP, retropharyngeal; RTOG, Radiation Therapy Oncology Group; UNI, upper neck irradiation; WNI, whole neck irradiation.

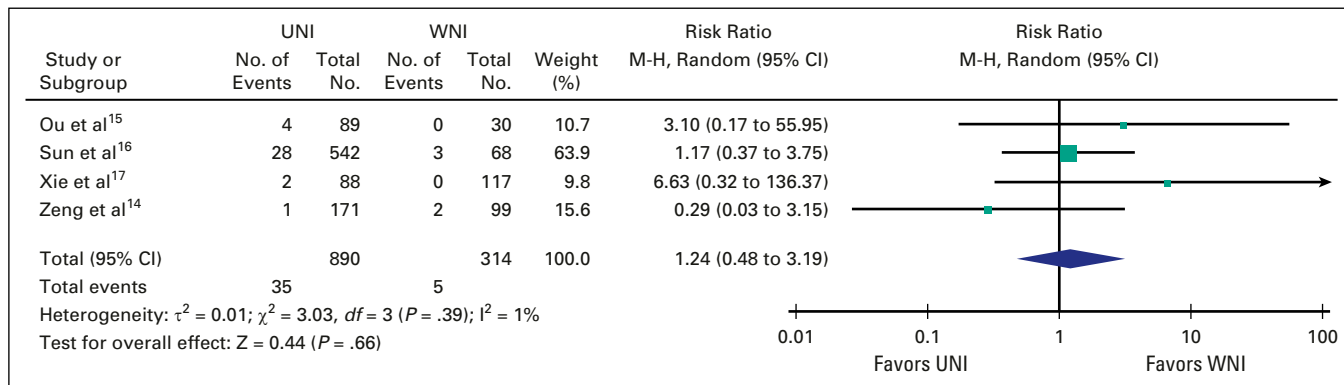
0.96 to 1.05; Fig 3) and 1.00 (95% CI, 0.94 to 1.06; Fig 4), respectively.

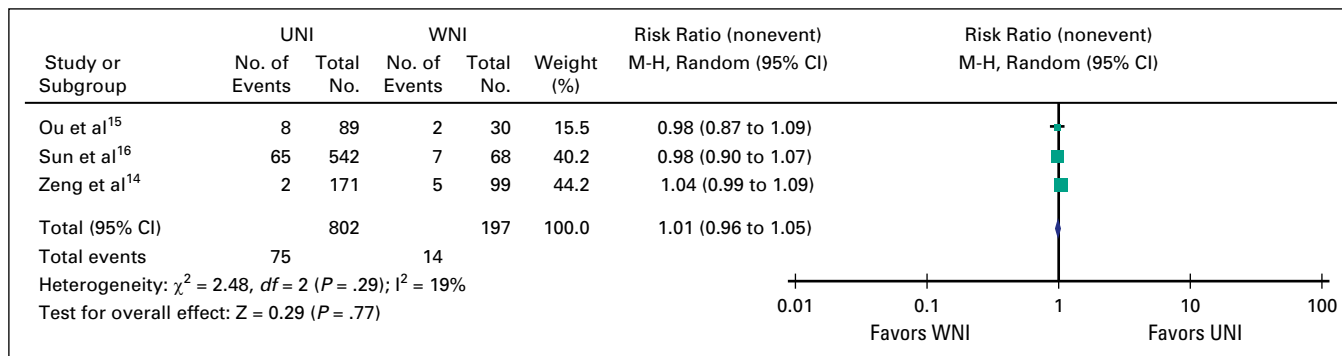
**DISCUSSION**

This review presented the overall evidence regarding the use of UNI versus WNI as ENI in patients with node-negative or limited RP node–positive NPC. We showed that there is no benefit of using WNI over UNI in terms of nodal relapse, distant

metastasis–free survival, and overall survival. On the basis of the National Health and Medical Research Council’s “additional levels of evidence and grades for recommendations for developers of guidelines” document<sup>11</sup> (Table 2), we recommend that the findings in this review regarding nodal relapse, distant metastasis, and overall survival can be trusted to guide clinical decision in most situations.

