

Critical Review

Efficacy and Safety Evaluation of the Various Therapeutic Options in Locally Advanced Cervix Cancer: A Systematic Review and Network Meta-Analysis of Randomized Clinical Trials



Niloy R. Datta, MD,* Emanuel Stutz, MD,* Silvia Gomez, MD,* and Stephan Bodis, MD*,†

*Centre for Radiation Oncology KSA-KSB, Kantonsspital Aarau, Switzerland; and †Department of Radiation Oncology, University Hospital Zurich, Switzerland

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Treatment options in locally advanced cervix cancer (LACC) have evolved around radiation therapy (RT) and/or chemotherapy (CT), hypoxic cell sensitizers, immunomodulators (Imm), and locoregional moderate hyperthermia (HT). A systematic review and network meta-analysis was conducted to synthesize the evidence for efficacy and safety in terms of long-term locoregional control (LRC), overall survival (OS), and grade ≥ 3 acute morbidity (AM) and late morbidity (LM). Five databases were searched, and 6285 articles (1974–2018) were screened per the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines. Fifty-nine randomized trials in untreated LACC without surgical intervention were shortlisted. These used 13 different interventions: RT alone and/or neoadjuvant CT (NACT), adjuvant CT (ACT), concurrent chemoradiation therapy (CTRT) (weekly cisplatin [CDDP]/3-weekly CDDP/combination CT with CDDP/non-CDDP-based CT), hypoxic cell sensitizers, Imm, or HT. Odds ratios (ORs) using random effects network meta-analysis were estimated. Interventions for each endpoint were ranked according to their corresponding surface under cumulative ranking curve values. Of the 9894 patients evaluated, the total events reported for LRC, OS, AM, and LM were 5431 of 8197, 4482 of 7958, 1710 of 7183, and 441 of 6333, respectively. ORs and 95% credible intervals (CrIs) for the 2 best strategies were HT + RT versus CTRT + ACT (OR, 1.23; 95% CrI, 0.49–3.19) for LRC, CTRT (3-weekly CDDP) versus HTCTRT (OR, 1.14; 95% CrI, 0.35–3.65) for OS, RT + ACT versus RT (OR, 0.01; 95% CrI, 0.00–1.04) for AM, and NACT + RT + ACT versus RT + Imm (OR, 0.42; 95% CrI, 0.02–7.39) for LM. The 3 interventions with the highest cumulative surface under cumulative ranking curve values for all 4 endpoints were HTRT, HTCTRT, and CTRT (3-weekly CDDP). Articles with low risk of bias and those published during 2004 to 2018 also retained these interventions as the best. Two-step cluster analysis grouped these 3 modalities in a single distinctive

Note—An online CME test for this article can be taken at <https://academy.astro.org>.

Reprint requests to: Niloy R. Datta, MD, Department of Radiation Oncology KSA-KSB, Kantonsspital Aarau, Tellstrasse, Aarau, CH - 5001, Switzerland. Tel: +41 62 8389559, +41 76 22922590; E-mail: niloyranjan.datta@ksa.ch or nrdatta@yahoo.com

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cluster. HTRT, HTCTRT, and CTRT with 3-weekly CDDP were identified as therapeutic modalities with the best comprehensive impact on key clinical endpoints in LACC. This warrants a phase 3 randomized trial among these strategies for a head-to-head comparison and additional validation. © 2018 Elsevier Inc. All rights reserved.

Introduction

Therapeutic challenges in the management of locally advanced cervix cancer (LACC; International Federation of Gynecology and Obstetrics stages IIB-IVA) have led to the pursuit of strategies to optimize the efficacy of radiation therapy (RT), the mainstay of treatment in LACC. Of these, most approaches have been undertaken with chemotherapy (CT) as neoadjuvant CT (NACT),¹⁻¹⁰ concurrent chemoradiation therapy (CTRT),¹¹⁻³⁷ adjuvant CT (ACT),^{31,38,39} or various combinations of these.^{38,40} Apart from CT, other interventions with RT include hypoxic cell sensitizers (HypCS) (RT + HypCS; chemical radiosensitizers or hyperbaric oxygen),⁴¹⁻⁴⁸ immunomodulators (Imm) (RT + Imm),⁴⁹⁻⁵⁴ hyperthermia (HT) with RT (HTRT),⁵⁵⁻⁶⁰ or HT with CTRT (HTCTRT).⁶¹ A systematic review and critical analysis of the outcomes is thus justified to evaluate the efficacy and safety of these interventions in LACC.

Presently, management decisions and treatment guidelines largely rely on the level of clinical evidence. Systematic reviews of randomized controlled trials (RCTs) and meta-analysis are considered to provide the highest level of evidence for the relative effectiveness of interventions.^{62,63} However, conventional meta-analysis is limited by allowing only a direct pair-wise comparison of 2 competing modalities. Network meta-analysis (NMA), an extension of the conventional meta-analysis, enables computation of relative effectiveness from both direct one-to-one comparison and indirect comparison with multiple interventions that were not evaluated in a head-to-head assessment.⁶⁴⁻⁶⁶ Furthermore, NMA objectively ranks the various treatment options based on the corresponding surface under the cumulative ranking curve (SUCRA). Thus, NMA has the virtue of providing increased statistical power, precise estimates, and objective ranking; therefore, it is regarded as the highest level of evidence in treatment guidelines.^{67,68} Consequently, over the last decade, NMA has been conducted in various clinical situations, and it forms a vital tool for treatment guidelines development, drug approval, and decision making by various national and international health agencies, including the World Health Organization.^{68,69} Because a detailed description of NMA is beyond the scope of this article, some key publications discussing the evidence synthesis using NMA may be worth reviewing.^{64,65,67,68,70-74}

Thus, with the diverse therapeutic approaches explored in LACC, it is relevant and significant to evaluate the outcomes of these interventions using NMA. A systematic review followed by NMA has therefore been performed to explore the efficacy and safety of each of these treatment modalities

for the clinically significant endpoints—namely, long-term locoregional control (LRC), overall survival (OS), and grade ≥ 3 acute morbidity (AM) and late morbidity (LM)—and subsequently to shortlist the most favorable nonsurgical approaches for the management of LACC.

Material and Methods

Search strategy

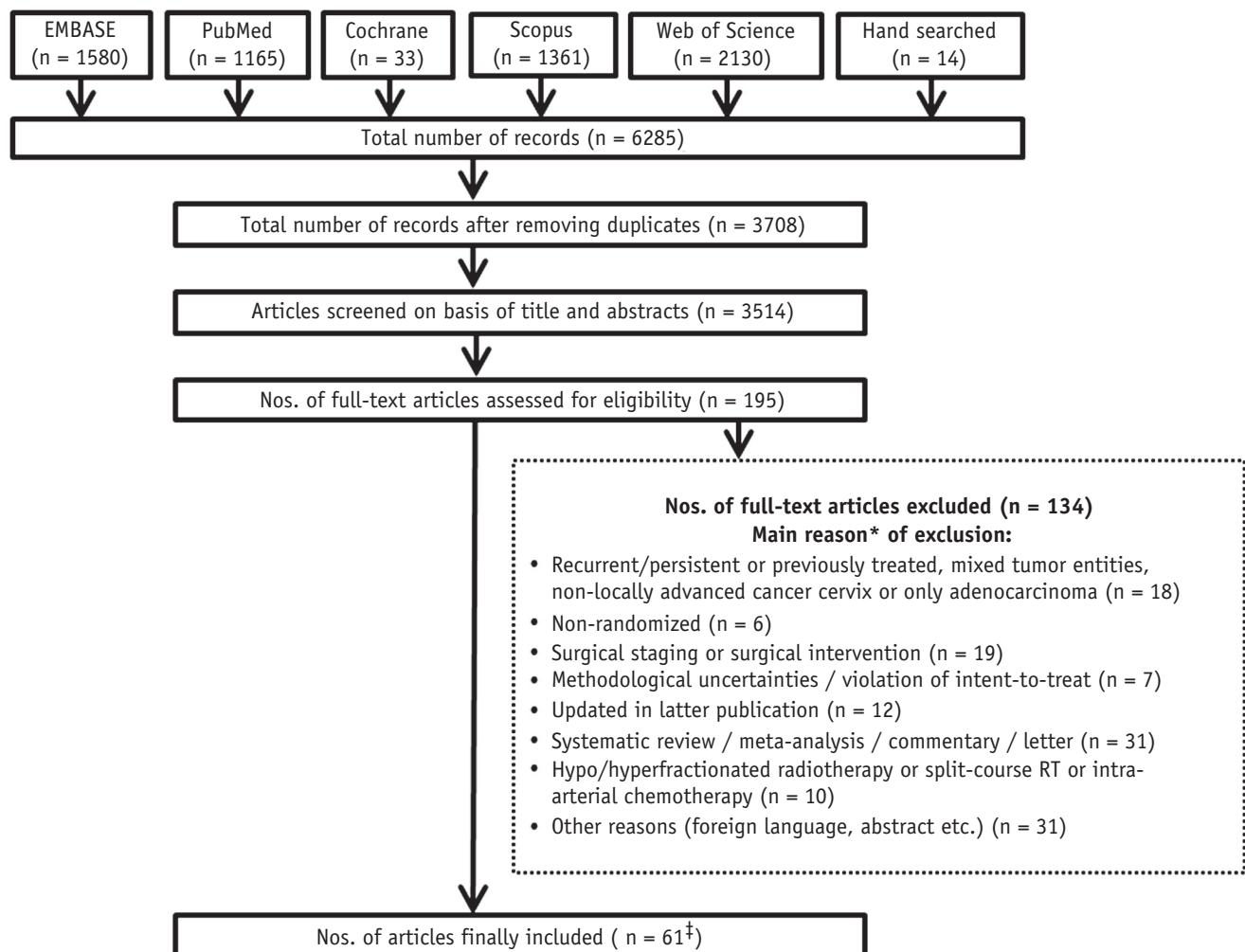
The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Fig. 1).⁷⁵ The study is registered with the International Prospective Register of Systematic Reviews CRD42018092771.⁷⁶ Five databases, namely PubMed, EMBASE, SCOPUS, Web of Science, and the Cochrane Library, were searched. The search terms used were “Uterine Cervical Neoplasms” [MeSH terms] AND “Randomized Controlled Trial” [Publication Type]. The search was limited to articles in the English language but was not restricted by date. The details of the search terms for each database are given in the extension of the PRISMA statement for quality of the reporting methods and results in NMA (Table E1; available online at <https://doi.org/10.1016/j.ijrobp.2018.09.037>).⁷⁷ The last search was performed on March 15, 2018. Additional papers were retrieved searching by hand. Only published, full-length articles were considered.

Inclusion criteria

The inclusion criteria were (1) prospective RCTs in previously untreated LACC with (2) no surgical staging or definitive surgery, (3) no altered fractionation external RT schedules, and (4) publication in English. In case of multiple publications from the primary study, updates of outcomes published over a period of time were considered.^{49,50,57,58}

Study selection

Of 6285 citations, 3708 records remained after removing duplicates. In addition, 3514 articles were omitted on the basis of their titles and abstracts (Fig. 1). Finally, 195 articles were subjected to full-text review to assess their suitability according to the inclusion criteria. One hundred thirty-four articles were excluded after full-paper review because of (1) nonrandomized or retrospective nature of the study; (2)



*Many papers had multiple exclusion criteria. The main reason is stated here and details for each is stated in Table E2.

[‡]In total 59 studies included. But for two trials, data was extracted from two publications of the same trial each.

Fig. 1. Flow chart indicating the study selection procedure. Table E2 (available online at <https://doi.org/10.1016/j.ijrobp.2018.09.037>).

recurrent or persistent tumors; (3) mixed tumor entities, mostly non-LACC, or only adenocarcinoma; (4) surgical interventions, including surgical staging; (5) methodological uncertainties and violation of intention-to-treat; and (6) use of altered fractionation schedules of external RT (other than 1.8-2.25 Gy/fraction). These exclusions were enforced to maintain a homogenous patient population and to ensure that the key assumptions of transitivity and indirectness were fulfilled for conducting NMA.^{64,66,70} All articles excluded after the full-text review are listed in Table E2 (available online at <https://doi.org/10.1016/j.ijrobp.2018.09.037>), along with the reasons for their exclusion. Finally, 61 articles from 59 RCTs were considered for the NMA.

Data extraction, quality assessment, and critical appraisal

All articles were extracted independently by 2 coauthors (N.R.D. and E.S.) and reviewed critically. In case of any

discrepancy, a consensus was reached in discussion with the other coauthors (S.G. and S.B.). The shortlisted papers were reviewed by all coauthors to ascertain the correctness of all entries.

Risk of bias was assessed as per the Cochrane Collaboration tool.⁷⁸ The quality of the evidence and its strength were rated as per the recommendations of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.⁷⁹

Evaluation of endpoints

The endpoints evaluated were LRC, OS, AM, and LM. LRC was considered if the patients had complete locoregional disease control at the end of their last reported follow-up. All patients alive contributed to OS regardless of their disease status. If the exact number of deaths or living patients was not reported, these were estimated directly from the Kaplan-Meir survival curves wherever feasible.

