International Journal of Surgery 66 (2019) 28–36

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.elsevier.com/locate/ijsu

Different therapeutic regimens in the treatment of metastatic prostate cancer by performing a Bayesian network meta-analysis

Qijie Zhang[1], Hong Cheng[1], Yi Wang[1], Ye Tian, Jiadong Xia, Yichun Wang, Xiang Zhou, Xianghu Meng, Yamin Wang, Min Gu**, Ninghong Song*

Department of Urology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, China

ARTICLE INFO

Keywords:
Radical prostatectomy
Radiation therapy
Androgen deprivation therapy
Metastatic prostate cancer
Network meta-analysis

ABSTRACT

Background: Although androgen deprivation therapy with or without chemotherapy are currently the mainstay of therapy for metastatic prostate cancer, accumulating data suggested the survival benefits from definitive local therapy such as radical prostatectomy or radiation therapy. Hence, this network meta-analysis was aimed to provide a hierarchy of different therapeutic regimens for mPCa.

Methods: Relevant studies were retrieved comprehensively by searching the online databases of PubMed, EMBASE and Web of Science, published before July 1st, 2018. With the help of R-3.4.0 software and "gemtc-0.8.2" package, network meta-analysis was performed by random-effect model within a Bayesian framework. Hazard ratios and corresponding 95% credible intervals were calculated by Markov chain Monte Carlo methods. The surface under the cumulative ranking curve was also incorporated to rank the corresponding therapeutic regimens.

Results: A total of 55,363 cases from 17 studies were ultimately involved in this study. Ten different therapeutic regimens and three clinical endpoints were finally assessed. As illustrated by our results, local therapy (such as radical prostatectomy or radiation therapy) could provide a relatively more favorable survival rate than systematic therapies (no local therapy, androgen deprivation therapy or androgen deprivation therapy + chemotherapy). Meanwhile, in the comparison of radiation therapy, brachytherapy and intensity modulated radiation therapy were among the best two therapies. Furthermore, radical prostatectomy had a relatively lower cancer specific mortality or all-cause mortality than brachytherapy or intensity modulated radiation therapy, in the comparison of local therapy, whereas brachytherapy showed a relatively longer overall survival than radical prostatectomy.

Conclusions: Our results indicated that local therapy was better than no local therapy. In a comprehensive comparison of three clinical endpoints (overall survival, cancer specific mortality or all-cause mortality), radical prostatectomy had a relatively lower cancer specific mortality or all-cause mortality than radiation therapy, whereas brachytherapy was superior to radical prostatectomy for overall survival.

1. Introduction

As the most common malignancy, prostate cancer (PCa) ranks the second leading cause of cancer mortality among the male population, with 164,690 newly estimated cases and 29,430 newly estimated deaths in the United States, 2018 [1]. Although the proportion of patients with metastatic prostate cancer (mPCa) in the United States is merely 3%, it carries a dismal 5-year survival rate of 29.3%, compared with almost 100% 5-year survival for low-volume organ-confined disease [2–4]. Currently, the standard therapy for mPCa was still androgen deprivation therapy (ADT) with or without chemotherapy, but its efficacy remained limited [5–7]. Along with the positive role of local treatment (LT) in reducing mortality rates of other metastatic malignancies [8–12], recent studies suggested that definitive LT such as radical prostatectomy (RP) or radiation therapy (RT) could also suppress systemic disease progression and improve survival rates for mPCa [13–16]. Faced with so many therapeutic regimens, both clinicians and patients felt confused and the ideal therapeutic regimen remained to be

* Corresponding author. Department of Urology, The First Affiliated Hospital of Nanjing Medical University, No. 300 Guangzhou Road, Nanjing, 210029, China.
** Corresponding author. Department of Urology, The First Affiliated Hospital of Nanjing Medical University, No. 300 Guangzhou Road, Nanjing, 210029, China.
E-mail addresses: Lancetgu@163.com (M. Gu), songninghong_urol@163.com (N. Song).
[1] Qijie Zhang, Hong Cheng and Yi Wang contributed equally to this work.

https://doi.org/10.1016/j.ijsu.2019.04.006
Received 16 September 2018; Received in revised form 11 April 2019; Accepted 12 April 2019
Available online 17 April 2019

completely identified.

