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ORIGINAL RESEARCH

Evidence from an updated meta-analysis of the prognostic impacts of postoperative radiotherapy and chemotherapy in patients with anaplastic thyroid carcinoma

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Background: Radiotherapy and chemotherapy are the two important postoperative management approaches for anaplastic thyroid carcinoma (ATC), and several studies have suggested that postoperative radiotherapy and chemotherapy can prolong the survival of patients with ATC. However, the results remain inconsistent.

Objective: A meta-analysis was performed to address whether postoperative radiotherapy and chemotherapy could prolong the survival of patients with ATC.

Methods: Relevant studies were included, and pooled hazard ratios (HRs) together with 95% confidence intervals (CIs) were calculated.

Results: Ten relevant studies on factors that affect the prognosis for ATC were included in this meta-analysis, evaluating a total of 1,163 patients. The pooled HR for overall survival (OS) was calculated using a random-effects model. The pooled results demonstrated that for all patients with resectable ATC, the combination of surgery and radiotherapy significantly reduced the risk of death compared with surgery alone (HR =0.51, 95% CI: 0.36–0.73, Z=3.66, P=0.0002). To investigate the prognostic impacts of chemotherapy in patients with ATC, we also calculated the pooled HR of chemotherapy for OS using a random-effects model; however, the pooled results suggested that chemotherapy did not prolong the survival of ATC patients compared with controls (HR =0.63, 95% CI: 0.33–1.21, Z=1.39, P=0.17).

Conclusion: This study provided evidence that currently, for patients with ATC, postoperative radiotherapy may prolong survival; in contrast, chemotherapy did not improve long-term survival.

Keywords: anaplastic thyroid carcinoma, postoperative radiotherapy, chemotherapy, prognosis, meta-analysis

Introduction

Thyroid cancers include papillary, follicular, medullary, and anaplastic carcinomas. Although anaplastic thyroid carcinoma (ATC) accounts for only 2%–5% of all thyroid cancers,[1–5] ATC is responsible for 14%–50% of all thyroid carcinoma-related deaths.[6–9] Thus, ATC is a special type of thyroid cancer with high degree of malignancy and poor prognosis. Patients with ATC are typically in their sixth or seventh decade of life. This disease is usually characterized by aggressive growth features and frequently causes extensive local invasion and distant metastases. Therefore, the management of patients with ATC is extremely difficult, and there is little consensus regarding a standard successful treatment protocol.[10,11] During the past few years, some studies

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have demonstrated that multidisciplinary treatment plays an important role for patients with ATC and that postoperative radiotherapy is the main treatment approach rather than chemotherapy.[12–14] However, it remains uncertain whether this multimodal treatment truly improves survival because most studies have a small sample size and poor statistical power due to the relatively low incidence of ATC.

Previously, we reported that radiotherapy combined with surgery appears to increase overall treatment efficacy for ATC patients and prolong survival; in contrast, chemotherapy was ineffective.[15] However, other studies have reported conflicting results.[16–18] Therefore, the objective of this study was to perform a meta-analysis to address whether chemotherapy and radiotherapy could prolong the survival of patients with ATC.

Methods

Literature search and data extraction

Two investigators (WW and QX) searched PubMed, Embase, Web of Science, VIP Database for Chinese Technical Periodicals, Wanfang Data Knowledge Service Platform, and China National Knowledge Infrastructure (CNKI) for articles published up to April 2017, using the terms ATC and anaplastic thyroid carcinoma. A database was then created, with no limits established with respect to language or study design. Studies included in this meta-analysis were required to be 1) original studies and 2) studies reporting hazard ratios (HRs) with 95% confidence intervals (CIs) or sufficient data to calculate HRs and 95% CIs. All studies were independently verified against the inclusion and exclusion criteria for this meta-analysis by two investigators. The first author, publication year, country, language, sample size for ATC patients, and reported HR(s) were extracted from each included study. These processes were performed independently by two investigators (WW and QX), and a consensus was reached.