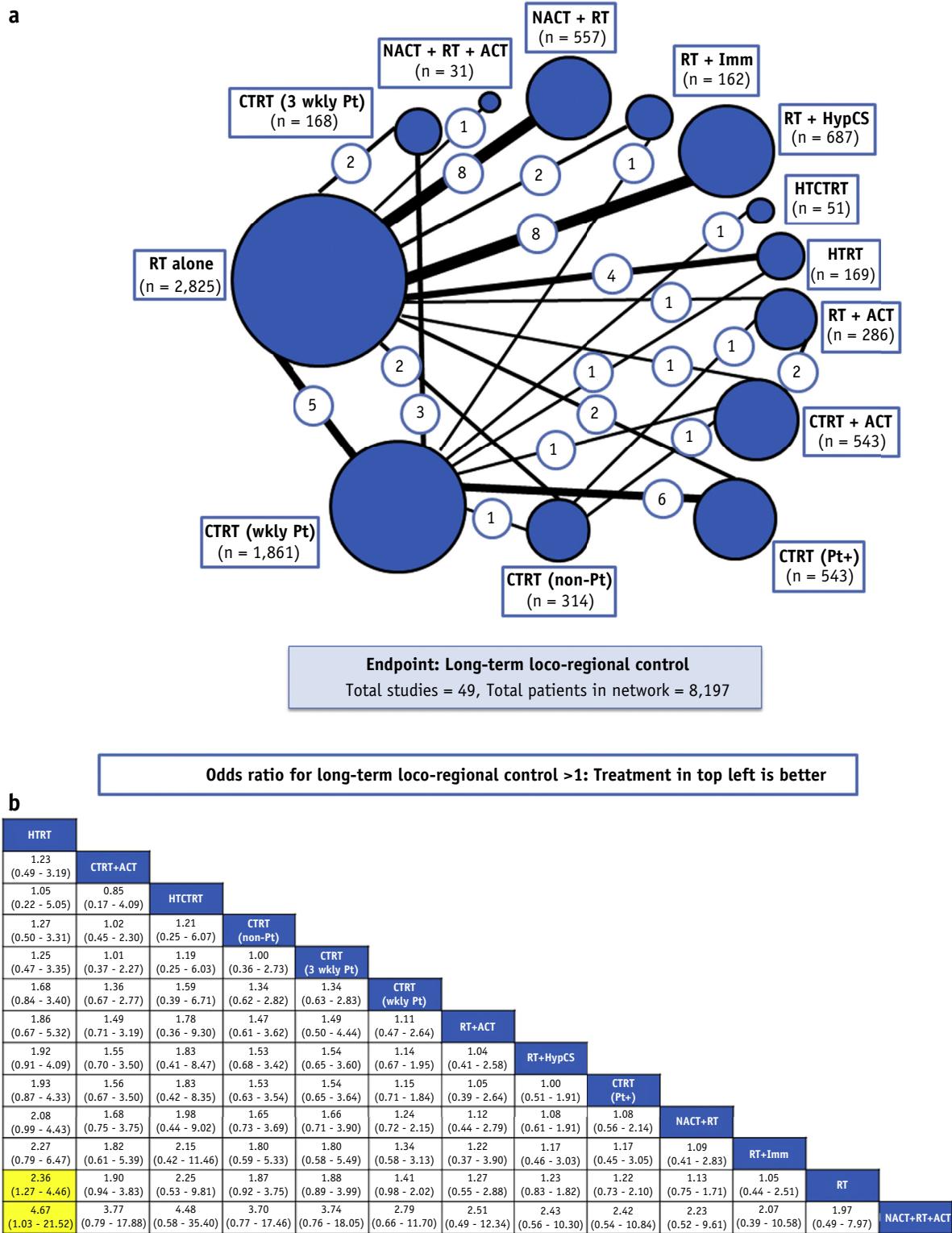
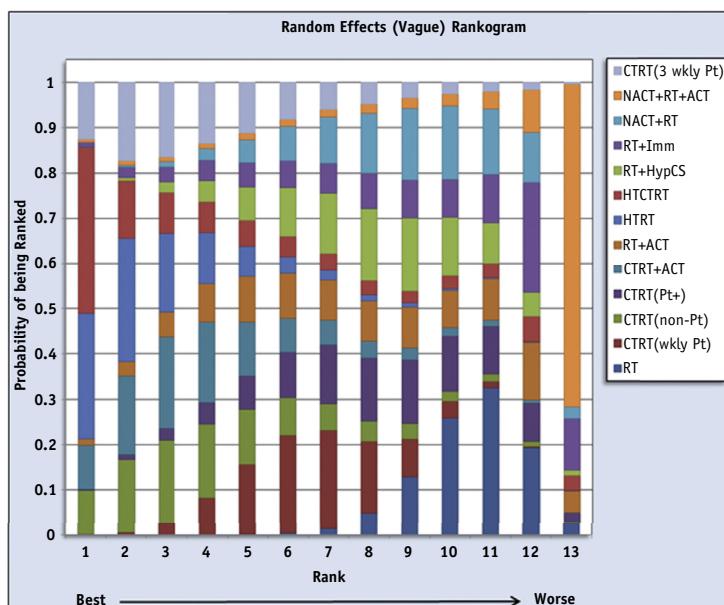


Fig. 2. Long-term locoregional control. (a) Network diagram. (b) League table for the odds ratios (ORs) with 95% credible interval (Crl) for each pair of interventions. Highlighted boxes indicate the significant ORs of the corresponding pairs. (c) Surface under the cumulative ranking curve (SUCRA) values for each intervention. Abbreviations: ACT = adjuvant chemotherapy; CTRT = concurrent chemoradiotherapy; HTCTRT = hyperthermia and chemoradiotherapy; HTRT = hyperthermia and radiation therapy; HypCS = hypoxic cell sensitizer; Imm = immunotherapy; NACT = neoadjuvant chemotherapy; Pt = cisplatin as single agent; non-Pt = noncisplatin as single agent; Pt + = cisplatin with combination chemotherapy; RT = radiation therapy alone.

C

Treatment	SUCRA
HTRT	0.8486
CTRT+ACT	0.7377
HTCTRT	0.7308
CTRT(non-Pt)	0.7193
CTRT(3 wkly Pt)	0.7165
CTRT(wkly Pt)	0.5340
RT+ACT	0.4344
RT+HypCS	0.4122
CTRT(Pt+)	0.4019
NACT+RT	0.3426
RT+Imm	0.3161
RT	0.2085
NACT+RT+ACT	0.0975

**Fig. 2.** *Continued*

The corresponding authors were contacted for updates and clarifications where required.

For AM and LM only grade ≥ 3 toxicities were considered. Because the citations spanned a period of 44 years, toxicity evaluation criteria for AM and LM were variable. Most of the studies reported toxicities using either Common Terminology Criteria for Adverse Events (CTCAE) version 0.2/0.3 ($n = 15$)⁸⁰ or Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC; $n = 14$) criteria.⁸¹

Structure of evidence nodes and network diagram

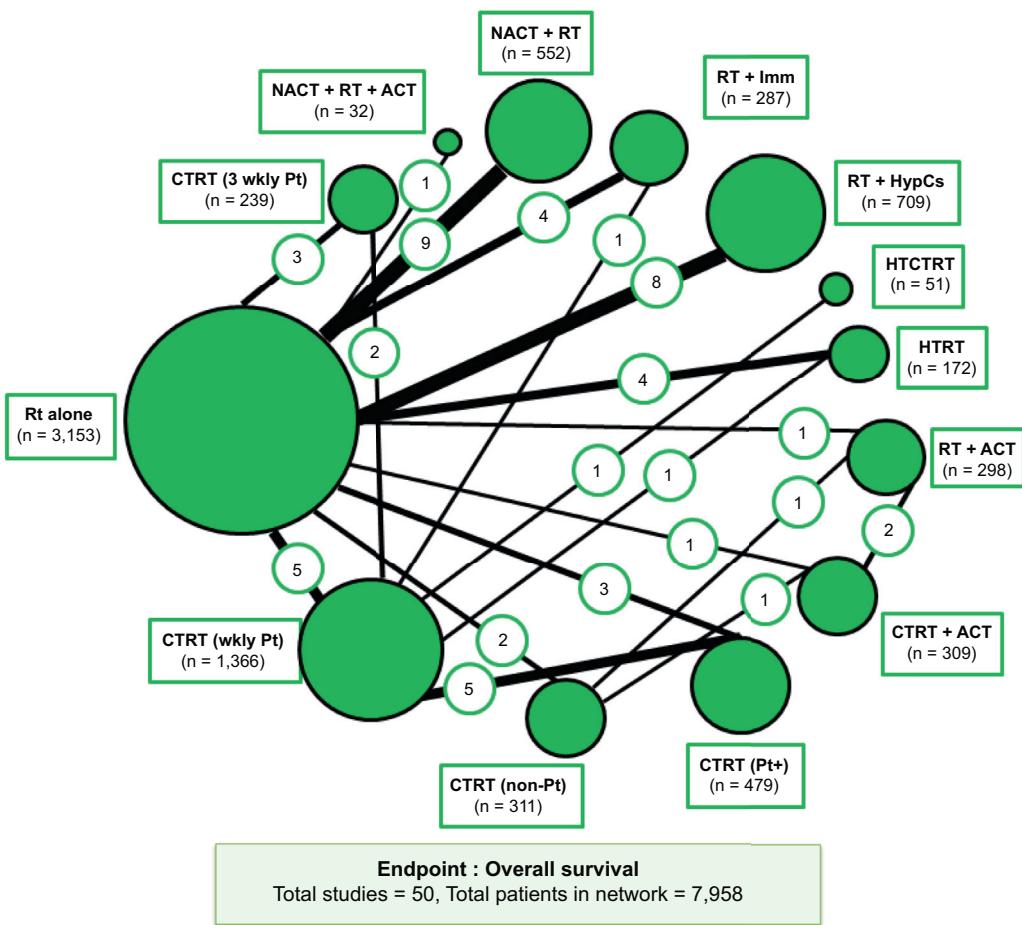
For each of the 4 evaluated endpoints, treatment nodes were identified for the various interventions. One RCT had 4 treatment arms, all of which were included in the respective node.³⁸ All others were 2-arm RCTs. A total of 13 treatment nodes were allocated: RT alone, CTRT with single-agent weekly cisplatin (CTRT[wkly Pt]), CTRT with single-agent triweekly cisplatin (CTRT [3wkly Pt]), CTRT with noncisplatin (CTRT[non-Pt]), CTRT with multiagent CT with cisplatin (CTRT[Pt +]), CTRT with ACT (CTRT + ACT), RT with ACT (RT + ACT), HTRT, HTCTRT, RT with HypCS (RT + HypCS), RT with Imm (RT + Imm), NACT followed by RT (NACT + RT), and NACT with RT and ACT (NACT + RT + ACT). The nodes in the network diagram represent the various therapeutic modalities for each endpoint, and their sizes are proportional to the number of randomized patients indicated beside each corresponding node. Each pair is joined by the intersecting line, the width of which reflects the number of trials as inscribed on these lines (Figs. 2a, 3a, 4a, and 5a).

Pairwise meta-analysis

Before conducting the NMA, a pairwise conventional meta-analysis was conducted for all studies using the Comprehensive Meta-analysis Software (version 3.0). Effect measures were computed for all dichotomous outcomes and scored as events. The odds ratios (ORs) for each of the desired endpoints were computed using the random effects model, and results were given by the point estimate with a 95% confidence interval (CI) and Z and P values. Heterogeneity was assessed using the I^2 statistic, which represents the estimated proportion of unexplained interstudy variance before pooling of the studies; $I^2 \leq 40\%$ confirmed the absence of any substantial heterogeneity.⁸² Potential publication bias was evaluated through funnel plots and rank correlation tests using Kendall's τ .⁸³ Subgroup analyses were performed on ORs using a mixed effects model. The Q value, degree of freedom, and P value were computed for each of the subgroups evaluated.

Methods of evidence synthesis in NMA

For the NMA, outcomes for each of the 4 endpoints were computed separately with a Bayesian approach using Net-MetaXL and WinBUGS version 1.4.3 (MRC Biostatistics Unit, Institute of Public Health, Cambridge, UK); this allowed the combination of direct and indirect evidence from various studies.^{65,73} Analysis was performed using Markov Chain Monte Carlo simulation.⁸⁴ A random effects model with vague prior distribution for interstudy variance was planned. The direct comparisons were compared head-to-head within a randomized trial, whereas the indirect

a**b**

Odds ratio for overall survival >1: Treatment in top left is better

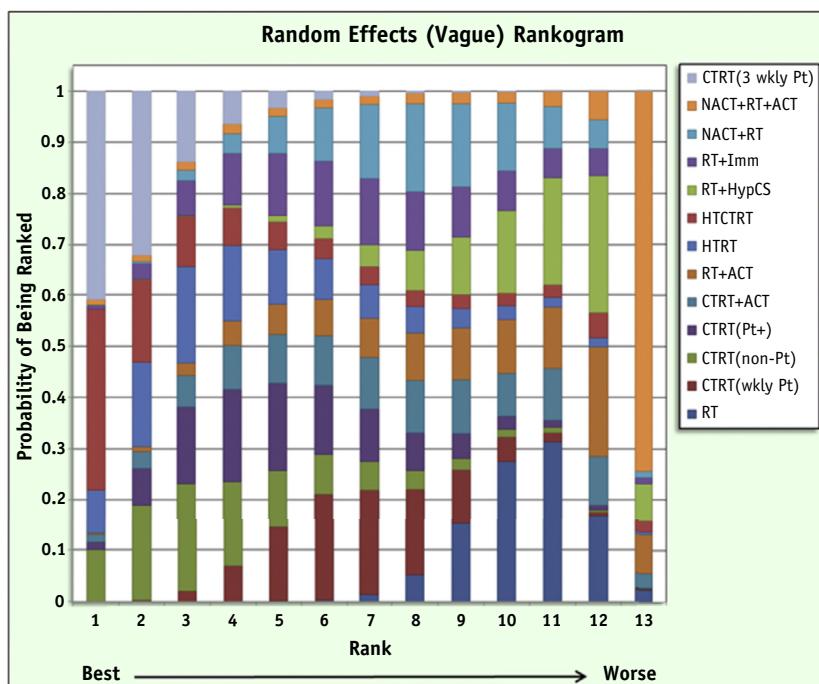
CTRT (3 wkly Pt)	HTCTRT	CTRT (non-Pt)	HTRT	CTRT (Pt+)	CTRT (wkly Pt)	RT+Imm	CTRT+ACT	NACT+RT	RT+ACT	RT+HypCs	RT	NACT+RT+ACT
1.14 (0.35 – 3.65)												
1.32 (0.63 – 2.79)	1.16 (0.34 – 3.87)											
1.38 (0.66 – 3.00)	1.21 (0.37 – 4.11)	1.04 (0.49 – 2.33)										
1.51 (0.81 – 2.85)	1.33 (0.44 – 4.12)	1.15 (0.58 – 2.25)	1.10 (0.55 – 2.11)	1.10 (0.78 – 1.72)								
1.72 (1.03 – 3.01)	1.52 (0.53 – 4.39)	1.31 (0.72 – 2.40)	1.26 (0.69 – 2.21)	1.14 (0.78 – 1.72)	CTRT (wkly Pt)							
1.73 (0.89 – 3.40)	1.53 (0.48 – 4.85)	1.31 (0.65 – 2.65)	1.27 (0.60 – 2.50)	1.14 (0.64 – 2.05)	1.14 (0.62 – 1.60)	RT+Imm						
1.82 (0.83 – 4.07)	1.61 (0.47 – 5.69)	1.39 (0.73 – 2.61)	1.34 (0.57 – 3.00)	1.21 (0.58 – 2.56)	1.06 (0.53 – 2.07)	1.06 (0.49 – 2.28)	CTRT+ACT					
1.91 (1.07 – 3.52)	1.68 (0.55 – 5.27)	1.44 (0.78 – 2.74)	1.39 (0.74 – 2.60)	1.26 (0.76 – 2.11)	1.10 (0.74 – 1.67)	1.10 (0.64 – 1.93)	1.04 (0.53 – 2.14)	NACT+RT				
2.09 (0.98 – 4.71)	1.85 (0.54 – 6.58)	1.58 (0.85 – 3.04)	1.53 (0.65 – 3.42)	1.38 (0.67 – 2.95)	1.21 (0.62 – 2.41)	1.21 (0.57 – 2.63)	1.14 (0.67 – 2.02)	1.10 (0.55 – 2.18)	RT+ACT			
2.27 (1.29 – 4.12)	1.99 (0.66 – 6.15)	1.72 (0.93 – 3.22)	1.66 (0.87 – 3.05)	1.49 (0.92 – 2.49)	1.31 (0.88 – 1.95)	1.31 (0.77 – 2.27)	1.23 (0.63 – 2.49)	1.19 (0.77 – 1.80)	1.08 (0.54 – 2.12)	RT+HypCs		
2.23 (1.37 – 3.73)	1.96 (0.67 – 5.86)	1.68 (0.98 – 2.94)	1.63 (0.92 – 2.80)	1.47 (0.98 – 2.22)	1.29 (0.99 – 1.69)	1.28 (0.83 – 2.04)	1.21 (0.66 – 2.30)	1.17 (0.85 – 1.58)	1.06 (0.57 – 1.96)	0.98 (0.73 – 1.32)	RT	
4.30 (1.00 – 20.78)	3.80 (0.67 – 23.99)	3.28 (0.75 – 15.72)	3.14 (0.70 – 15.30)	2.85 (0.68 – 13.01)	2.48 (0.62 – 11.16)	2.48 (0.59 – 11.53)	2.35 (0.51 – 11.53)	2.26 (0.56 – 9.96)	2.07 (0.44 – 9.92)	1.91 (0.46 – 8.47)	1.93 (0.49 – 8.39)	NACT+RT+ACT

Heterogeneity (Vague) = 0.25; 95% CrI : 0.05 – 0.45

Fig. 3. Overall survival. (a) Network diagram. (b) League table for the odds ratios (ORs) with 95% credible interval (CrI) for each pair of interventions. Highlighted boxes indicate the significant ORs of the corresponding pairs. (c) Surface under the cumulative ranking curve (SUCRA) values for each intervention. Abbreviations: ACT = adjuvant chemotherapy; CTRT = concurrent chemoradiotherapy; HTCTRT = hyperthermia and chemoradiotherapy; HTRT = hyperthermia and radiation therapy; HypCS = hypoxic cell sensitizer; Imm = immunotherapy; NACT = neoadjuvant chemotherapy; Pt = cisplatin as single agent; non-Pt = noncisplatin as single agent; Pt + = cisplatin with combination chemotherapy; RT = radiation therapy alone.