Until now, treatment regimens for mPCa mainly included androgen deprivation therapy (ADT) with or without chemotherapy (Chemo), radical prostatectomy (RP), conformal radiation therapy (CRT), intensity modulated radiation therapy (IMRT), brachytherapy (BT), external-beam radiation therapy (EBRT), no local therapy (NLT) and so on [17,18]. As indicated by Carneiro et al. and our previous pairwise meta-analysis, LT or RP could improve the survival benefit of mPCa. However, due to the absence of direct statistical analysis and limited evidence, the direct comparison of RP and RT was seldom involved [19,20]. As we knew, when direct comparisons were unavailable, the existence of a Bayesian network meta-analysis could allow the investigators to overcome the limitation of traditional meta-analysis and gain their efficiency or accuracy indirectly. Hence, we conducted a Bayesian network meta-analysis to comprehensively evaluate the efficacy of different therapeutic regimens for mPCa [21,22].

After selection based on inclusion and exclusion criteria, ten different eligible therapeutic regimens were ultimately enrolled in this article. They were RP, BT, CRT, IMRT, EBRT, NLT, ADT, ADT + chemo, RP or RT (RP/RT), BT or IMRT or CRT or EBRT (BT/IMRT/CRT/EBRT), separately; and three clinical outcomes were finally analyzed: overall survival (OS), cancer specific mortality (CSM) and all-cause mortality (ACM). Hopefully, our results were anticipated to providing some evidence for clinicians to develop the best strategy for mPCa patients.

2. Materials and methods

Ethical approval for this study was not applicable because it was a review of existing literature and did not involve any handling of individual patient's data. Moreover, this work has been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), OQAQ (Overview Quality Assessment Questionnaire) and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines.

2.1. Search strategy

Eligible articles were identified from online databases of Pubmed, Embase and Web of Science, published before July 1st, 2018. The search strategy was mainly consisted of two parts (different treatment regimens, and metastatic prostate cancer), using the following keywords in combination with Medical Subject Headings (MeSH) terms and text words: Androgen deprivation therapy (ADT), radical prostatectomy (RP), chemotherapy (Chemo), radiation therapy (RT), conformal radiation therapy (CRT), intensity modulated radiation therapy (IMRT), brachytherapy (BT), external-beam radiation therapy (EBRT), no local therapy (NLT) and metastatic prostate cancer (mPCa). Two reviewers individually performed initial research by screening titles and abstracts of retrieved articles. Irrelevant articles were excluded and full texts of involved articles were evaluated for inclusion. To minimize article omissions, the reference lists of relevant studies were also manually screened for additional publications. The study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the code CRD42018093864.

2.2. Inclusion and exclusion criteria

Studies enrolled in this article should meet the following criteria: (1) Subjects involved in the study were patients with metastatic prostate cancer. (2) The comparison between different managements should be at least two of previously mentioned regimens. (3) At least one of the endpoints have to be included, such as overall survival (OS), all-cause mortality (ACM) or cancer specific mortality (CSM). (4) Sufficient data should be provided in the original studies. Studies would be excluded if they met the following criteria: (1) The types of publication studies were abstract, conference paper, or review; (2) The study cannot provide sufficient and qualified data.

2.3. Data extraction

All relevant data of eligible studies was independently identified by two investigators and controversial data would be reviewed by a third investigator. Important information extracted from original articles included the first author's name, year of publication, numbers of enrolled subjects, interventions, endpoints (OS, CSM and ACM), survival data (hazard ratio, HR) and corresponding 95% confidence interval (CI). When data could not be directly obtained from some articles, it was extracted from Kaplan-Meier curves to extrapolate HRs with 95% CIs by using previously described methods [23,24].

2.4. Quality assessment

As one of the most useful scale to evaluate the quality of non-randomized studies, Newcastle-Ottawa Scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm) was applied to evaluate the methodological quality assessment of eligible studies by two blind reviewers [25]. The criteria of each quality assessment were displayed as follows: (1) Representativeness of the exposed cohort; (2) Selection of the non-exposed cohort; (3) Ascertainment of exposure; (4) Outcome of interest not present at start of study; (5) Control for important factor or additional factor; (6) Assessment of outcome; (7) Follow-up long enough for outcomes to occur; (8) Adequacy of follow up of cohorts. If one met the criteria, it would be awarded a star, except for the numbered 5 item which would be granted a maximum of two stars. The whole quality scores were between 0 and 9 and if the final score > 6, it was considered to be of high quality. Detailed rankings of each study were presented in Table 1.