Statistical analyses

Pooled HRs and 95% CIs were calculated.[19] In addition, χ^2-based Q statistics and I^2 metrics were used to assess the heterogeneity between studies. When $I^2<50\%$, a fixed-effects model was used to calculate pooled HR; otherwise, a random-effects model was used for this purpose. The prognostic impacts of chemotherapy and postoperative radiotherapy in ATC patients were assessed by meta-analysis. All statistical analyses were performed using the Review Manager software (v.5.2; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and STATA (v. 12.0; StataCorp LP, College Station, TX, USA).

Results

A database that included each article's first author, publication year, country, language, sample size, and other important information was established based on the information extracted from 10 relevant studies[15–18,20–25] that satisfied the inclusion criteria (Table 1). The original search yielded a total of 2,563 articles related to the keywords. Figure 1 summarizes the selection process of this study. After titles, keywords, and abstracts were screened, 2,478 of these articles were excluded. The full texts of 85 articles were reviewed, and an additional 75 articles were excluded (with 74 articles excluded for not providing usable data and one article excluded due to the duplication of the same article in different languages); thus, 10 studies (a total of 1,163 patients) remained for further review.

The pooled HR for overall survival (OS) was calculated using a random-effects model. The pooled results demonstrated that for all patients with resected ATC, the combination of surgery and radiotherapy significantly reduced the risk of death compared with surgery alone (HR =0.51, 95% CI: 0.36–0.73, Z=3.66, P=0.0002) (Figure 2). In addition, to investigate the prognostic impact of chemotherapy in ATC patients, we calculated the pooled HR of chemotherapy for OS using a random-effects model; however, the pooled results demonstrated that ATC patients treated with chemotherapy did not exhibit prolonged survival relative to patients who did not receive chemotherapy (HR =0.63, 95% CI: 0.33–1.21, Z=1.39, P=0.17) (Figure 3).

To assess the stability of our results, a sensitivity analysis was performed by removing one study at a time. The pooled HR for patients who received a combination of surgery and radiotherapy or chemotherapy compared with control patients was not significantly changed, suggesting that our results were stable. Funnel plots for this meta-analysis were symmetric (Figure 4), indicating the absence of publication bias. Finally, we used STATA software to perform Egger's test to calculate publication bias. No publication bias was detected via Egger's test, which was performed to provide statistical evidence for funnel plot symmetry (P=0.183 for surgery combined with radiotherapy; P=0.441 for chemotherapy).

Discussion

ATC is one of the most aggressive types of malignant tumor in humans,[26] and the prognosis of patients with ATC is extremely poor; in particular, only 20% of affected patients survive for 1 year, and the median survival duration is 3–9 months after diagnosis.[1–5,11,27] There is currently no standardized therapeutic regimen for ATC patients. Multimodal

Table 1 Characteristics of studies included in the meta-analysis

Study	Country	Language	Study period	Design	Patients (n)	Age	Group	Stage (IV A/IV B/IV C) (%)	Radiation dose (range, Gy)	Chemotherapy/radiotherapy (%)	MI (%)	R0/R1 (N)	Outcome reports	Multivariate analysis
Kobayashi et al (1996)[23]	Japan	English	1971–1993	Retrospective	21 16	68	Surgery + PORT Surgery	76/18/6 86/14/0	14–70	86.5/36.8	24.3	19/5	OS	No
Kebebew et al (2005)[22]	USA	English	1973–2000	Retrospective	155 98	71	Surgery + PORT Surgery	NR NR	NR	NR	43	NA	CSS	Yes
Roche et al (2010)[17]	France	English	1990–2006	Retrospective	14 12	72.1	Surgery + PORT Surgery	NR NR	NR	19.2/53.8	15.4	12/14	OS	No
Palestini et al (2010)[25]	Italy	English	2003–2010	Retrospective	16 4 1 3	74	Surgery + PORT Surgery Chemotherapy Without chemotherapy	NR NR NR NR	36–40	85/80	50	6/7	OS	Yes
Ito et al (2012)[21]	Japan	English	1985–2009	Retrospective	11 8	71	Chemotherapy Without chemotherapy	0/64/36 0/12.5/87.5	45–60	55/70	37.5	0/2	CSS	No
Sun et al (2013)[15]	China	English	1980–2010	Retrospective	15 12 8 12	58[a]	Surgery + radiotherapy Surgery Chemotherapy Without chemotherapy	0/100/0 0/100/0 NR NR	44–70	NR	26.7	NA	OS	No
Brignardello et al (2014)[18]	Italy	English	1999–2012	Retrospective	24 12	73.15[a]	Surgery + chemotherapy + PORT Surgery + chemotherapy	0/33/67 0/46/54	50–54	88/66.7	56.4	4/5	OS	Yes
Nachalon et al (2015)[16]	Israel	English	2008–2013	Retrospective	11 15	NR	Chemotherapy Without chemotherapy	NR NR	60–70	42/46.2	46.2	3/2	OS	No
Liu et al (2016)[24]	China	English	1990–2006	Retrospective	14 14	60[a]	Surgery + PORT Surgery	NR NR	30–70	16/32	32	17/21	OS	No
Baek et al (2016)[20]	Korea	English	2000–2012	Retrospective	84 94 10 94	68.1[a]	Surgery + PORT Surgery Chemotherapy Without chemotherapy	25/63/12 23/48/29 22/22/56 23/48/29	NR	46.8/40.7	31.3	NA	OS	Yes