C

Treatment	SUCRA
CTRT (3 wkly Pt)	0.9055
HTCTRT	0.7554
CTRT(non-Pt)	0.7480
HTRT	0.7029
CTRT(Pt+)	0.6431
CTRT (wkly Pt)	0.5137
RT + Imm	0.5039
CTRT + ACT	0.4514
NACT+ RT	0.4083
RT + ACT	0.3237
RT + HypCS	0.2198
RT	0.2157
NACT+RT+ACT	0.1085

**Fig. 3.** *Continued*

comparisons analyzed the results of randomized trials with common comparators.⁸⁵

Models were run using 10,000 burn-in iterations followed by 10,000 sampling iterations.⁸⁶ The pairwise summary paired OR estimates and 95% credible interval (CrI) (or Bayesian CI) were presented in league tables. In addition, forest plots with heterogeneity estimates (I^2 with 95% CrI) were generated. For individual interventions, SUCRA values were computed for each outcome, and these ranged between 0 and 1, with values nearer to 1 indicating the preferred treatment.^{65,87} Rankograms based on SUCRA values for the various therapeutic modalities were also plotted.

Inconsistency between direct and indirect estimates was assessed by comparing the deviance information criteria (DIC) values between models (differences ≥ 5 were considered to indicate evidence of inconsistency).^{65,77} For each analysis, posterior residual deviance was matched with the total number of data points to assess adequacy of model fit. Reductions in the total residual deviance (totresdev) and between-study heterogeneity (standard deviation [SD]) in the inconsistency model compared with the consistency model in NMA suggested inconsistency.⁸⁸

Sensitivity analysis

A sensitivity analysis was performed for trials with low selective reporting bias. As the median cutoff year for publications was 2004, a separate analysis included only trials published during or after 2004. NMAs for all the 4

endpoints were performed to ascertain any likely change in the rankings based on these 2 factors.

Cluster analysis of the interventions

After NMA, the various treatment options were subjected to a 2-step cluster analysis by inputting the SUCRA values for LRC, OS, AM, and LM. Considering the optimal cluster quality (regarded as good) and the ratio of cluster sizes, 6 cluster models were chosen. Cluster comparisons were plotted to visualize the differences in the SUCRA values of each endpoint in various clusters. Analysis was carried using IBM SPSS version 24.

Assessment of GRADE and certainty of confidence

The certainty of confidence contributing to the NMA estimates was evaluated per the GRADE recommendations using the software Confidence in Network Meta-Analysis version 1.4.1. The program considers the 5 basic domains of the GRADE recommendations: study limitations, imprecision, inconsistency (heterogeneity and incoherence), indirectness, and publication bias. The software runs with R program in the background and combines the judgments about direct evidence with their statistical contribution to the NMA results, allowing evaluation of the credibility of the NMA treatment effects.⁸⁹

All estimates were conducted for the binary data with random effects for OR. The risk of bias was considered average, and the imprecision of the network treatment

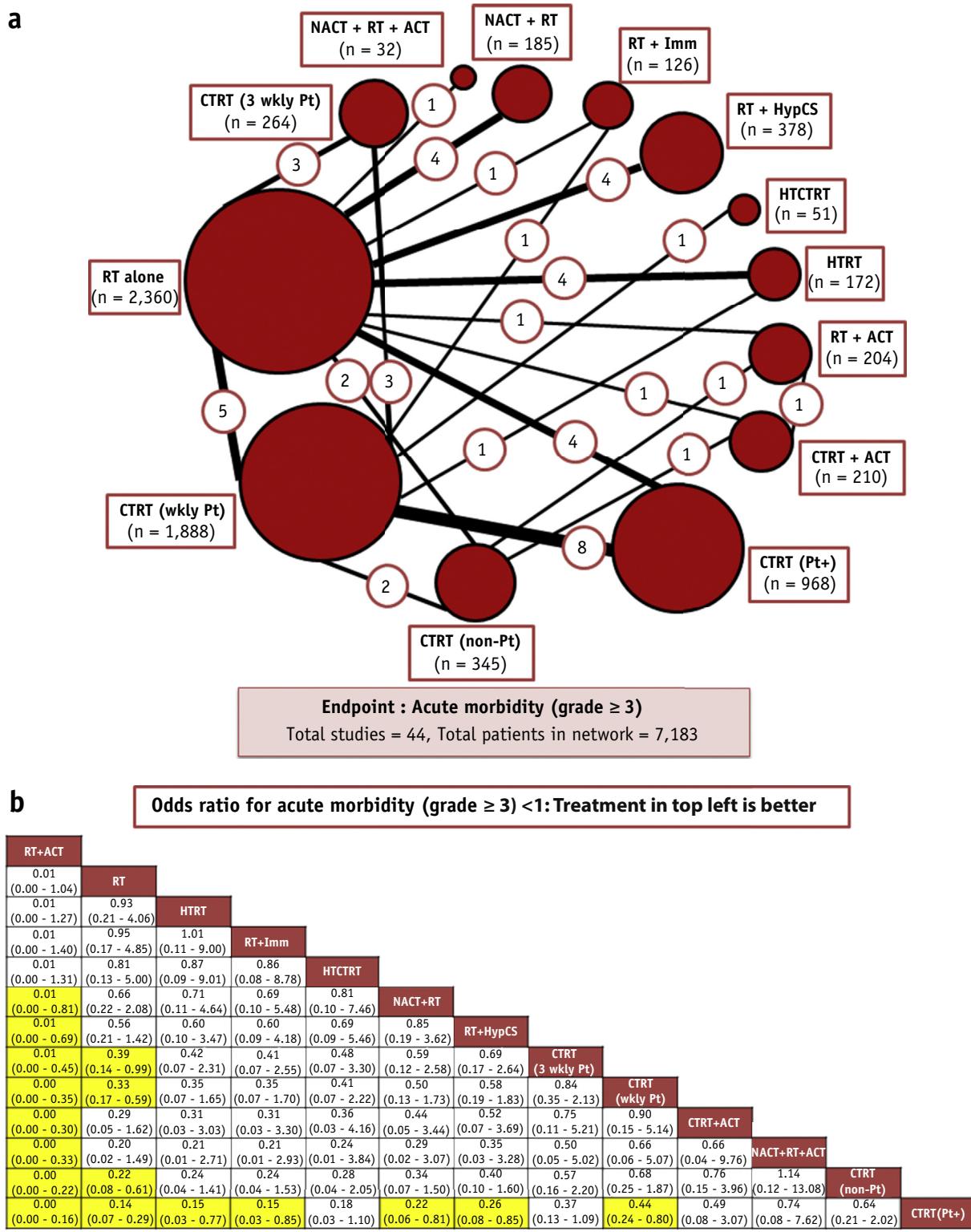


Fig. 4. Acute morbidity (grade ≥ 3). (a) Network diagram. (b) League table for the ORs with 95% credible interval (CrI) for each pair of interventions. Highlighted boxes indicate the significant ORs of the corresponding pairs. (c) Surface under the cumulative ranking curve (SUCRA) values for each intervention. Abbreviations: ACT = adjuvant chemotherapy; CTRT = concurrent chemoradiotherapy; HTCTRT = hyperthermia and chemoradiotherapy; HTRT = hyperthermia and radiation therapy; HypCS = hypoxic cell sensitizer; Imm = immunotherapy; NACT = neoadjuvant chemotherapy; Pt = cisplatin as single agent; non-Pt = noncisplatin as single agent; Pt+ = cisplatin with combination chemotherapy; RT = radiation therapy alone.

C

Treatment	SUCRA
RT+ACT	0.9848
RT	0.7654
HTRT	0.6939
RT+Imm	0.6928
HTCTRT	0.6423
NACT+RT	0.5962
RT+HypCS	0.5396
CTRT(3 wkly Pt)	0.4047
CTRT(wkly Pt)	0.3325
CTRT+ACT	0.3275
NACT+RT+ACT	0.2332
CTRT(non-Pt)	0.2085
CDDP(Pt+)	0.0787

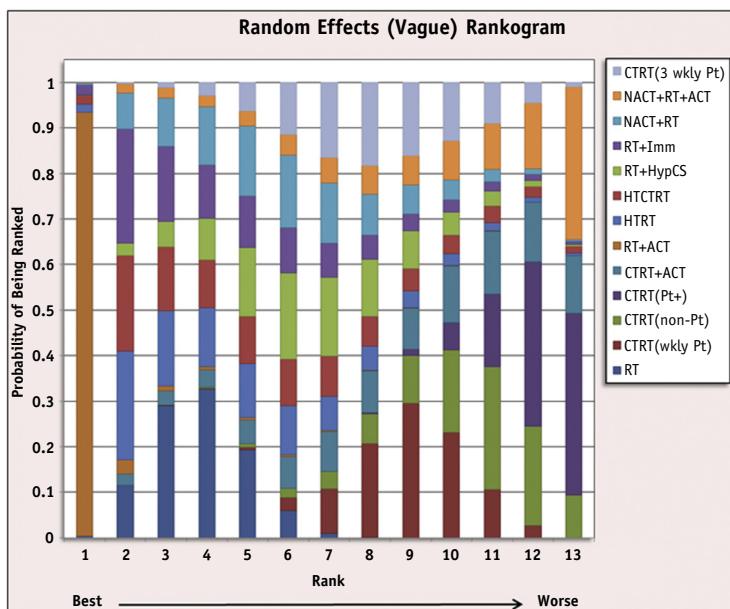


Fig. 4. Continued

effects was set for an OR of 0.8 for all endpoints. The outcomes of the analysis for each of the 5 domains of the GRADE recommendations for mixed and indirect comparative evidences were reported as “no concern,” “some concern”, or “major concern.” A summary was compiled, and the confidence in the quality of estimates were classified as high, moderate, low, and very low according to the GRADE recommendations.⁷⁹ “No concern” domains were not downgraded, whereas each of the domains with “some concern” was downgraded by 0.5 level and those with “major concern” by 1 level. Thus, the final confidence was based on the extent of downgrade: “high” if the quality was downgraded to ≤ 0.5 level; “moderate” for >0.5 to 1.5 level; “low” for >1.5 to 2.5 level; and “very low” for >2.5 levels.

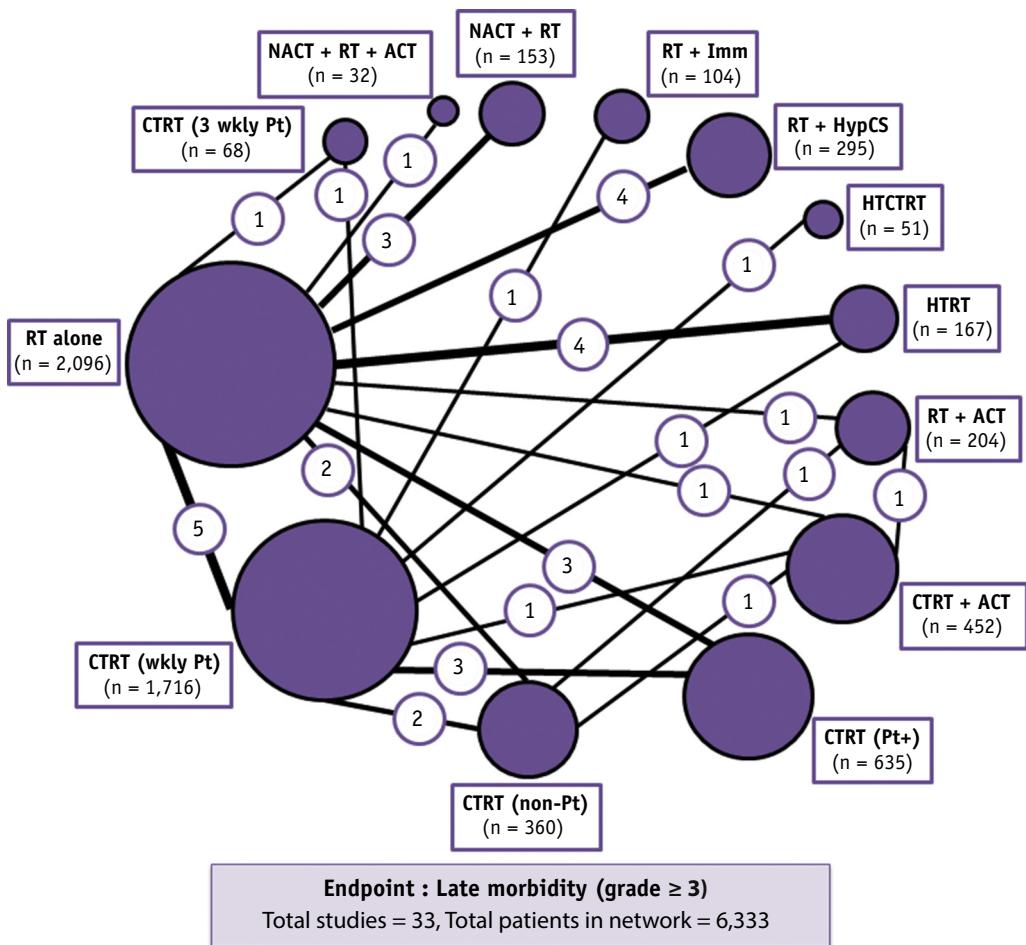
Results

Study characteristics

The 59 shortlisted RCTs were reported between 1974 and 2018, and 9894 patients were included in these studies (control group, n = 4729; study group, n = 5165). The details of the studies along with the interventions in the control and study groups are listed in Table 1. Total number of patients included in these trials varied from 39 to 926 (mean \pm SD: 167.7 \pm 172.1).^{17,38} Fifty-eight of the 59 studies were 2-arm trials. One trial had 4 comparative arms: RT (n = 242), CTRT(non-Pt; n = 233), RT + ACT (n = 221), and CTRT + ACT (n = 230).³⁸ For RT versus HTRT, 2 publications^{57,58} reported supplementary endpoints from the same study, as did a trial of RT versus RT + Imm.^{49,50}

LACC was present in 97.4% of patients, and 91.1% of cases were histopathologically confirmed as squamous cell cancer. Age was reported either as mean or median in various studies and ranged from 41.5 to 67 years. Based on individual institution policies, the external RT dose varied between 30.6 and 64.8 Gy at 1.8 to 2.25 Gy per fraction with or without midline shielding. RT was delivered by telecobalt (n = 13), linear accelerator (n = 25), and telecobalt or linear accelerator (n = 12). In 9 studies, the details were not stated. Brachytherapy techniques were variable and included manual preloaded sources and afterloading intracavitary brachytherapy with varying dose rates (Table 1).