2.5. Statistical analysis

We conducted a pair-wise meta-analysis to combine studies addressing the same endpoint as well as the same treatments. Meanwhile, HR with 95% CI was calculated. The Chi-square test and I-square test were applied to assess the heterogeneity; If $I^2 > 50\%$ or Chi-square test $P > 0.10$, it was deemed to existing significant heterogeneity. For groups without significant heterogeneity, fixed-effect model was

Table 1
Newcastle-Ottawa quality assessments scale.

Author	Year	Selection				Comparability	Exposure			Scores
		1	2	3	4	5	6	7	8	
Leyh-Bannurah	2017	★	★	★	★	★★	★	★	–	8
Moschini	2017	★	★	–	★	★★	★	★	★	8
Sooriakumaran	2017	★	–	★	★	★★	★	★	★	8
Rulach	2017	★	–	★	★	★★	–	★	★	7
Parikh	2017	–	★	★	★	★★	★	★	★	8
Sweeney	2016	★	–	★	★	★★	★	★	★	8
Rusthoven	2016	★	★	–	★	★★	★	★	–	7
Löppenberg	2016	–	★	★	★	★★	★	★	–	7
Satkunasivam	2015	★	★	★	★	★★	★	–	★	8
Culp	2014	★	★	–	★	★★	★	★	★	8
Antwi	2014	–	★	★	★	★★	★	★	–	7
Shao	2014	★	★	★	★	★★	–	★	★	8
Gratzke	2014	–	★	★	★	★★	★	–	–	6
Gravis	2013	★	★	★	★	★★	–	★	★	8
Millikan	2008	–	★	–	★	★★	★	★	★	7
Thompson	2002	★	–	★	★	★★	★	★	–	6
Murphy	1983	★	–	★	★	★★	–	★	–	6

1.Representativeness of the exposed cohort; 2.Selection of the non-exposed cohort; 3.Ascertainment of exposure; 4.Outcome of interest not present at start of study; 5.Control for important factor or additional factor; 6.Assessment of outcome; 7.Follow-up long enough for outcomes to occur; 8.Adequacy of follow up of cohorts.