Note: [a]Median value (years).

Abbreviations: CSS, cancer-specific survival; NR, not reported; OS, overall survival; PORT, postoperative radiotherapy.

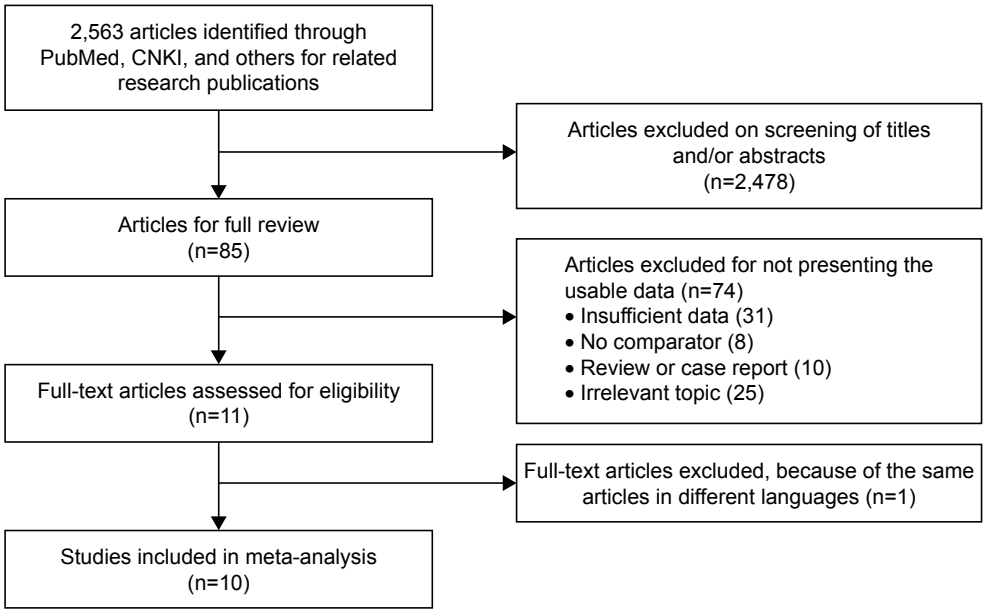

Figure 1 Flow diagram of the search and selection process in this study.
Abbreviation: CNKI, China National Knowledge Infrastructure.