Thus, with 13 different interventions in the control and study groups, a maximum of 21 pairwise comparisons between the competing modalities was feasible. These included RT versus CTRT(wkly Pt) (n = 5),¹¹⁻¹⁵ RT versus CTRT(3 wkly Pt) (n = 3),³²⁻³⁴ RT versus CTRT(non-Pt) (n = 2),^{16,38} RT versus CTRT(Pt+) (n = 4),¹⁹⁻²² RT versus RT + ACT (n = 1),³⁸ RT versus CTRT + ACT (n = 1),³⁸ CTRT(non-Pt) versus CTRT + ACT (n = 1),³⁸ RT + ACT versus CTRT(non-Pt) (n = 1),³⁸ RT versus NACT + RT (n = 10),¹⁻¹⁰ RT versus NACT + RT + ACT (n = 1),⁴⁰ RT versus RT + HypCS (n = 8),⁴¹⁻⁴⁸ RT versus RT + Imm (n = 4),⁴⁹⁻⁵³ RT versus HTRT (n = 4),⁵⁵⁻⁵⁹ CTRT(wkly Pt) versus CTRT(non-Pt) (n = 2),^{17,18} CTRT(wkly Pt) versus CTRT(Pt+) (n = 8),²³⁻³⁰ CTRT(wkly Pt) versus CTRT + ACT (n = 1),³¹ RT + ACT versus CTRT + ACT (n = 2),^{38,39} CTRT(wkly Pt) versus HTRT (n = 1),⁶⁰ CTRT(wkly Pt) versus HTCTRT (n = 1),⁶¹ CTRT(wkly Pt) versus RT + Imm (n = 1),⁵⁴ and CTRT(wkly Pt) versus CTRT(3wkly Pt) (n = 3).³⁵⁻³⁷ A conventional pairwise meta-analysis was undertaken for these direct comparisons

a**b**

Odds ratio for late morbidity (grade ≥ 3) <1: Treatment in top left is better

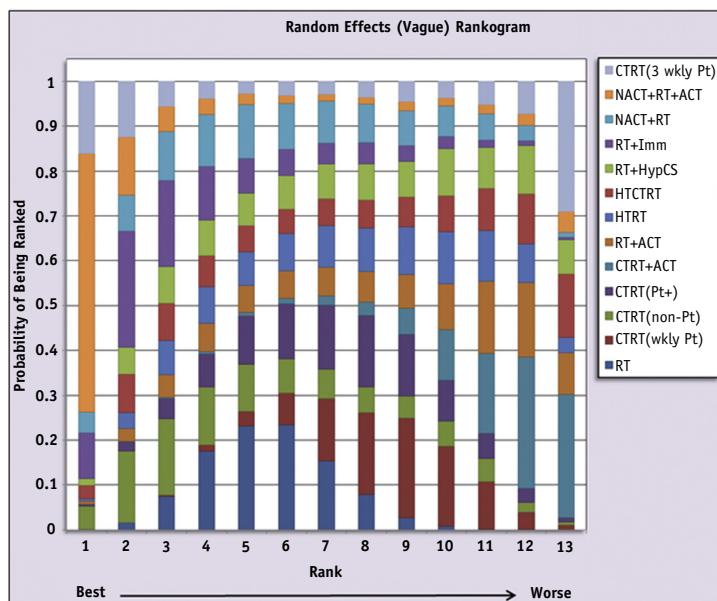
NACT+RT+ACT		RT+Imm		CTRT(non-Pt)		RT		NACT+RT		CTRT(Pt+)		CTRT(3 wkly Pt)		RT+HypCS		HTRT		HTCTRT		CTRT(wkly Pt)		RT+ACT		CTRT+ACT	
0.42 (0.02 - 7.39)		0.84 (0.19 - 3.60)		0.91 (0.30 - 2.53)		0.98 (0.47 - 2.07)		0.87 (0.34 - 2.25)		0.91 (0.34 - 2.25)		0.91 (0.04 - 30.43)		0.98 (0.28 - 2.71)		1.01 (0.04 - 32.98)		1.02 (0.30 - 3.85)		0.98 (0.16 - 4.76)		0.94 (0.22 - 4.00)		0.97 (0.30 - 3.90)	
0.32 (0.02 - 6.32)		0.75 (0.26 - 1.99)		0.72 (0.21 - 2.43)		0.88 (0.24 - 3.50)		0.84 (0.49 - 1.51)		0.77 (0.03 - 21.11)		0.77 (0.02 - 21.54)		0.77 (0.21 - 2.72)		0.91 (0.03 - 26.31)		1.10 (0.03 - 33.74)		1.02 (0.16 - 4.76)		1.01 (0.24 - 2.90)		0.94 (0.17 - 4.83)	
0.31 (0.02 - 4.72)		0.75 (0.26 - 1.99)		0.91 (0.30 - 2.53)		0.72 (0.21 - 2.43)		0.88 (0.24 - 3.50)		0.77 (0.49 - 1.51)		0.77 (0.03 - 21.11)		0.77 (0.21 - 2.72)		0.91 (0.03 - 26.31)		1.10 (0.03 - 33.74)		1.02 (0.16 - 4.76)		1.01 (0.24 - 2.90)		0.94 (0.17 - 4.83)	
0.30 (0.01 - 4.82)		0.72 (0.21 - 2.43)		0.72 (0.21 - 2.43)		0.88 (0.24 - 3.50)		0.98 (0.47 - 2.07)		0.84 (0.49 - 1.51)		0.84 (0.03 - 21.11)		0.84 (0.21 - 2.72)		0.91 (0.03 - 26.31)		1.10 (0.03 - 33.74)		1.02 (0.16 - 4.76)		1.01 (0.24 - 2.90)		0.94 (0.17 - 4.83)	
0.27 (0.01 - 4.29)		0.64 (0.22 - 1.92)		0.77 (0.23 - 2.23)		0.77 (0.23 - 2.23)		0.77 (0.49 - 1.51)		0.77 (0.03 - 21.11)		0.77 (0.21 - 2.72)		0.77 (0.28 - 2.05)		0.87 (0.34 - 2.25)		0.91 (0.04 - 30.43)		0.98 (0.28 - 2.71)		1.01 (0.04 - 32.98)		1.02 (0.30 - 3.85)	
0.25 (0.00 - 17.76)		0.55 (0.02 - 17.39)		0.70 (0.02 - 22.31)		0.70 (0.02 - 22.31)		0.76 (0.03 - 21.11)		0.76 (0.02 - 21.54)		0.76 (0.03 - 26.31)		0.76 (0.21 - 2.72)		0.91 (0.04 - 30.43)		0.98 (0.28 - 2.71)		1.02 (0.16 - 4.76)		1.01 (0.24 - 2.90)		0.94 (0.17 - 4.83)	
0.25 (0.01 - 4.53)		0.58 (0.14 - 2.29)		0.72 (0.15 - 2.77)		0.72 (0.15 - 2.77)		0.79 (0.28 - 2.05)		0.79 (0.28 - 2.05)		0.80 (0.21 - 2.72)		0.94 (0.28 - 2.71)		0.98 (0.04 - 30.43)		1.02 (0.16 - 4.76)		1.01 (0.24 - 2.90)		1.01 (0.30 - 3.85)		0.94 (0.22 - 4.00)	
0.25 (0.01 - 4.23)		0.59 (0.18 - 1.86)		0.71 (0.20 - 3.38)		0.78 (0.38 - 1.67)		0.78 (0.28 - 2.33)		0.81 (0.38 - 1.67)		0.81 (0.28 - 2.33)		0.91 (0.38 - 2.49)		1.10 (0.04 - 32.98)		1.10 (0.30 - 3.85)		1.02 (0.16 - 4.76)		1.01 (0.24 - 2.90)		0.94 (0.22 - 4.00)	
0.23 (0.01 - 4.68)		0.56 (0.11 - 2.46)		0.67 (0.12 - 3.58)		0.76 (0.20 - 2.60)		0.76 (0.17 - 3.25)		0.78 (0.20 - 2.60)		0.78 (0.17 - 3.25)		0.90 (0.20 - 3.73)		0.90 (0.03 - 33.74)		0.98 (0.16 - 4.76)		1.02 (0.16 - 4.76)		1.01 (0.24 - 2.90)		0.94 (0.22 - 4.00)	
0.23 (0.01 - 3.50)		0.55 (0.22 - 1.33)		0.67 (0.20 - 2.14)		0.74 (0.48 - 1.11)		0.74 (0.31 - 1.71)		0.77 (0.46 - 1.54)		0.77 (0.46 - 1.54)		0.88 (0.04 - 24.80)		0.99 (0.32 - 2.75)		0.93 (0.42 - 1.98)		0.93 (0.30 - 3.90)		0.93 (0.30 - 3.90)		0.94 (0.22 - 4.00)	
0.21 (0.01 - 3.75)		0.49 (0.12 - 1.99)		0.61 (0.18 - 1.65)		0.66 (0.24 - 1.82)		0.66 (0.19 - 2.43)		0.67 (0.24 - 2.33)		0.67 (0.24 - 2.33)		0.78 (0.03 - 25.35)		0.84 (0.20 - 3.54)		0.86 (0.24 - 2.90)		0.83 (0.17 - 4.83)		0.83 (0.17 - 4.83)		0.90 (0.30 - 2.65)	
0.15 (0.01 - 2.47)		0.34 (0.10 - 1.16)		0.43 (0.14 - 1.09)		0.47 (0.20 - 0.99)		0.47 (0.15 - 1.39)		0.57 (0.21 - 1.33)		0.61 (0.02 - 17.16)		0.61 (0.16 - 2.13)		0.61 (0.19 - 1.65)		0.59 (0.19 - 1.65)		0.62 (0.19 - 2.92)		0.63 (0.27 - 1.41)		0.71 (0.26 - 1.81)	

Heterogeneity (Vague) = 0.16; 95% CrI : 0.00 - 0.66

Fig. 5. Late morbidity (grade ≥ 3). (a) Network diagram. (b) League table for the odds ratios (ORs) with 95% credible interval (CrI) for each pair of interventions. (c) Surface under the cumulative ranking curve (SUCRA) values for each intervention. Abbreviations: ACT = adjuvant chemotherapy; CTRT = concurrent chemoradiotherapy; HTCTRT = hyperthermia and chemoradiotherapy; HTRT = hyperthermia and radiation therapy; HypCS = hypoxic cell sensitizer; Imm = immunotherapy; NACT = neoadjuvant chemotherapy; Pt = cisplatin as single agent; non-Pt = noncisplatin as single agent; Pt+ = cisplatin with combination chemotherapy; RT = radiation therapy alone.

C

Treatment	SUCRA
NACT+RT+ACT	0.8254
RT+Imm	0.7415
CTRT (non-Pt)	0.6489
RT	0.6201
NACT+RT	0.5743
CTRT(Pt+)	0.4764
CTRT (3 wkly Pt)	0.4553
RT + HypCS	0.4378
HTRT	0.4371
HTCTRT	0.4249
CTRT(wkly Pt)	0.3625
RT + ACT	0.3507
CTRT + ACT	0.1451

**Fig. 5. Continued**

for LRC, OS, AM, and LM (Fig. E1; available online at <https://doi.org/10.1016/j.ijrobp.2018.09.037>).

In addition, NMA allowed direct, indirect, and mixed estimation of effect measures (OR) among all the 13 interventions within the preceding treatment network for each of the 4 evaluable endpoints (Figs. 2-5).

Long-term loco-regional control

LRC was reported in 49 of the studies in the network, and 5431 of 8197 patients had LRC at the end of their follow-up (Table 2; Fig. 2a). From all 21 pairwise comparative studies, the overall OR was estimated as 1.32 (95% CI, 1.18-1.47; $P < .001$; $I^2 = 50.6$) in favor of the study group (Fig. E1a; available online at <https://doi.org/10.1016/j.ijrobp.2018.09.037>). HTRT versus RT had the highest OR (2.61; 95% CI, 1.55-4.39; $P < .001$). No significant publication bias was evident (Kendall's $\tau = 0.02$; P is not significant; Fig. E2a, available online at <https://doi.org/10.1016/j.ijrobp.2018.09.037>). The forest plots ($I^2 = 0.43$; 95% CrI, 0.24-0.66; Fig. E3a, available online at <https://doi.org/10.1016/j.ijrobp.2018.09.037>) and league tables from NMA showed HTRT to be superior to RT and NACT + RT + ACT (Fig. 2b). In the rankogram based on SUCRA values, the top 3 interventions in order of rank were HTRT, CTRT + ACT, and HTCTRT (Fig. 2c).

Overall survival

Fifty studies reported OS, and 4482 of the 7958 patients were reported to be alive at the end of their follow-up (Table 2; Fig. 3a). An overall OR of 1.19 (95% CI, 1.08-1.31; $P < .001$; $I^2 = 22.9$) from 19 head-to-head

comparisons indicated the efficacy of study groups over control groups (Fig. E1b; available online at <https://doi.org/10.1016/j.ijrobp.2018.09.037>). CTRT(3wkly Pt) versus CTRT(wkly Pt) had the largest OR (3.04; 95% CI, 1.18-7.84; $P = .02$). No significant publication bias was evident (Kendall's $\tau = 0.07$; P is not significant; Fig. E2b, available online at <https://doi.org/10.1016/j.ijrobp.2018.09.037>). In the NMA forest plots ($I^2 = 0.24$; 95% CrI, 0.05-0.45; Fig. E3b, available online at <https://doi.org/10.1016/j.ijrobp.2018.09.037>) and league table, CTRT(3wkly Pt) emerged as the leading intervention for OS (Fig. 3b). This finding was also mirrored in the SUCRA values and rankogram with CTRT(3wkly Pt) as the best option followed by HTCTRT and CTRT(non-Pt; Fig. 3c).