**Fig 2 –** Nodal relapse in node-negative nasopharyngeal cancer using upper neck irradiation (UNI) versus whole neck irradiation (WNI). M-H, Mantel-Haenszel test.





**Fig 3 –**

Five-year distant metastasis-free survival in node-negative nasopharyngeal cancer using upper neck irradiation (UNI) versus whole neck irradiation (WNI). M-H, Mantel-Haenszel test.

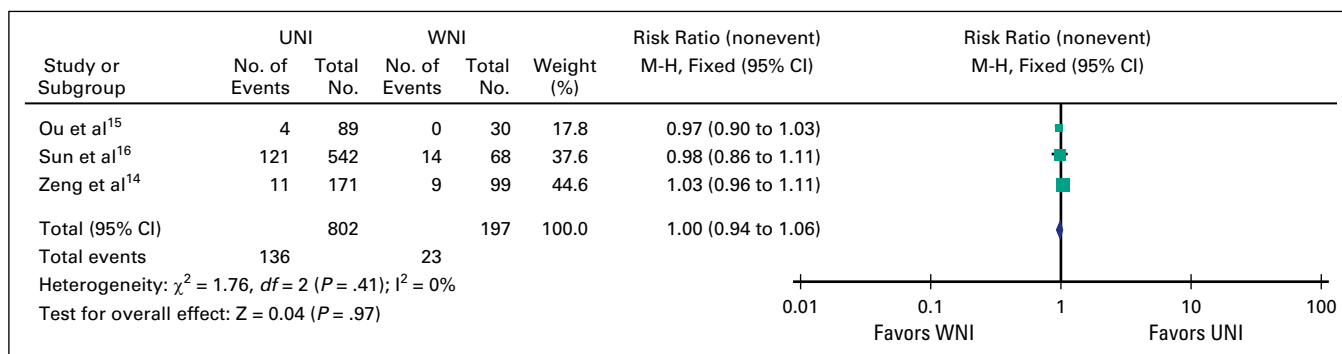
NPC is a common malignancy seen in southern China and Southeast Asian regions. In the Philippines, recent study showed that the incidence may still be under-reported, and the estimated incidence is approximately 2.3 per 100,000.<sup>18</sup> NPC has a predilection for lymphatic metastasis as a result of its extensive avascular submucosal cervical lymph drainage. There is orderly progression of lymph node metastasis in NPC, with the RP node being the most common, followed by levels II, III, V, and VI and the supraclavicular fossa, with only a 0.5% chance of skip metastasis.<sup>7</sup> Approximately 85% of patients with NPC present with clinical cervical lymph node involvement, but a minority of patients will have node-negative disease at presentation.<sup>7</sup> Although lymphatic metastasis is correlated with a higher chance of distant metastasis,<sup>19</sup> it may be reasonable and logical to treat node-negative NPC with limited neck irradiation and withhold low neck radiation. A retrospective study showed that 40% of patients had nodal relapse among patients with node-negative NPC staged using clinical palpation when elective nodal irradiation was omitted. Most of these nodal relapses are successfully treated with salvage therapy, but high rates of distant metastasis (> 20%) affect overall survival.<sup>20</sup> However, the results of the study by Lee et al<sup>20</sup> are currently limited because of a lack of CT or MRI nodal

staging in this study as well as no prophylactic irradiation in the upper neck, which in our review is a standard for all patients. A recent one-arm trial reported excellent 5-year overall survival (85%) in patients with neck-negative NPC treated with limited upper neck radiation.<sup>21</sup> This is in consonance with the results of this review, in which omission of lower neck radiotherapy did not affect nodal relapse, distant metastasis, or overall survival. Because there is an orderly progression of lymph node metastasis, one or two nodal levels beyond the involved node may be sufficient for ENI. Nodal relapse may occur in the lower neck if there is insufficient coverage to this area, which may harbor microscopic disease. In three included studies, five of seven nodal relapses in the UNI arm occurred at in-field sites,<sup>14,15,17</sup> whereas another study reported only 16 patients (2.7%) of the total cohort with relapse in the elective nodal area; the study also reported relapse in 13 patients (2.1%) in the out-of-field area, and relapse in two patients (6.5%) in both the in-field and out-of-field areas.<sup>16</sup> The results show that coverage was adequate with UNI because treatment failures occurred mostly at in-field sites.