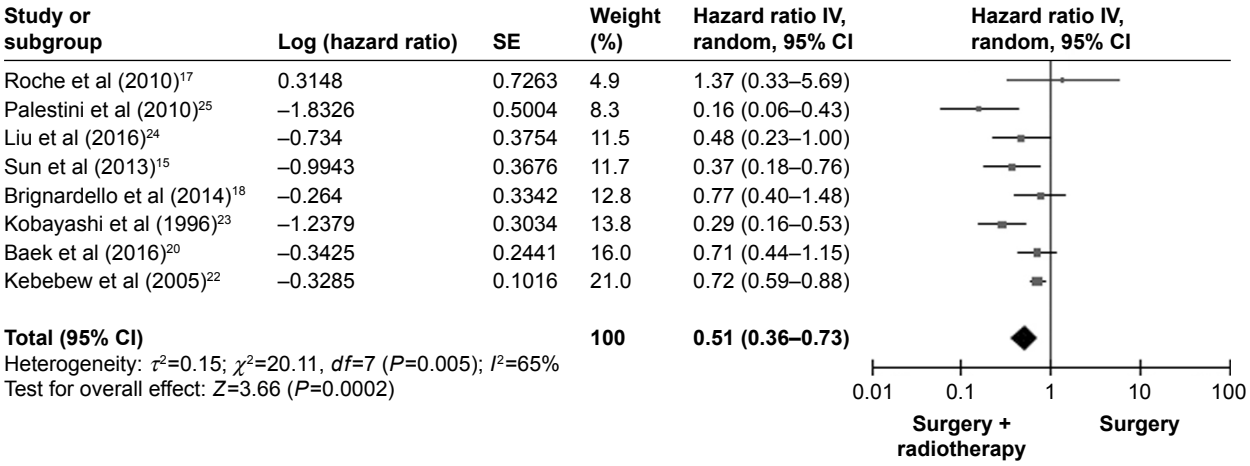

Figure 2 Forest plots for patients treated with surgery combined with radiotherapy and patients treated with surgery alone.
Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

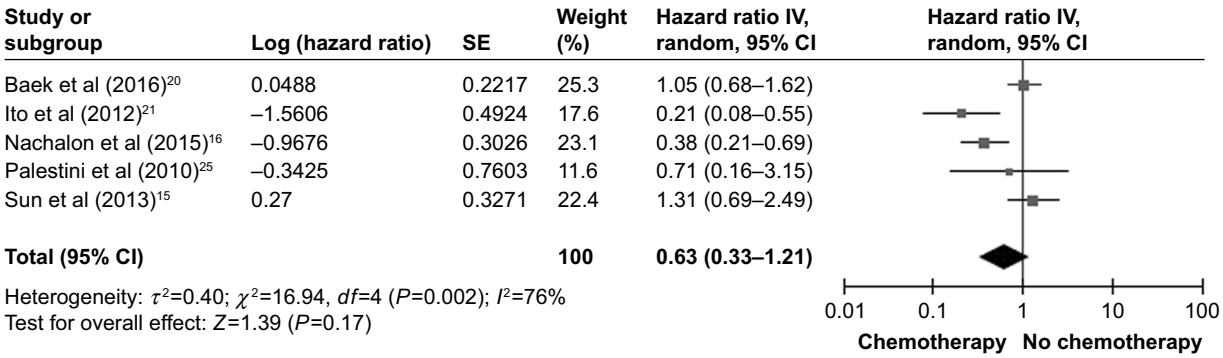

Figure 3 Forest plots for patients treated with chemotherapy and patients treated without chemotherapy.
Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