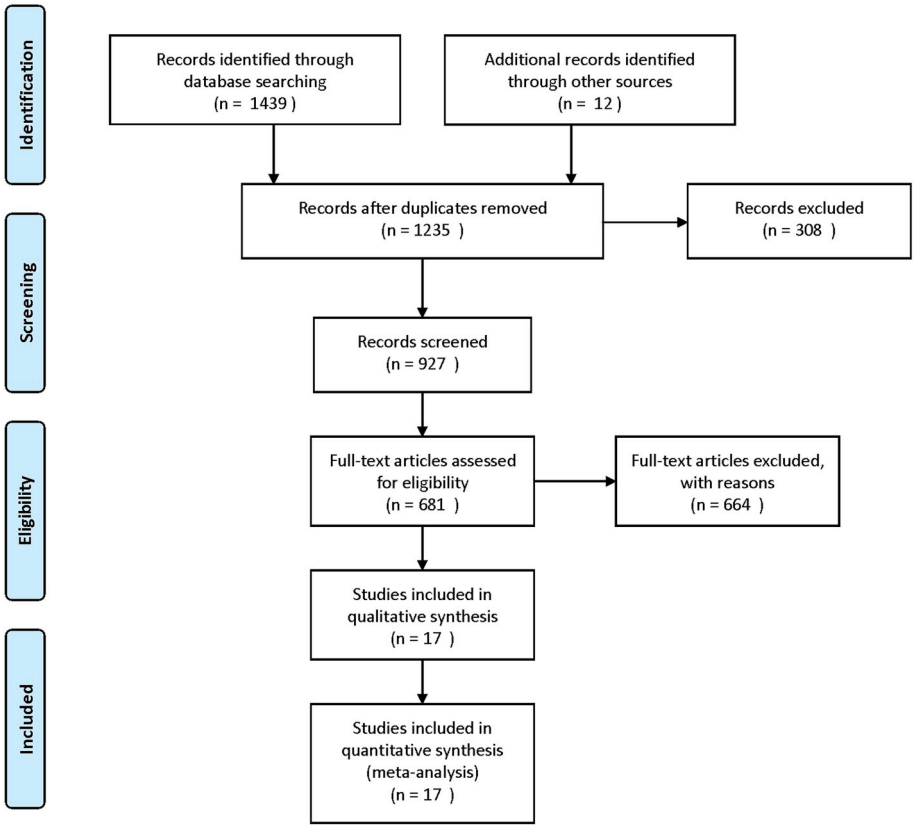

Fig. 1. The flow diagram of the literature selection process.

applied and HRs were calculated by the Mantel-Haenszel method; otherwise, random-effect model and DerSimonian and Laird method were applied. Sensitivity analyses were conducted by discarding individual studies sequentially to assess the influence of a single study on the overall results. Publication bias was evaluated by Begg's and Egger's test [26]. *P* values were adopted by a two-sided test and $P < 0.05$ was considered to be statistically significant. In addition, all calculations were performed by STATA 12.0 (Stata Corp, College Station, TX) software.

In addition to pairwise meta-analysis making direct comparison between two managements, a network meta-analysis concerning multiple managements was performed by random-effect model within a Bayesian framework. HRs and corresponding 95% credible intervals (CrIs) were calculated by Markov chain Monte Carlo methods with the help of the 0.8.2 “gemtc” package of R software (version 3.4.0; R Foundation, Vienna, Austria) [27]. This network analysis enabled the incorporation of indirect comparisons constructed from two articles that had one studied management in common. The method combined both direct and indirect evidence for any given pair of managements and certain endpoints. The function mtc.run was applied to generate samples and we set 5,000 simulations for each chain as the “burn-in” period, yielding 20,000 iterations to obtain the HR of model parameters, when three Markov chains run simultaneously. Meanwhile, Brooks-Gelman-Rubin plots method, trace plot and density plot were used to access the model convergence [28]. Besides, rank probabilities would be calculated to obtain the hierarchy of each treatment and the matrix as well as the plot of rank probabilities was provided by the “gemtc” package simultaneously [29].

The consistency between direct and indirect comparisons were estimated by comparing the pooled HRs from the network meta-analysis and HRs from pair-wise meta-analysis of direct comparisons. To assess the consistency, the node-splitting method was used to calculate the inconsistency of the model. The method separated the evidence concerning certain comparison into direct and indirect evidence, and the inconsistency was reported by its Bayesian *P* value, when a loop connecting three arms existed [30]. Last but not least, the mtc.anohe command of the “gemtc” package would be utilized to evaluate the global heterogeneity, based on the bias of the magnitude of heterogeneity variance parameter I^2.

3. Results

3.1. Search results and study characteristics

Based on previously described search strategy, the literature search yielded 1,451 records and 324 citations were excluded because of reviews, letters, case-reports, duplicates and so on, after screening the tittles and abstracts. The full texts of the remaining 1,004 articles were evaluated by the reviewers and 987 studies were excluded with reasons. Finally, a total of 17 articles including 55,363 patients were enrolled [14,18,31–45]. A flow diagram of the study selection process was displayed in Fig. 1.

The year of publication was ranged from 1983 to 2018. The quality assessment of all these enrolled studies was evaluated by Newcastle-Ottawa Scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm) and the detailed rankings of each study were displayed in Table 1. We could easily find that they were all above 6. In other words, it was considered to be of high quality. In addition, Subjects involved in this article included the following therapeutic regimens: RP, BT, CRT, IMRT, EBRT, NLT, ADT, ADT + chemo, RP/RT, BT/IMRT/CRT/EBRT. Amongst them, CRT, IMRT, BT and EBRT belonged to RT. RP and RT belonged to LT. Clinical endpoints included OS, CSM or ACM. All of them were summarized in Table 2.

Table 2
Main characteristics of eligible studies included in the network meta-analysis.