Although most of the structures in the neck receive tolerated doses in WNI, it is prudent to limit the dose to this area if oncologic outcomes are not compromised. A recent study showed a dose-response

**Fig 4 –**

Five-year overall survival in node-negative nasopharyngeal cancer using upper neck irradiation (UNI) versus whole neck irradiation (WNI). M-H, Mantel-Haenszel test.





**Table 2** – National Health and Medical Research Council Additional Levels and Grades for Recommendations for Developers of Guidelines

Components	Grade	Comments
<b>Evidence base</b>		
Nodal relapse	C	Four studies had retrospective two-arm designs, <sup>14-17</sup> whereas one study is a randomized controlled trial <sup>13</sup>
Distant metastasis-free survival	C	Four studies had retrospective two-arm designs, <sup>14-17</sup> whereas one study is a randomized controlled trial <sup>13</sup>
Overall survival	C	Four studies had retrospective two-arm designs, <sup>14-17</sup> whereas one study is a randomized controlled trial <sup>13</sup>
<b>Consistency</b>		
Nodal relapse	A	All five studies were consistent in the result showing no difference between upper neck RT and whole neck RT
Distant metastasis-free survival	A	All five studies were consistent in the result showing no difference between upper neck RT and whole neck RT
Overall survival	A	All five studies were consistent in the result showing no difference between upper neck RT and whole neck RT
<b>Clinical impact</b>		
Nodal relapse	B	Omitting low-neck irradiation may provide some benefit regarding some early and late effects of RT; the studies reported CI
Distant metastasis-free survival	B	Omitting low-neck irradiation may provide some benefit regarding some early and late effects of RT; the studies reported CI
Overall survival	B	Omitting low-neck irradiation may provide some benefit regarding some early and late effects of RT; the studies reported CI
<b>Generalizability</b>		
Nodal relapse	B	May be generalizable to all patients with node-negative NPC regardless of tumor stage classification
Distant metastasis-free survival	B	May be generalizable to all patients with node-negative NPC regardless of tumor stage classification
Overall survival	B	May be generalizable to all patients with node-negative NPC regardless of tumor stage classification
<b>Applicability</b>		
Nodal relapse	A	Node-negative NPC is present in our local setting and selective upper neck RT may be given
Distant metastasis-free survival	A	Node-negative NPC is present in our local setting and selective upper neck RT may be given
Overall survival	A	Node-negative NPC is present in our local setting and selective upper neck RT may be given
<b>Overall</b>		
Nodal relapse	B	
Distant metastasis-free survival	B	
Overall survival	B	

Abbreviations: NPC, nasopharyngeal carcinoma; RT, radiotherapy.

curve demonstrating an increased chance of development of hypothyroidism.<sup>22</sup> Furthermore, limiting dose to this area may prevent intima media thickening,<sup>23</sup> esophagitis, and pulmonary apical fibrosis in this subset of patients. In the studies included in this review, two studies showed no significant difference in the rates of acute and late effects, except more patients had lower neck dermatitis, skin atrophy, and lung apex fibrosis in the WNI group.<sup>13,14</sup> One study reported that three patients had cranial neuropathy and one patient had unilateral laryngeal nerve palsy in the WNI group.<sup>15</sup>

With the advent of modern imaging, the staging of NPC has evolved from mere clinical palpation to image-guided staging. CT scan is not able to predict and differentiate primary tumor from RP nodes; the advantage of MRI is that it can delineate these nodes specifically. RP lymph node involvement may be present in 86.4% of patients when staged using MRI.<sup>21</sup> The presence of positive RP nodes has prognostic implications. In the sixth edition of the AJCC/UICC staging system, the presence of positive RP nodes was staged as NO, but most studies have shown that a positive RP node behaves like N1 disease. For this reason, in the seventh edition of the AJCC/UICC staging system, disease with positive RP node was considered N1 disease. All of the studies included in this review were staged according to the sixth edition staging classification. As such, it is possible that some of the patients may have been RP node-positive. This further supports our hypothesis that radiation to one or two lymph nodes beyond the affected echelon may be adequate as ENI.