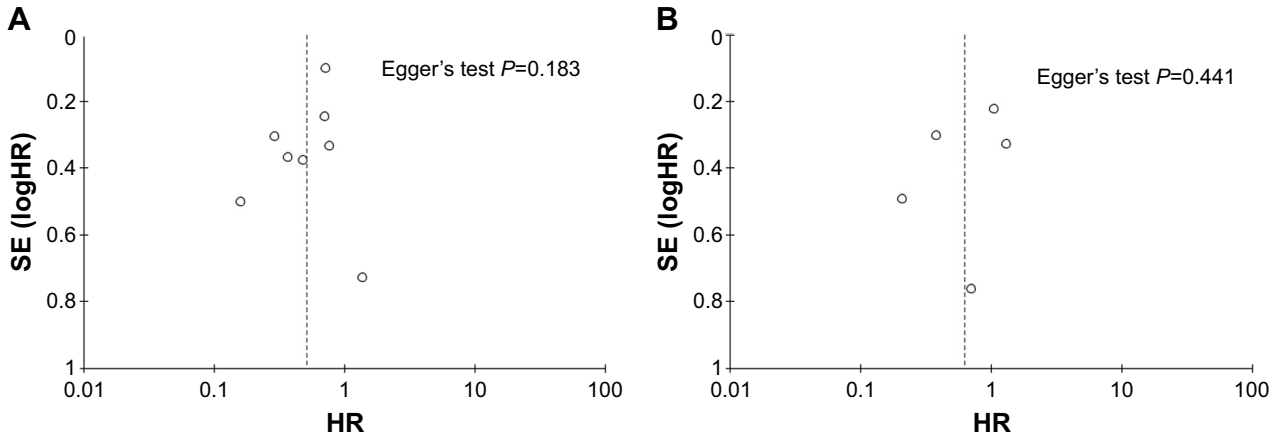

Figure 4 Funnel plots for publication bias.
Notes: Patients treated with surgery combined with radiotherapy or surgery alone (*P*=0.183, Egger's test) (**A**). Patients treated with or without chemotherapy (*P*=0.441, Egger's test) (**B**).
Abbreviations: HR, hazard ratio; SE, standard error.

therapy has been reported to achieve better results than unimodal treatment;[12–14] however, no firm conclusions have been reached and no individualized treatment regimens have been established.[10,11] Although most studies have demonstrated that postoperative radiotherapy can prolong the survival of ATC patients while chemotherapy is ineffective for this purpose, it remains unclear which treatment truly improves survival because most studies have a small sample size and poor statistical power due to the relatively low incidence of ATC. In this study, we performed a meta-analysis to address whether postoperative radiotherapy or chemotherapy could prolong the survival of ATC patients and attempted to determine the best treatment strategy to guide therapeutic decisions.

Our pooled results demonstrated that for all patients with resectable ATC, the combination of surgery and postoperative radiotherapy significantly reduced the risk of death compared with surgery alone; in contrast, chemotherapy did not prolong the survival of ATC patients. In fact, American Thyroid Association (ATA) guidelines already recommend that definitive radiotherapy should be offered after complete or near complete surgical resection (R0/R1) in patients without metastatic disease.[28] In addition, it has been suggested that for patients whose performance statuses permit such treatment, multimodal regimens that include chemotherapy result in the longest median survival.[5,11,29,30] The aforementioned findings raise the following question: if surgery followed by radiotherapy and chemotherapy truly improves the long-term survival of ATC patients, why would prior studies have reported differing curative effects for this therapeutic approach?[17,20,22,25] To address this question, we performed a literature review; based on this review, we considered the following potential explanations for differences in reported curative effects. First, there is no standard protocol for either chemotherapy or radiotherapy for ATC, and these treatments cannot be continued because rapid enlargement occurs, particularly in elderly patients.[31] Second, for radiotherapy, the dose appears to be important; several studies have demonstrated a clear improvement in survival among patients given higher doses of radiotherapy.[32] Furthermore, there is currently no general consensus regarding which chemotherapy regimens are best, although several studies have compared different agents and demonstrated that toxic regimens are poorly tolerated.[5,11,33,34] Although the pooled result in our study suggested that chemotherapy is ineffective, we still cannot completely exclude its potential for producing beneficial effects.

In contrast, several limitations of the current meta-analysis should be noted. First, despite our best attempts to gather evidence from the literature, we were unable to perform a methodological assessment of certain studies due to a lack of usable data. Additional work must be performed in the future. Second, there is potential publication bias in this study because we did not consider several unpublished articles and abstracts because these unpublished works were not available. In addition, our meta-analysis only included studies published in English or Chinese, with other publications excluded due to our language criteria; this restriction may also have introduced bias and affected our findings. Finally, our meta-analysis may have been too underpowered to acquire original data from the included studies. Despite all of the aforementioned limitations, this study provided evidence

that for ATC patients, surgery combined with radiotherapy may offer prolonged survival; in contrast, postoperative chemotherapy did not improve long-term survival.

Conclusion

This study provided evidence that surgery combined with radiotherapy may prolong survival in ATC patients; in contrast, postoperative chemotherapy did not improve long-term survival.

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Disclosure

The authors report no conflicts of interest in this work.

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