Acute morbidity (grade ≥3)

Reporting of both AM and LM did not follow uniform guidelines because the studies were conducted over a period of 44 years. A majority of the studies (52.7%) reported morbidity using CTCAE and RTOG/EORTC criteria. In 11 studies, no specific details regarding the grading of morbidity were stated. Thus, for AM, 44 studies with 7183 patients were included in the network, with 1710 events (Table 2; Fig. 4a).

The overall OR for pairwise meta-analysis from 19 pairwise comparisons was 1.71 (95% CI, 1.39-2.1; $P < .001$), indicating that the AM was significantly lower in control groups (Fig. E1c; available online at <https://doi.org/10.1016/j.ijrobp.2018.09.037>). The significant heterogeneity ($I^2 = 71.5$; $P < .001$) observed could be a direct reflection of the lack of uniformity in the reporting of AM. Subgroup analysis indicated a significant difference

Table 1 Summary of the studies included in the network meta-analysis and evaluated endpoints for each study

Study	% LACC	% SCC	Comparator group/s A*			Comparator group/s B†			Evaluated endpoints			
			n	Treatment offered	n	Treatment offered			LRC	OS	AM	LM
Shrivastava et al ¹¹	100.0	100.0	426	ERT: 50 Gy/25 fr BRT: LDR 25-30 Gy/1fr; HDR 14-21 Gy/2-3 fr	424	RT: As in control group CTRT: CDDP 40 mg/m ² , q1w × 5			Yes	Yes	Yes	Yes
Zuliani et al ¹²	100.0	100.0	75	ERT: 45 Gy/25 fr BRT: HDR dose NA	72	RT: As in control group CTRT: CDDP 40 mg/m ² , q1w × 5			Yes	Yes	Yes	Yes
Srivastava et al ¹³	91.5	98.4	150	ERT: 50 Gy/25 fr BRT: LDR 35 Gy [§] ; HDR 18 Gy/2-3 fr	155	RT: As in control group CTRT: CDDP 40 mg/m ² , q1w × 5			Yes	Yes	Yes	Yes
Pearcey et al ¹⁴	78.3	100.0	126	ERT: 45 Gy/25 fr BRT: LDR 35 Gy/1 fr; MDR 27 Gy/2 fr; HDR 24 Gy/3 fr	127	RT: As in control group CTRT: CDDP 40 mg/m ² , q1w × 5			Yes	Yes	Yes	Yes
Mitra et al ¹⁵	100.0	97.5	80	ERT: 50 Gy/25 fr BRT: LDR 25 Gy [§]	80	RT: As in control group CTRT: CDDP 30 mg/m ² , q1w × 5			Yes	Yes	Yes	Yes
Roberts et al ¹⁶	86.9	100.0	82	ERT: 40-56 Gy/20-28 fr BRT: LDR 2000-2500 mg Ra-eq-hr	78	RT: As in control group CTRT: MMC 15 mg/m ² , q6w × 2			Yes	Yes	Yes	Yes
Lorvidhaya et al ³⁸	100.0	88.8	242	ERT: 50-66 Gy/25-28 fr BRT: MDR 25-28 Gy/1 fr or 28-35 Gy/2 fr; HDR 28- 30 Gy/4 fr	233	RT: As in control group CTRT: 5-FU 300 mg/d, po, d1-14, 29-42 + MMC 10 mg/m ² , d1, 29			Yes	Yes	Yes	Yes
Coronel et al ¹⁷	84.6	79.5	20	ERT: 50.4 Gy/28 fr BRT: Dose rate: NA, 30- 35 Gy [§] CTRT: CDDP 40 mg/m ² , q1w × 6	19	RT: As in control group CTRT: VNB 60 mg/m ² , q1w × 6			Yes	No [‡]	Yes	Yes
Roy et al ¹⁸	100.0	100.0	24	ERT: 50 Gy/25 fr BRT: HDR 22.5 Gy/3 fr CTRT: CDDP 40 mg/m ² , q1w × 5	30	RT: As in control group CTRT: GEM 150 mg/m ² , q1w × 5			No	No [‡]	Yes	Yes
Negi et al ¹⁹	99.0	94.1	52	ERT: 45 Gy/20 fr BRT: LDR 35 Gy [§]	50	RT: As in control group CTRT: CDDP 40 mg/m ² , d1 + 5-FU 500 mg/m ² , d2-5, q3w × 2			Yes	No [‡]	Yes	Yes
Ke et al ²⁰	100.0	73.2	28	ERT: 50-56 Gy/25-28 fr BRT: HDR 18-30 Gy/3-5 fr	28	RT: As in control group CTRT: CDDP 20 mg/ m ² + DXT 35 mg/m ² , q1w × 5			No	Yes	Yes	No
Tseng et al ²¹	100.0	100.0	62	ERT: 44 Gy/22 fr BRT: HDR 25.8 Gy/6 fr	60	RT: As in control group CTRT: CDDP 50 mg/m ² , d1, VCR 1 mg/m ² , d2; BLM 25 mg/m ² , d2-4, q3w × 4			Yes	Yes	Yes	Yes

(continued on next page)

Table 1 (continued)

Study	% LACC	% SCC	Comparator group/s A*			Comparator group/s B†			Evaluated endpoints			
			n	Treatment offered	n	Treatment offered			LRC	OS	AM	LM
Zeng et al ²²	100.0	95.4	142	ERT: 45-50 Gy/23-25 fr BRT: HDR Tandem 30-36 Gy/4-5 fr or vaginal cylinder 20-36 Gy/2-3 fr	143	RT: As in control group CTRT (3 regimens): BLM 30 mg im + CDDP 20 mg/m ² or PTX 40 mg/m ² + CBP 80 mg/m ² or CDDP 20 mg/m ² + 5-FU 750 mg/m ² , all q1w × 6			No	Yes	Yes	Yes
Roy et al ²³	100.0	96.0	25	ERT: 50 Gy/25 fr BRT: HDR 21 Gy/3 fr CTRT: CDDP 40 mg/m ² , q1w × 5	25	RT: As in control group CTRT: CDDP 40 mg/m ² + GEM 125 mg/m ² , q1w × 5			Yes	Yes	Yes	No
Thakur et al ²⁴	98.8	92.6	42	ERT: 50 Gy/25 fr BRT: LDR 35 Gy/1 fr CTRT: CDDP 40 mg/m ² , q1w × 5	39	RT: As in control group CTRT: CDDP 30 mg/m ² + PTX 50 mg/m ² , q1w × 5			Yes	Yes	Yes	No
Nedovic et al ²⁵	100.0	97.0	64	ERT: 50.4-54 Gy/27-28 fr BRT: HDR 30-34 Gy/5 fr CTRT: CDDP 40 mg/m ² , q1w × 6	70	RT: As in control group CTRT: CDDP 75 mg/m ² , d2 + 5-FU 1 g/m ² , d2-5, q3w × 3			Yes	Yes	Yes	Yes
Veerasarn et al ²⁶	100.0	80.8	235	ERT: 50-66 Gy/25-33 fr BRT: MDR/HDR dose NA CTRT: CBP 100 mg/m ² , q1w × 6	234	RT: As in control group CTRT: CBP 100 mg/m ² (d1) + UFT 225 mg/m ² /d, q1w × 6			No	No [‡]	Yes	Yes
Kim et al ²⁷	100.0	95.5	77	ERT: 41.4-50.4 Gy/23-28 fr BRT: HDR 30-35 Gy/6-7 fr CTRT: CDDP 30 mg/m ² , q1w × 6	78	RT: As in control group CTRT: CDDP 20 mg/m ² + 5-FU 1 g/m ² , d1-5, q4w × 3			Yes	Yes	Yes	Yes
DiSilvestro et al ²⁸	76.8	84.9	194	ERT: 41.4-45 Gy/23-25 fr BRT: LDR 35-43.6 Gy [§] , HDR 27-31.5 Gy/5 fr CTRT: CDDP 40 mg/m ² , q1w × 6	185	RT: As in control group CTRT: CDDP 75 mg/m ² , q2w × 3 + TPZ 220 mg/m ² , d 8, 10, 12, 22, 24, 26			Yes	No [‡]	Yes	No
Wang et al ²⁹	95.6	100.0	37	ERT: 45 Gy/25 fr BRT: HDR 25.8 Gy/6 fr CTRT: CDDP 40 mg/m ² , q1w × 6	37	RT: As in control group CTRT: CDDP 40 mg/m ² + GEM 125 mg/m ² , q1w × 6			Yes	Yes	Yes	No
Ke et al ³⁰	100.0	71.1	26	ERT: 40 Gy/20 fr BRT: HDR 18-30 Gy/3-5 fr CTRT: CDDP 20 mg/m ² , q1w × 4	26	RT: As in control group CTRT: As in control group Endostar: 7.5 mg/m ² /d for 4 weeks			No	Yes	Yes	No
Dueñas-González et al ³¹	100.0	93.8	256	ERT: 50.4 Gy/28 fr BRT: LDR/MDR 30-35 Gy [§] CTRT: CDDP 40 mg/m ² , q1w × 6	259	RT: As in control group CTRT: CDDP 40 mg/m ² + GEM 125 mg/m ² , q1w × 6 ACT: CDDP 50 mg/m ² , d1 + GEM 1 g/m ² (d 1, 8), q3w × 2			Yes	No [‡]	No	Yes
Wang et al ³⁹	100.0	100.0	77	ERT: 46-50 Gy/23-25 fr BRT: 40-48 Gy/10-12 fr, dose rate NA ACT: CDDP 40 mg, d1-3 + DXT 60 mg/m ² , d1, q3w × 3	79	RT: As in control group CTRT: CDDP 40 mg, q1w × 5 ACT: As in control group			Yes	Yes	No	No

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Table 1 (continued)

Study	% LACC	% SCC	n	Comparator group/s A*		Comparator group/s B†		Evaluated endpoints			
					Treatment offered		Treatment offered	LRC	OS	AM	LM
Franckena et al ⁵⁵	100.0	85.1	56	ERT: 46-50.4 Gy/23-28 fr with para-aortic RT in 48% patients BRT: MDR 20-30 Gy/1 fr, HDR 17 Gy/2 fr or 18 Gy/ 3 fr		58	RT: As in control group, para-aortic RT in 43% patients HT: 42°C for 60 mins, after RT (interval NA), q1w × 6	Yes	Yes	Yes	Yes
Harima et al ⁵⁶	100.0	87.5	20	ERT: 52.2 Gy/29 fr BRT: HDR 30 Gy/4 fr		20	RT: As in control group HT: Average 40.6°C for 60 min, after RT (within 30 min), q1w × 3	Yes	Yes	Yes	Yes
Sharma et al ^{57,58}	94.0	100.0	25	ERT: 45 Gy/20 fr BRT: LDR 35 Gy/1 fr		25	RT: As in control group Intraluminal HT: 42°-43°C for 30 min, before RT (within 30 min), thrice a week × 4	Yes	Yes	Yes	Yes
Datta et al ⁵⁹	100.0	100.0	26	ERT: 60-70 Gy/30-35 fr BRT: None		27	RT: As in control group HT: 42.5°C for 35-50 min, before RT (immediate), twice a week × 7	Yes	Yes	Yes	Yes
Lutgens et al ⁶⁰	69.1	85.7	42	ERT: 50 Gy/25 fr BRT: LDR 32 Gy/1-2 fr; MDR 29 Gy/1-2 fr; HDR 21 Gy/3 fr CTRT: CDDP 40 mg/m ² , q1w × 5		42	RT: As in control group HT: Temperature NA, for 60 min, after RT (within 1-4 h), once a week × 5	Yes	Yes	Yes	Yes
Harima et al ⁶¹	99.0	89.1	50	ERT: ~50 Gy/25-28 fr BRT: HDR 20-30 Gy/5-6 fr CTRT: CDDP 30-40 mg/m ² , q1w × 3-5		51	CTRT: As in control group HT: Average 41.1°C for 60 min, after RT (within 30 min), once per week × 4-6	Yes	Yes	Yes	Yes
Dische et al ⁴⁶	100.0	80.9	92	ERT: 50 Gy/25 fr BRT: LDR 20 Gy [§] , HDR dose: **		91	RT: As in control group HypCS: PIMO 750 mg/m ² / d with ERT	Yes	Yes	Yes	No
Dobrowsky et al ⁴⁵	100.0	100.0	173	ERT: 45-50.8 Gy/20-28 fr BRT: LDR/HDR with TD of 70 Gy to point A in 1-3 fr [§]		160	RT: As in control group HypCS: SANA 0.6 mg/m ² , d 1, 3, 5, weekly with ERT	Yes	Yes	Yes	Yes
Grigsby et al ⁴²	100.0	100.0	61	ERT: 56 Gy/28-31 fr (para-aortic: 45-46 Gy) [§] [#] BRT: LDR 34 Gy/1-2 fr		59	RT: As in control group HypCS: MISO 400 mg/m ² / d with ERT (total 12 g/m ²)	Yes	Yes	Yes	Yes
Overgaard et al ⁴³	100.0	100.0	167	ERT: 40-65 Gy [§] BRT: Various dose rates [#]		164	RT: As in control group HypCS: MISO total 12 g/m ² in 6 weeks with ERT ± BRT	Yes	Yes	No	No
Dische et al ⁴⁴	100.0	100.0	71	ERT: 42 Gy/20 fr BRT: LDR 43 Gy/2 fr or 35 Gy/1 fr; HDR 17 Gy/2 fr		68	RT: As in control group HypCS: MISO 500 mg/m ² / d with ERT ± BRT (total 11-13 g/m ²)	Yes	Yes	Yes	No
Chan et al ⁴¹	79.5	87.7	34	ERT: 45 Gy/20 fr BRT: LDR 40 Gy [§]		39	RT: As in control group HypCS: MISO 450 mg/m ² / d with RT, d 1-5, q1w × 4	Yes	Yes	No	Yes
Dische et al ⁴⁷	100	93.5	42	ERT: 5500 R/27 fr BRT: 1 × 1900 R [§] Breathing air during ERT and BRT		45	RT: As in control group HBO: 3 atmosphere, 15 min pre-RT	Yes	Yes	No	Yes
Watson et al ⁴⁸	100	NA	82	ERT: 4250-4500 rad/20 fr BRT: 3500 rad/1 fr		80	RT: As in control group HBO: details NA	Yes	Yes	No	No

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Table 1 (continued)