The use of cisplatin-based chemotherapy has been a standard in locally advanced NPC as concurrent treatment with radiation with or without neoadjuvant or adjuvant chemotherapy. Cisplatin has been shown to increase local control and overall survival.<sup>3,4</sup> Only 33% of patients included in the review (n = 509) received some form of chemotherapy as concurrent, neoadjuvant, or adjuvant therapy. Given that only 33% of patients received chemotherapy, in the absence of subset analysis, it may be reasonable to conclude that chemotherapy did not compensate for the lack of WNI therapy to address possible microscopic disease. The 5-year survival rates of the patients, regardless of whether or not chemotherapy was given, approached the survival rates of landmark trials. This could be because high tumor stage is related to a local problem, whereas distant metastasis is related to nodal burden.

A major limitation of this review is that most of the studies are retrospective. This reflects the fact that there is a low incidence of node-negative NPC compared with node-positive NPC, as well as the lack of randomized controlled trials in node-negative NPC. Another limitation is the heterogeneity of the patients; both node-negative and RP node-positive patients were included, and the latter are considered to have N1 disease in the latest staging system. Because of the scarcity of data from randomized controlled trials, there is a need for more randomized clinical trials; these trials should stratify between N0 and RP node-positive disease. There is also a need to include late effects, such as neck fibrosis and thyroid function, as secondary outcomes. It must be noted that one study was excluded as a result of the

lack of an English version of the full text, which prevented the reviewer from adequate critical appraisal of the article.<sup>12</sup> Although excluded, the results of this study paralleled those of the five included studies and would not affect the overall conclusion of the review if included in the analysis.

In conclusion, in node-negative or limited RP node-positive NPC, the current evidence demonstrates the possibility of treating only the upper neck (levels II, III, and VA) without compromising nodal control, distant metastasis, and overall survival. Because of a lack of data, more randomized controlled trials are warranted in this subset of patients.

DOI: [10.1200/JGO.2016.006759](https://doi.org/10.1200/JGO.2016.006759)

Published online on [jgo.ascopubs.org](http://jgo.ascopubs.org) on November 30, 2016.

#### AUTHOR CONTRIBUTIONS

**Conception and design:** All authors

**Collection and assembly of data:** All authors

**Data analysis and interpretation:** All authors

**Manuscript writing:** All authors

**Final approval of manuscript:** All authors

**Accountable for all aspects of the work:** All authors

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered

compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to [www.asco.org/rwc](http://www.asco.org/rwc) or [jco.ascopubs.org/site/ifc](http://jco.ascopubs.org/site/ifc).