Study	% LACC	% SCC	Comparator group/s A*			Comparator group/s B†			Evaluated endpoints			
			n	Treatment offered	n	Treatment offered			LRC	OS	AM	LM
Okamura et al ^{49,50}	92.8	98	96	ERT and BRT: Variable among institutions [#]	99	RT: As in control group RT Imm: SPG 40 mg IM, 1-2 × per week with RT (as long as possible)			No	Yes	No	No
Okawa et al ⁵¹	100.0	100.0	23	ERT: Mean 51.4 Gy in 1.8-2 Gy/fr BRT: Mean 27 Gy [§]	26	ERT: Mean 51.3 Gy in 1.8-2 Gy/fr BRT: Mean 29.2 Gy [§] RT Imm: LC9018 0.2 mg/wk SC or 0.4-0.5 mg/wk ID in 1-2 × doses, 2 weeks before to 4 weeks after RT			No	Yes	No	No
Yazigi et al ⁵²	100.0	100.0	38	ERT: 50.4 Gy/28 fr (+parametrium boost, TD = 60-70 Gy ^{§, **} BRT: LDR 3000-4000 mg-Ra-eq	36	RT: As in control group RTImm: INF α-2b 3M units/m ² sc, daily with ERT			Yes	Yes	No	No
Veerasarn et al ⁵³	100.0	100.0	23	ERT: 40-50 Gy/20-25 fr BRT: LDR, dose NA/1 fr	22	RT: As in control group RT Imm: INF α-2b 3M units/m ² SC, 3×/wk + 13-CIS-RA 1 mg/kg/d, PO with ERT			Yes	Yes	Yes	No
Basu et al ⁵⁴	100.0	92.3	105	ERT: 50 Gy/25 fr BRT: HDR 21 Gy/3 fr CTRT: CDDP 40 mg/m ² , q1 × 5	104	RT: As in control group RT Imm: INF α-2b 3M units/m ² , SC, 3×/wk for 4 weeks + 13-CIS-RA 40 mg/d, PO for 30 days			Yes	Yes	Yes	Yes
Kumar et al ¹	100.0	100.0	88	ERT: 50 Gy/27 fr [#] BRT: LDR/MDR 30 Gy [§]	89	RT: As in control group, 14 d after NACT NACT: CDDP 50 mg/m ² , d 1 + BLM 15 mg, d 1 + IF 1 g/m ² , d 1-5, q3w × 2			Yes	Yes	No	No
Kumar et al ²	100.0	100.0	36	ERT: 50 Gy/27 fr [#] BRT: LDR/MDR 30 Gy [§]	36	RT: As in control group, 14d after NACT NACT: CDDP 50 mg/m ² , d 1 + BLM 15 mg, d 1 + IF 1 g/m ² , d 1-5, q3w × 3			No	Yes	No	No
Sundfor et al ³	100.0	100.0	47	ERT: 64.8 Gy/36 fr BRT: None	47	RT: As in control group, 14d after NACT NACT: CDDP 100 mg/m ² , d 1 + 5-FU 1 g/m ² , d 1-5, q3w × 3			Yes	Yes	Yes	Yes
Herod et al ⁴	92.4	93.0	86	ERT: NA BRT: NA	86	RT: As in control group, time interval to CT; NA NACT: CDDP 50 mg/m ² + BLM 30 mg + IF 5 g/m ² , qxw NA × 2-3			No	Yes	No	No
Tabata et al ⁵	100.0	100.0	29	ERT: 50 Gy/25 fr BRT: HDR 40 Gy [§]	32	RT: As in control group, time interval to CT; NA NACT: CDDP 10 mg/m ² (d 1-7), BLM 5 mg/kg, d 1-7 + VCR 0.7 mg/m ² , d 7 + MMC 7 mg/m ² , d 7, q4w × 3			Yes	Yes	Yes	No

(continued on next page)

Table 1 (continued)

Study	% LACC	% SCC	n	Comparator group/s A*		Comparator group/s B†		Evaluated endpoints			
					Treatment offered		Treatment offered	LRC	OS	AM	LM
Tattersall et al ⁶	100.0	85.9	37	ERT: 40-55 Gy/4-5 weeks [§] BRT: Details NA		34	RT: As in control group, during 3rd NACT cycle NACT: CDDP 50 mg/m ² , d 1 + BLM 15 mg, d 1,8,15 IM + VBL 4 mg/m ² , d 1, q3w × 3	Yes	Yes	Yes	Yes
Tattersall et al ⁷	100.0	90.8	131	ERT: 40-55 Gy/4-5 weeks [§] BRT: 30-35 Gy [§] , dose rate NA		129	RT: As in control group, time interval different [#] NACT: CDDP 60 mg/m ² + EPR 110 mg/m ² , q3w × 3	Yes	No [†]	No	No
Symonds et al ⁸	100.0	94.6	100	ERT: 40-43 Gy/20 fr BRT: MDR/LDR 24-33.75 Gy [§]		104	RT: As in control group, 6 weeks after initiation of NACT NACT: CDDP 50 mg/m ² + MTX 100 mg/m ² , q2w × 3	Yes	Yes	No	No
Sardi et al ⁹	100.0	100.0	53	ERT: 50-60 Gy in 1.8-2 Gy/fr BRT: 25-30 Gy/1-2 fr, dose rate NA		52	RT: As in control group NACT: CDDP 50 mg/m ² , d 1 + BLM 25 mg/m ² , d 1-3 + VCR 1 mg/m ² , d 1, q10d × 3	Yes	Yes	No	No
Sardi et al ¹⁰	100.0	100.0	72	ERT: 50 Gy in 1.8-2 Gy/fr BRT: 35-40 Gy/1-2 fr, dose rate NA		71	RT: As in control group NACT: CDDP 50 mg/m ² , d 1 + BLM 25 mg/m ² , d 1-3 + VCR 1 mg/m ² , d 1, q10d × 3	Yes	Yes	Yes	Yes
Chiara et al ⁴⁰	100.0	85.2	29	ERT: 40 Gy/20 fr + parametrial boost 15-20 Gy after BRT BRT: LDR 40 Gy [§]		32	RT: As in control group, time interval to CT NA NACT: CDDP 60 mg/m ² , q15d × 2 ACT: CDDP 60 mg/m ² , q15d × 4	Yes	Yes	Yes	Yes
Li et al ³²	100.0	100.0	96	ERT: 46 Gy/23 fr BRT: HDR 10 Gy/2 fr		96	RT: As in control group CTRT: CDDP 20 mg/m ² , d 1-5, q3w × 5	No	Yes	Yes	No
Garipağaoğlu et al ³³	100.0	100.0	22	ERT: 46-50 Gy/23-25 fr BRT: HDR 10 Gy/2 fr		22	RT: As in control group CTRT: CDDP 20 mg/m ² , d 1-6, q3w × 2	Yes	Yes	Yes	No
Singh et al ³⁴	100.0	100.0	41	ERT: 50 Gy/25 fr BRT: LDR/MDR 23-25 Gy/1 fr		43	RT: As in control group CTRT: CDDP 16 mg/m ² , d 1-5, q3w × 2 during ERT + CDDP 40 mg/m ² (1×) during BRT	Yes	Yes	Yes	Yes
Ryu et al ³⁵	100.0	89.4	51	ERT: 50-50.4 Gy/25-28 fr + 5-10 Gy [§] ERT boost to parametrium)** BRT: LDR 30-40 Gy/1-2 fr CTRT: CDDP 40 mg/m ² , q1w × 6		53	RT: As in control group CTRT: CDDP 75 mg/m ² , q3w × 3	Yes	Yes	Yes	No
Jain et al ³⁶	100.0		25	ERT: 46 Gy/20 fr BRT: HDR 15-22.5 Gy/2-3 fr CTRT: CDDP 30 mg/m ² , q1w × 6		25	RT: As in control group CTRT: CDDP 100 mg/m ² , q3w × 3	Yes	Yes	Yes	Yes

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Table 1 (continued)

Study	% LACC	% SCC	Comparator group/s A*			Comparator group/s B†			Evaluated endpoints			
			n	Treatment offered	n	Treatment offered	LRC	OS	AM	LM		
Pathy et al ³⁷	100.0	98.0	25	ERT: 50 Gy/27 fr BRT: HDR 21 Gy/3 fr CTRT: CDDP 40 mg/m ² , q1w × 6	25	RT: As in control group CTRT: CDDP 20 mg/m ² , d 1-5, q3w × 2	Yes	No [‡]	Yes	No		

Abbreviations: 5-FU = 5-fluorouracil; 13-CIS-RA = 13-cis-retinoic acid; ACT = adjuvant CT; AM = acute morbidity; BLM = bleomycin; BRT = brachytherapy with doses prescribed to point A; CBP = carboplatin; CT = chemotherapy; CTRT = concurrent chemoradiotherapy; CDDP = cisplatin; DXT = docetaxel; EPR = epirubicin; ERT = external radiation therapy; fr = fractions; HBO = hyperbaric oxygen; HDR = high-dose-rate; HT = hyperthermia; HTRT = HT and RT; HTCTRT = HT and CTRT; HypCS = hypoxic cell sensitizer; ICRT = intracavitary brachytherapy; ID = intradermally; IF = ifosfamide; IM = intramuscular; INF = interferon; IV = intravenous; LACC = locally advanced cancer cervix, stages IIA-IVA; LDR = low-dose-rate; LM = late morbidity; LRC = long-term loco-regional control; MDR = medium-dose-rate; MISO = misonidazole; MMC = mitomycin-C; MTX = methotrexate; NA = not available; NACT = neoadjuvant CT; ORNI = ornidazole; OS = overall survival; PIMO = pimonidazole; PO = per oral; PTX = paclitaxel; RT = radiation therapy and includes ERT and BRT as stated; RT Imm = Immunomodulator with RT; SANA = sanazole; SC = subcutaneously; SCC = squamous cell cancer; SPG = sизofиran; TD = total dose; TPZ = tirapazamine; UFT = tegafur-uracil; VNB = vinorelbine; VCR = vincristine.

CT schedule described as: drug, dose (mg/m²), application q(x) = every x weeks; route IV unless mentioned, x = number of cycles.

* Usually control group.

† Usually study groups as stated in most trials.

‡ Exact numbers of patients alive not stated.

§ Specific fractions not stated by the author.

|| Not included in the main network meta-analysis, as the study was the only trial including Endostar in study group and as a maximum of 50 studies could be included in NetMetaXL software, but included in sensitivity analysis with year of publication.

¶ If paraaortic lymph node metastases were present.

Please check article text for details.

** Based on physician or institutional choice.

between the various subgroups of interventions ($Q = 78.16$; degrees of freedom = 18; $P < .001$). No significant publication bias was observed (Kendall's $\tau = 0.01$; P is not significant; Fig. E2c, available online at

<https://doi.org/10.1016/j.ijrobp.2018.09.037>). The NMA league table and forest plots ($I^2 = 0.73$; 95% CrI, 0.44–1.13) were plotted, and RT + ACT was scored as the best option in the rankogram (Figs. 4b and 4c; Fig. E3c,

Table 2 Intervention characteristics of the trials included in the network meta-analysis for each of the evaluated endpoints (trials included the treatment interventions either as their control group or study groups)

Treatment	Long-term locoregional response			Acute morbidity (grade ≥3)			Late morbidity (grade ≥3)		
	Trials	Events*/Patients	Overall survival	Trials	Events†/Patients	Trials	Events†/Patients	Trials	Events†/Patients
RT	34	1646/2825	39	1615/3153	28	438/2360	23	139/2096	
CTRT (wkly Pt)	19	1316/1861	15	780/1366	21	707/1888	15	134/1716	
CTRT (non-Pt)	3	255/314	2	252/311	4	51/345	4	7/360	
CTRT (Pt+)	8	407/543	8	349/479	12	314/968	6	52/635	
CTRT + ACT	3	420/543	2	199/309	1	9/210	2	22/452	
RT + ACT	2	180/286	2	187/298	1	0/204	1	10/204	
HTRT	5	118/169	5	120/172	5	4/172	5	16/167	
HTCTRT	1	44/51	1	39/51	1	25/51	1	8/51	
RT + HypCS	8	412/687	8	333/709	4	44/378	4	11/295	
RT + Imm	3	111/162	5	157/287	2	13/126	1	14/104	
NACT + RT	8	369/557	9	244/552	4	29/185	3	27/153	
NACT + RT + ACT	1	10/31	1	23/32	1	11/32	1	1/32	
CTRT (3wkly Pt)	5	143/168	5	184/239	6	65/264	2	0/68	
Total	5431/8197			4482/7958			1710/7183		441/6333

Abbreviations: ACT = adjuvant chemotherapy; CTRT = concurrent chemoradiotherapy; HTRT = hyperthermia and radiation therapy; HTCTRT = hyperthermia and chemoradiotherapy; HypCS = hypoxic cell sensitizer; Imm = immunotherapy; NACT = neoadjuvant chemotherapy; non-Pt = noncisplatin as single agent; Pt = cisplatin as single agent; Pt+ = cisplatin with combination chemotherapy; RT = radiation therapy alone.

* Patients with locoregional disease control at the end of follow-up.

† Patients alive at the end of follow-up.

‡ Patients with acute or late morbidity (grade ≥3).

available online at <https://doi.org/10.1016/j.ijrobp.2018.09.037>; this was followed by RT and HTRT. CTRT(Pt +) had the highest AM.

Late morbidity (grade ≥3)

LM was reported in 33 studies, and 441 of the 6333 patients in the entire network had grade ≥ 3 LM (Table 2; Fig. 5a). An overall OR of 1.12 (95% CI, 0.93-1.35; $P = .223$; $I^2 = 0.00$) from 17 head-to-head comparisons indicated no significant differences in LM between both control and study groups (Fig. E1d; available online at <https://doi.org/10.1016/j.ijrobp.2018.09.037>). No significant publication bias was evident (Kendall's $\tau = -0.14$; P is not significant; Fig. E2d, available online at <https://doi.org/10.1016/j.ijrobp.2018.09.037>). NACT + RT + ACT was placed at the top of the league table with least LM (Fig. 5b). Corresponding NMA forest plots ($I^2 = 0.16$; 95% CrI, 0.00-0.66) are given in Figure E3d (available online at <https://doi.org/10.1016/j.ijrobp.2018.09.037>). The SUCRA values ranked NACT + RT + ACT, RT + Imm, and CTRT(non-Pt) as the 3 best interventions with the least LM (Fig. 5c).

Cumulative ranking based on SUCRA values of all endpoints and cluster analysis

The rankings of various interventions were different for each of the 4 endpoints. In a clinical context, although higher LRC and OS would certainly be desirable, a high prevalence of AM and LM would impose additional burden, especially in low-resource settings. For an overall assessment of the best therapeutic option, a cumulative SUCRA score was derived by summing the individual SUCRA values of each endpoint for all 13 interventions. Thus, the 3 best options in order of ranking were HTRT, HTCTRT, and CTRT(3wkly Pt) (Fig. 6).

Subsequently the 2-step cluster analysis based on the SUCRA values of LRC, OS, AM, and LM placed these 3 interventions in a distinct cluster, further reinforcing the shortlisting of these 3 as the best options (Fig. 7). The mean SUCRA values for this cluster for the 4 endpoints were 0.765 for LRC (SD, ± 0.07), 0.787 for OS (SD, ± 0.10), 0.580 for AM (SD, ± 0.15), and 0.439 for LM (SD, ± 0.01).