#### Jayson L. Co

No relationship to disclose

#### Michael Benedict A. Mejia

No relationship to disclose

#### Janine Margarita R. Dizon

No relationship to disclose

## REFERENCES

1. Whelan SL: Cancer incidence in five continents: Coding practices. *IARC Sci Publ* 120:31-38, 1992
2. World Health Organization: Estimated cancer incidence, mortality, prevalence and disability adjusted life years (DALYS) worldwide in 2008. <http://globocan.iarc.fr/>
3. Al-Sarraf M, LeBlanc M, Giri PG, et al: Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: Phase III randomized Intergroup study 0099. *J Clin Oncol* 16:1310-1317, 1998
4. Wee J, Tan EH, Tai BC, et al: Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union Against Cancer stage III and IV nasopharyngeal cancer of the endemic variety. *J Clin Oncol* 23:6730-6738, 2005
5. National Comprehensive Cancer Network: Head and Neck Cancers. 2.2014. [https://www.nccn.org/professionals/physician\\_gls/f\\_guidelines.asp#site](https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site)
6. Sham JS, Choy D, Wei WI: Nasopharyngeal carcinoma: Orderly neck node spread. *Int J Radiat Oncol Biol Phys* 19:929-933, 1990
7. Tang L, Mao Y, Liu L, et al: The volume to be irradiated during selective neck irradiation in nasopharyngeal carcinoma: Analysis of the spread patterns in lymph nodes by magnetic resonance imaging. *Cancer* 115:680-688, 2009
8. RTOG Foundation: A phase II study of intensity modulated radiation therapy (IMRT) +/- chemotherapy for nasopharyngeal cancer. <https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0225>
9. RTOG Foundation: A phase II study of concurrent chemoradiotherapy using three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiation therapy (IMRT) + bevacizumab (BV) for locally or regionally advanced nasopharyngeal cancer. <https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0615>
10. Centre for Evidence-Based Medicine: Levels of evidence. <http://cebm.net/index.aspx?o=1025>
11. National Health and Medical Research Council: NHRMC additional levels of evidence and grades for recommendation for developers of guidelines. [http://www.nhmrc.gov.au/\\_files\\_nhmrc/file/guidelines/developers/nhmrc\\_levels\\_grades\\_evidence\\_120423.pdf](http://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

12. Li Y, Cao KJ, Chen QY, et al: Radiotherapy on neck for nasopharyngeal carcinoma patients with negative cervical lymph node [in Chinese]. *Ai Zheng* 24:627-630, 2005
13. Li JG, Yuan X, Zhang LL, et al: A randomized clinical trial comparing prophylactic upper versus whole-neck irradiation in the treatment of patients with node-negative nasopharyngeal carcinoma. *Cancer* 119:3170-3176, 2013
14. Zeng L, Sun XM, Chen CY, et al: Comparative study on prophylactic irradiation to the whole neck and to the upper neck for patients with neck lymph node-negative nasopharyngeal carcinoma. *Head Neck* 36:687-693, 2014
15. Ou X, Shen C, Kong L, et al: Treatment outcome of nasopharyngeal carcinoma with retropharyngeal lymph nodes metastasis only and the feasibility of elective neck irradiation. *Oral Oncol* 48:1045-1050, 2012
16. Sun JD, Chen CZ, Chen JZ, et al: Long term outcomes and prognostic factors of N0 stage nasopharyngeal carcinoma: A single institutional experience of 610 patients. *Asian Pac J Cancer Prev* 13:2101-2107, 2012
17. Xie FY, Peng M, Hu WH, et al: Prophylactic irradiation of cervical lymph nodes for stage-N0 nasopharyngeal carcinoma [in Chinese]. *Chin J Cancer* 29:106-110, 2010
18. Sarmiento MP, Mejia MB: Preliminary assessment of nasopharyngeal carcinoma incidence in the Philippines: A second look at published data from four centers. *Chin J Cancer* 33:159-164, 2014
19. Perez CA, Devineni VR, Marcial-Vega V, et al: Carcinoma of the nasopharynx: Factors affecting prognosis. *Int J Radiat Oncol Biol Phys* 23:271-280, 1992
20. Lee AW, Poon YF, Foo W, 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* 23:261-270, 1992
21. Gao Y, Zhu G, Lu J, et al: Is elective irradiation to the lower neck necessary for N0 nasopharyngeal carcinoma? *Int J Radiat Oncol Biol Phys* 77:1397-1402, 2010
22. Fujiwara M, Kamikonya N, Odawara S, et al: The threshold of hypothyroidism after radiation therapy for head and neck cancer: A retrospective analysis of 116 cases. *J Radiat Res* 56:577-582, 2015
23. Gianicolo ME, Gianicolo EA, Tramacere F, et al: Effects of external irradiation of the neck region on intima media thickness of the common carotid artery. *Cardiovasc Ultrasound* 8:8, 2010