Inconsistency evaluation

The posterior summaries from the random effects consistency NMA model and inconsistency models were estimated and are summarized in Table E3 (available online at <https://doi.org/10.1016/j.ijrobp.2018.09.037>) and plots shown in Figure E4a to E4d (available online at <https://doi.org/10.1016/j.ijrobp.2018.09.037>). The differences in DIC values between the consistency and inconsistency models were 6.24, 2.77, 4.43, and 6.76 for LRC, OS, AM, and LM, respectively. The totresdev was higher in the inconsistency model for all endpoints except OS (-0.30), whereas SD

was higher in all except LRC (-0.02). Taking into consideration the DIC, totresdev, and SD for each endpoints, significant inconsistency between direct and indirect estimates could be potentially ruled out.

Risk of bias assessment

The risk of bias was assessed for each of the 59 trials per the Cochrane Collaboration tool.⁷⁸ Because all studies were randomized, there was no selection bias. The criterion of “blinding of the participants and personnel” was not applicable for these patients and hence was ignored. The nature of interventions might not always allow blinding of patients, personnel, and outcome assessors. Low risk of bias for “incomplete outcome data,” “selective reporting,” and “other bias” categories was judged for 72.9%, 62.7%, and 69.5% of the studies, respectively (Fig. E5; available online at <https://doi.org/10.1016/j.ijrobp.2018.09.037>).

Sensitivity analysis

Sensitivity analysis was carried out for trials with low risk of selective bias reporting (37 of 59) and trials published during or after 2004 (the median value for all publications) (32 of 59). SUCRA values and rankings were generated for each endpoint for the 2 subsets. Scatter plots of the SUCRA values for both subsets consistently show that the HTRT, HTCTRT, and CTRT(3wkly Pt) were best for LRC and OS (Fig. 8). A comprehensive ranking based on all 4 endpoints ranked HTRT, CTRT(3wkly Pt), and HTCTRT as the best for trials with low risk of selective bias reporting. For those published during or after 2004, the rankings were same as those with all 59 trials—that is, HTRT, HTCTRT, and CTRT(3wkly Pt). Thus, the sensitivity analysis consistently maintained the superiority of these 3 interventions.

Assessment of GRADE and certainty of confidence

Assessments for certainty of confidence for each of the endpoints are summarized in Tables E4 to E7 (available online at <https://doi.org/10.1016/j.ijrobp.2018.09.037>). The certainty of confidence for all endpoints varied from “high” to “moderate” with none in “low” or “very low” categories. For LRC, the confidence for mixed estimates was high in 4.7% and moderate in 95.2%. All indirect estimates were in the moderate category. For OS, the confidence of evidence for mixed estimates was high in 10.5% and moderate in 89.5%, whereas for indirect estimates, 5.1% were high and 94.9% were moderate. For AM, 15% and 85% were high and moderate for mixed estimates, whereas 5.2% and 94.8% were high and moderate for indirect estimates, respectively. In LM, high and moderate confidence was noted in 22.2% and 77.8% for mixed and 2.1% and 97.9% for indirect estimates, respectively.

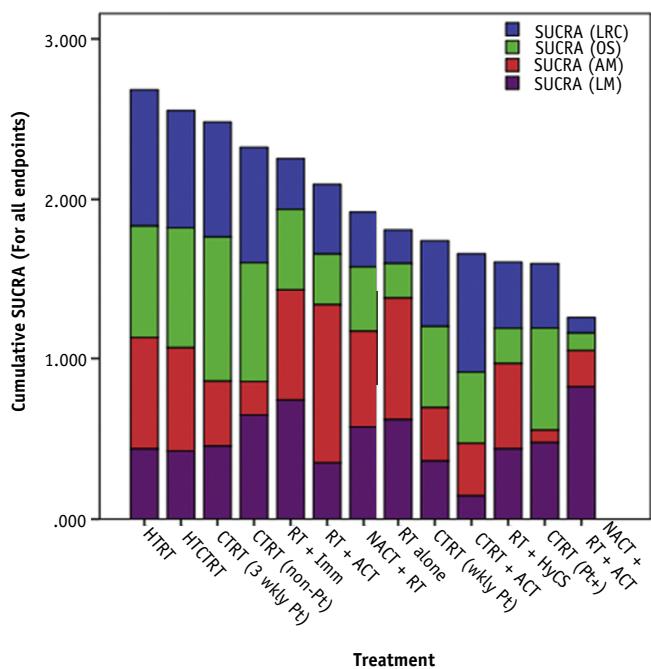


Fig. 6. Surface under the cumulative ranking curve (SUCRA) values for endpoints from all studies (1974–2018). Abbreviations: ACT = adjuvant chemotherapy; AM = acute morbidity (grade ≥ 3); CTRT = concurrent chemoradiotherapy; HTCTRT = hyperthermia and chemoradiotherapy; HTRT = hyperthermia and radiation therapy; HypCS = hypoxic cell sensitizer; Imm = immunotherapy; LM = late morbidity (grade ≥ 3); LRC = loco-regional control; NACT = neoadjuvant chemotherapy; OS = overall survival; Pt = cisplatin as single agent; non-Pt = noncisplatin as single agent; Pt+ = cisplatin with combination chemotherapy; RT = radiation therapy alone.

Discussion

Globally, cervix cancer is the fourth commonest cancer in the women; 87% of cases occur in less-developed countries, with almost 10-fold greater mortality compared with patients in the developed regions.⁹⁰ Late clinical presentation owing to inadequate screening measures could be a contributory factor, in which case surgical options are usually ruled out and management decisions are often centered on RT combined with other modalities. The present NMA represents the outcomes in LACC in these regions: 55.9% of the studies contributing 63.3% of the total patients included in this study are from low- and middle-income countries. Thus, of the nonsurgical options evaluated in LACC, it is important to analyze their outcomes systematically to arrive at the optimal treatment strategy, both in terms of efficacy and safety.

Systematic reviews and meta-analyses have been recognized to provide level I evidence for clinical practice, and a number of pairwise comparative meta-analyses have been reported for study interventions versus control.^{91–101}

However the comparative effect measures from pairwise meta-analyses are limited to only 2 treatment options. NMA, with its ability to synthesize data from direct pairwise meta-analysis, multiarm RCTs, and indirect comparisons, provides an opportunity to render a comprehensive assessment of the various therapeutic options.^{64–66,68,74} Through indirect measures, NMA enables estimation of comparative efficacy for interventions that have not been investigated in direct head-to-head randomized trials. Furthermore, the objective ranking of these interventions by NMA is compelling. Thus, NMA offers a global appraisal of all interventions, with higher precision and larger sample sizes, and is thus accepted by decision-making bodies as the highest level of clinical evidence.^{67,69}

Of all the nonoperative therapeutic interventions evaluated, HTRT, HTCTRT, and CTRT(3 wkly Pt) were ranked highest in terms of comprehensive efficacy and safety, as evidenced by their SUCRA values. The ranking of the interventions for the individual endpoints was also reconfirmed using R program, a frequentist method compared with the Bayesian approach in NetMetaXL.¹⁰² The rankings based on P scores obtained using R were in good agreement with the SUCRA values from NetMetaXL for all 4 endpoints (Fig. E6; available online at <https://doi.org/10.1016/j.ijrobp.2018.09.037>). In both, the best rankings for LRC, OS, and AM were HTRT, CTRT(3wkly Pt), and RT + ACT, respectively. For LM, there was a mutual interchange of the ranks of RT + Imm and NACT + RT + ACT, the former being ranked best based on P score and latter being based on SUCRA.

A 2-step cluster analysis was performed as an exploratory exercise to identify the therapeutic interventions that could be grouped homogenously based on the SUCRA values of the 4 endpoints obtained by NMA. Six clusters were chosen to obtain a good cluster quality, as evident on the silhouette measure of cohesion and separation between these clusters (Fig. 7a). The cluster comparisons for the first 5 clusters with respect to the SUCRA values of each of the 4 endpoints are shown in Figure 7b. As is evident from the SUCRA values, the top-ranked treatment varied depending on the endpoint evaluated (Figs. 2c, 3c, 4c, 5c). Summation of the individual SUCRA values for each of the 4 endpoints shows that HTRT, HTCTRT, and CTRT (3 wkly Pt) are the 3 top-ranked modalities in LACC (Fig. 6). Thus, the cluster analysis further validated that these 3 modalities can be considered a homogenous group. Moreover, because these 3 treatment approaches had not been subjected to a head-to-head comparison in a randomized setting, the grouping obtained by the cluster analysis endorsed that these interventions should be considered in a future phase 3 randomized trial. Moreover, in the sensitivity analysis conducted for publications with low risk of selective reporting bias and those published in 2004 and later, the 3 interventions of HTRT, HTCTRT, and CTRT (3wkly Pt) maintained their superiority in terms of efficacy and safety in LACC (Fig. 8). Thus, the 3 options consistently score over the other treatment strategies in LACC.

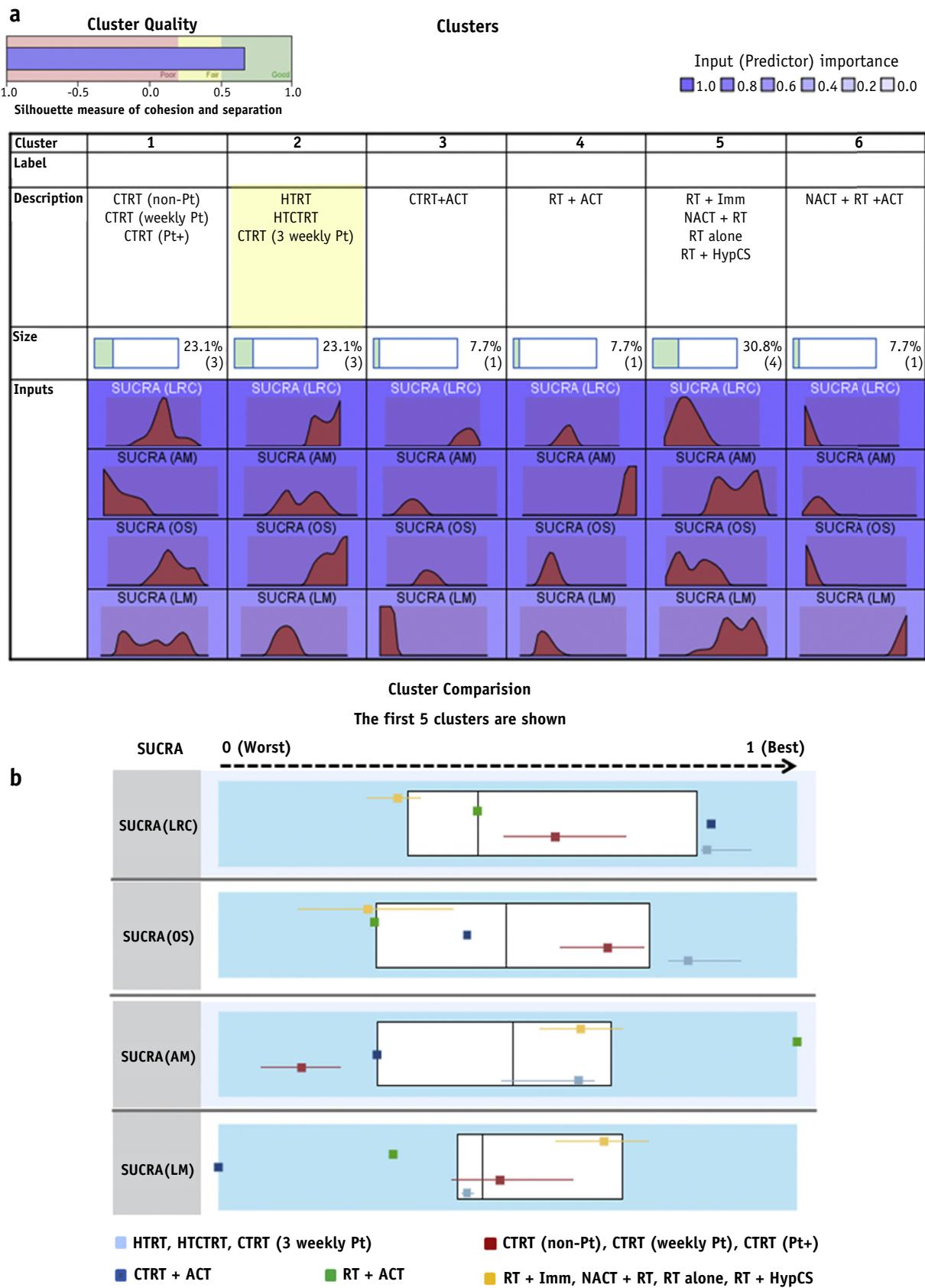


Fig. 7. Two-step cluster analysis for treatment interventions for all studies based on the SUCRA values of endpoints. (a) Six clusters are shown with HTRT, HTCTRT, and CTRT (3 weekly) grouped in a single cluster. (b) Cluster comparison of the first 5 clusters each of the 4 endpoints. The overall median and interquartile range of the SUCRA value of each endpoint is

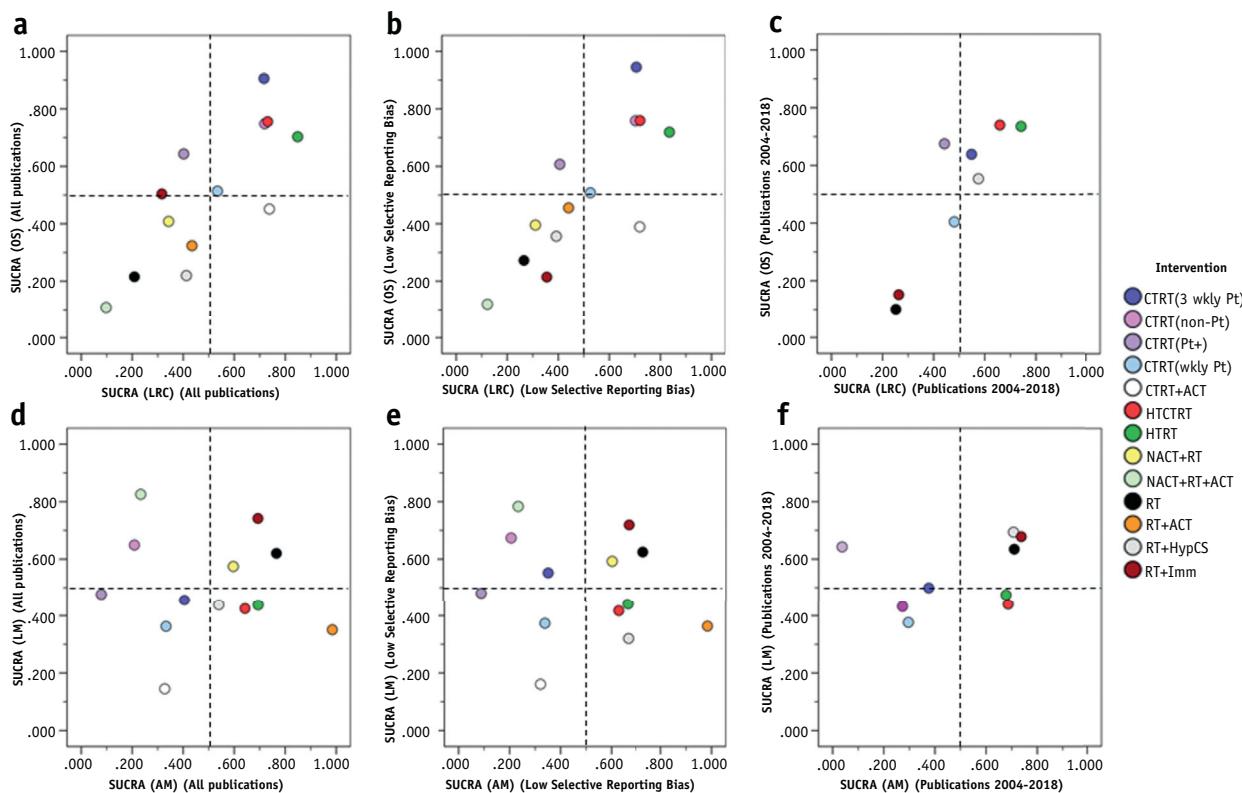


Fig. 8. Sensitivity analysis with cumulative ranking curve (SUCRA) values. (a, d) All publications (1974-2018). (b, e) Trials with only low bias for selective reporting. (c, f) Trials published during 2004 to 2018. Upper panels (a, b, c) indicate locoregional control (LRC) and overall survival (OS), and lower panels (d, e, f) indicate acute (AM) and late (LM) morbidities. Abbreviations: ACT = adjuvant chemotherapy; CTRT = concurrent chemoradiotherapy; HTCTRT = hyperthermia and chemoradiotherapy; HTRT = hyperthermia and radiation therapy; HypCS = hypoxic cell sensitizer; Imm = immunotherapy; NACT = neoadjuvant chemotherapy; Pt = cisplatin as single agent; non-Pt = noncisplatin as single agent; Pt+ = cisplatin with combination chemotherapy; RT = radiation therapy alone.

Hyperthermia at 39°C to 43°C displays selective cytotoxicity toward radioresistant hypoxic cells and S-phase cells and reduces radiation-induced DNA repair.¹⁰³ Recent developments based on the thermo-radiobiologic rationale of HT indicate it to be a potent radiosensitizer and chemosensitizer.¹⁰⁴⁻¹⁰⁷ This has been further corroborated through positive clinical outcomes in various tumor sites using HTRT or HTCTRT approaches.¹⁰⁸⁻¹¹² Lately, in vitro and in vivo studies also indicate a unique immunomodulatory feature of HT, especially when combined with RT.^{113,114} Furthermore, human papillomavirus-induced cervix cancer has been reported to be sensitive individually both to RT and HT.^{115,116} This adds yet another unique dimension to the effectiveness of HTRT in cervix cancer.

The technological advances in hardware and software over the last decade have led to safer locoregional HT delivery, thermal treatment planning, thermal dose monitoring through noninvasive thermometry, and online adaptive temperature modulation.^{105,117-121} Temperature monitoring during HT in cervix cancer and the adjacent normal organs of bladder and rectum can be performed effectively through noninvasive temperature sensors. Effectiveness of HTRT over RT was also reported in an earlier pairwise meta-analysis in LACC.⁹⁴ Furthermore, in a limited NMA involving RT, HTRT, HTCTRT, and CTRT, it was also evident that HTCTRT or HTRT could achieve a favorable outcome compared with CTRT in LACC.¹¹¹

represented in the boxplots. Overlaid on these boxplots is the median and interquartile range for each cluster with respect to the SUCRA value of the specified endpoint. Abbreviations: ACT = adjuvant chemotherapy; CTRT = concurrent chemoradiotherapy; HTCTRT = hyperthermia and chemoradiotherapy; HTRT = hyperthermia and radiation therapy; HypCS = hypoxic cell sensitizer; Imm = immunotherapy; NACT = neoadjuvant chemotherapy; Pt = cisplatin as single agent; non-Pt = noncisplatin as single agent; Pt+ = cisplatin with combination chemotherapy; RT = radiation therapy alone.

The Cochrane meta-analysis for CTRT versus RT reported a stage-dependent advantage of CTRT, with benefit decreasing as the stage of the disease increased.⁹² CTRT has been the preferred treatment option in LACC, and a number of chemotherapeutic options have been explored. In a recently published meta-analysis of CTRT versus RT in LACC treated with cisplatin alone, cisplatin-based combination CT, or mitomycin-C based CT, CTRT significantly improved the LRC and OS over RT alone, but at a cost of 10.4% higher incidence of grade 3/4 acute toxicities ($P < .001$). Subgroup analysis and metaregression did not reveal any significant difference in outcomes among the diverse CTRT regimens.⁹⁵

The potential benefit of weekly versus 3-weekly cisplatin-based concurrent CTRT in LACC has also been investigated in 2 meta-analyses,^{122,123} and a retrospective single-institution review.¹²⁴ The conclusions from these studies are blurred because of the inclusion of both single-agent cisplatin and mostly combination regimes in a tri-weekly arm and the inclusion of retrospective studies with adjuvant CTRT in patients postoperatively.^{122,123} The safety and efficacy of CTRT(3wkly Pt) over CTRT(wkly Pt) has been demonstrated in 3 randomized trials in LACC.³⁵⁻³⁷ A phase 3 randomized trial targeting 590 patients with LACC is currently underway to compare weekly versus triweekly cisplatin-based CTRT.¹²⁵ The outcome is likely to be reported after 2023. However, recently a phase 3 RCT reported a significant advantage of 3-weekly over weekly cisplatin-based CTRT in LRC in locally advanced head and neck cancers.¹²⁶ Thus, these reports and results of the present NMA suggest a distinct advantage of CTRT(3wkly Pt) over CTRT(wkly Pt).

A number of conceptual and technical challenges require consideration to interpret the outcome of an NMA.^{64,66,72} The transitivity and consistency assumptions need to be satisfied. The transitivity assumption implies that the various interventions and patient populations in all studies are comparable with respect to the characteristics that could potentially influence the relative effects. For transitivity to hold, the direct comparisons from included studies should be sufficiently similar in all respects apart from the therapeutic interventions.^{64,66,72,89} To fulfill transitivity assumptions, the inclusion criteria were limited to LACC (mean \pm SD, $97.4\% \pm 6.5\%$). As surgical interventions and altered RT dose-fractionation schedules could be potential effect modifiers, these were considered exclusion criteria. Furthermore, it was ensured that the same RT schedules had been followed in both arms of the individual trials. In studies with multiple treatment arms, only the nonoperative group was considered.^{9,10}

Consistency is the statistical agreement between the direct and indirect comparisons for every pairwise comparison in the closed loop of a network. Inconsistency occurs when these are divergent.^{64,66,68,71,72,89} Consistency was tested for all endpoints for both heterogeneity and incoherence using Confidence in Network Meta-Analysis.

There were no major concerns regarding consistency in LRC, OS, and LM. In only 3 estimates of AM (mixed evidence for CTRT(Pt+) vs CTRT(wkly Pt), CTRT(wkly Pt) vs RT) and indirect evidence for CTRT(Pt+) vs RT + HypCS was a major concern for heterogeneity noted (Tables E4-E7; available online at <https://doi.org/10.1016/j.ijrobp.2018.09.037>). There was no concern for incoherence in any estimates for AM. The observed heterogeneity in the 3 estimates could be the result of differences in the use of different guidelines for reporting of AM, as described previously. Furthermore, although different combinations of CT, HypCSs (both chemical and hyperbaric oxygen), and immunomodulatory agents were used in individual trials, these were grouped in their respective groups of CTRT(Pt+), RT + HypCS, and RT + Imm to arrive at a meaningful conclusion.

One of the concerns regarding the confidence of NMA estimates was the imprecision regarding the GRADE recommendations (Tables E4-E7; available online at <https://doi.org/10.1016/j.ijrobp.2018.09.037>).⁷⁹ As per the GRADE recommendations, imprecision is scored if the studies include relatively few patients and few events, thereby resulting in a wide CI.⁷⁹ For dichotomous outcomes, GRADE recommends downgrading the quality of evidence for imprecision unless the sample size is very large (at least 2000 and perhaps 4000 patients) and if the optimal information size (OIS) is not met. The OIS is applied as a rule if the total number of patients included in a systematic review is less than the number of patients generated by conventional sample size calculation for a single adequately powered trial. Thus, the OIS rating falls, resulting in imprecision. Because the total number of patients included in these 59 studies varied from 39 to 926 (median, 114), the rating for the imprecision had to be lowered to “major concern” or “some concern” accordingly.

The outcome of this NMA should be interpreted in the light of the unavoidable and inevitable limitations that are usually associated with such analyses. Considerable effort was taken to have a uniform population of patients with untreated LACC, without any definitive surgical interventions, and treated with standard fractionated RT. However, the external RT and brachytherapy schedules were variable, per the standard practice of the institutions. Furthermore, the RT techniques also differed because the studies were reported over a span of 44 years (1974- 2018) and depended on the availability of the treatment facilities at each center (Table 1). In addition, the recent innovations in image-guided brachytherapy, which might also improve local control, could not be evaluated in this NMA because they have not been subject to an RCT. The CT schedules (for CTRT, NACT, and ACT) used in a specific group also varied regarding choice of CT agents and their dosage schedule. Different immunomodulating agents were used for patients in the RT + Imm group. The same was evident for the RT + HypCS group, which had different hypoxic cell sensitizers. However, individual studies with similar treatment approaches were grouped together to maintain uniformity in the basic therapeutic interventions, thus allowing us to derive

meaningful conclusions from the NMA. This, however, does not rule out the possibility that despite similar mechanisms of action, individual interventions might have varying degrees of effect. Furthermore, the overlapping of individual ORs in some of the comparisons of various arms might be a consequence of the low number of patients in some groups for specific endpoints. In addition, for morbidity reporting (both AM and LM), different measures were used in these studies, although most adopted the CTCAE v0.2/0.3 or RTOG/EORTC criteria. During conventional pairwise meta-analysis, significant heterogeneity was observed in 2 of the 4 endpoints, namely LRC ($I^2 = 50.6; P < .001$) and AM ($I^2 = 71.5; P < .001$; Figs. E2a and E2c, available online at <https://doi.org/10.1016/j.ijrobp.2018.09.037>). This could be somewhat expected because of the different types of interventions used with varying effects on the respective endpoints, and to some extent because of the pragmatism in the formulation of these trials, which were designed to determine the effects of an intervention under usual or real-world conditions in contrast to ideal or controlled circumstances, as in explanatory trials.¹²⁷

Distant metastasis (DM) was not included in this NMA. Of the 59 studies, 17 (28.8%) had not reported on DM, and reporting of DM was inconsistent in 13 (22%). The reasons for this were that (1) some included total number of sites of DM, whereby more than 1 site could be involved in a given patient; (2) some reported DM in only those who continued to have pelvic control; (3) in a few studies, it was not apparent whether DM was reported for all included patients in the trials; and (4) in some there were discrepancies in the numbers of DM reported. Thus, although 29 of 59 studies consistently reported DM, this covered only 37.7% of the total patients in the NMA. In view of the overlaying factors discussed here, evaluation of DM could have resulted in substantial ambiguity and hence was not considered.

In the present NMA, CTRT (3 wkly Pt) was evaluated against either RT alone or CTRT(wkly Pt) in 6 studies ($n = 524$ patients). HT with RT and/or CT was included in 6 studies, totaling 442 patients.⁵⁵⁻⁶¹ A number of studies that had used HT with RT and/or CT in LACC but failed to meet our inclusion criteria had to be excluded (Table E2; available online at <https://doi.org/10.1016/j.ijrobp.2018.09.037>). The relatively low number of patients treated with HT could be anticipated because of the limited availability of HT treatment facilities worldwide.

Apprehensions have been expressed regarding conclusions from NMA being based solely on the rankings derived from the SUCRA values.¹²⁸ Thus, to address this likely pitfall, every effort was undertaken to look at the entire computations in a holistic manner to the extent possible with the available data. These included (1) having strict inclusion criteria for RCTs so as to meet the basic assumptions of transitivity, with less than 1% of all papers screened being finally included in this NMA; (2) evaluating the effect sizes of ORs through both conventional pairwise meta-analysis and league tables from NMA; (3) evaluating the inconsistency between the direct and indirect estimates

by NMA; (4) basing final ranking not just on a single SUCRA value of an endpoint, but a cumulative SUCRA value encompassing all 4 key clinical endpoints of relevance; (5) assessing the risk of bias for all 59 studies; (6) conducting separate sensitivity analysis for publications with low risk of selective reporting and those published during or after 2004; (7) performing cluster analysis to identify the interventions that could be grouped together based on their SUCRA values for all endpoints; and (8) assessing the GRADE and certainty of confidence for each endpoint. The 3 modalities of HTRT, HTCTRT, and CTRT (3wkly) outshone the others under scrutiny.

HT is a unique therapeutic modality with multifaceted actions—a potent radiosensitizer, synergistic action with a host of chemotherapeutic drugs, and an immunomodulator akin to “in situ tumor vaccination.”^{103-107,113,114,116} These actions, coupled with the technological advancements in HT delivery, planning, online thermometry, and adaptive temperature modulation, should encourage integration of HT with RT and/or CT not only in LACC but also in other sites.^{105,108-112,117-121,129} It is noteworthy that 3 modalities—HTRT, HTCTRT, and CTRT(3wkly Pt)—maintained their superiority in terms of safety and efficacy in LACC, even after the sensitivity analysis for all trials published during or after 2004. The outcomes of the 2 ongoing multicentric-randomized trials in LACC—namely, OUTBACK¹³⁰ and INTERLACE¹³¹—addressing NACT + CTRT(wkly Pt) versus CTRT(wkly Pt) and CTRT(wkly Pt) + ACT versus CTRT(wkly Pt), respectively, would be of considerable interest. However, by systematically analyzing and quantifying the outcomes of the various therapeutic approaches used to date, this NMA provides a rational basis for embarking on a head-to-head phase 3 multicentric trial using the 3 highest ranked interventions: HTRT, HTCTRT, and CTRT(3wkly Pt) in the nonoperative management of LACC.

Conclusions

Taking into account the reported outcomes from all available randomized trials using various therapeutic intervention strategies for nonoperative management of LACC, the NMA indicates that the modalities of HTRT, HTCTRT, and CTRT(3wkly Pt) are likely to be the most optimal strategies in terms of both efficacy and safety in LACC. However, because these interventions have not yet undergone a direct head-to-head comparison, a phase 3 multicentric RCT would be warranted for additional validation.

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