Study	Year	Treatment Arm (N)	Control Arm (N)	Survival Analysis	Endpoints	HR	LCI	UCI	Source of HR
Overall survival (OS)									
Rulach	2017	ADT + Chemo(103)	ADT(167)	NA	OS	0.17	0.076	0.4	reported
Parikh	2017	RP(419)	NLT(4,183)	Multivariable	OS	0.51	0.45	0.59	reported
		IMRT(40)	NLT(4,183)	Multivariable	OS	0.47	0.31	0.72	reported
		CRT(119)	NLT(4,183)	Multivariable	OS	1.04	0.86	1.27	reported
Sweeney	2016	ADT + Chemo(397)	ADT(393)	NA	OS	0.61	0.47	0.8	reported
Rusthoven	2016	RP(69)	ADT(5,844)	Multivariate	OS	0.38	0.25	0.58	reported
		EBRT(537)	ADT(537)	Multivariate	OS	0.67	0.57	0.79	reported
Löppenberg	2016	RP(294)	NLT(14,031)	Multivariable	OS	0.48	0.39	0.59	SC
		BT(44)	NLT(14,031)	Multivariable	OS	0.34	0.22	0.54	SC
		EBRT(1132)	NLT(14,031)	Multivariable	OS	0.64	0.55	0.74	SC
Satkunasivam	2015	RP(47)	NLT(3,827)	Multivariable	OS	0.44	0.27	0.72	SC
Gratzke	2014	RP(74)	ADT(635)	Multivariable	OS	0.48	0.35	0.68	SC
		RP(74)	EBRT(389)	Multivariable	OS	0.46	0.33	0.65	SC
Gravis	2013	ADT + Chemo(192)	ADT (193)	Multivariable	OS	1.01	0.75	1.36	reported
Millikan	2008	ADT + Chemo(137)	ADT(149)	NA	OS	0.87	0.63	1.2	SC
Thompson	2002	RP (148)	ADT (919)	Multivariable	OS	0.77	0.57	1.05	reported
Murphy	1983	ADT + Chemo(77)	ADT(83)	NA	OS	0.7	0.61	0.8	SC
Cancer specific mortality (CSM)									
Leyh-Bannurah	2017	BT(161)	NLT(644)	Multivariable	CSM	0.48	0.35	0.66	reported
		RP(313)	NLT(1,252)	Multivariable	CSM	0.35	0.26	0.46	reported
		RP(161)	BT(161)	Multivariable	CSM	0.59	0.35	0.99	reported
		RP/RT(474)	NLT(1,896)	Multivariable	CSM	0.40	0.32	0.5	reported
Moschini	2017	RP(31)	ADT(16)	Univariable	CSM	0.53	0.17	1.69	reported
Sooriakumaran	2017	RP/RT(575)	ADT(575)	Multivariable	CSM	0.29	0.21	0.39	reported
Satkunasivam	2015	RP(47)	NLT(3,827)	Multivariable	CSM	0.48	0.27	0.85	reported
		CRT(107)	NLT(3,827)	Multivariable	CSM	0.85	0.64	1.14	reported
		IMRT(88)	NLT(3,827)	Multivariable	CSM	0.38	0.24	0.61	reported
Culp	2014	RP(245)	NLT(7,811)	Multivariate	CSM	0.38	0.27	0.53	reported
		BT(129)	NLT(7,811)	Multivariate	CSM	0.68	0.49	0.93	reported
Antwi	2014	RP(222)	NLT(7,516)	Multivariate	CSM	0.28	0.20	0.39	reported
		BT(120)	NLT(7,516)	Multivariate	CSM	0.46	0.33	0.64	reported
Shao	2014	RP(171)	RT(171)	Multivariable	CSM	0.68	0.38	1.22	reported
		RP(287)	RT(287)	Multivariable	CSM	0.51	0.36	0.73	reported
All-cause mortality (ACM)									
Löppenberg	2016	RP/RT(1,470)	NLT(14,031)	Multivariable	ACM	0.61	0.56	0.66	reported
Satkunasivam	2015	RP(47)	NLT(3,827)	Multivariable	ACM	0.43	0.26	0.72	reported
		CRT(107)	NLT(3,827)	Multivariable	ACM	0.90	0.70	1.14	reported
		IMRT(88)	NLT(3,827)	Multivariable	ACM	0.45	0.31	0.65	reported
Antwi	2014	RP(222)	NLT(7,516)	Multivariate	ACM	0.27	0.20	0.38	reported
		BT(120)	NLT(7,516)	Multivariate	ACM	0.43	0.31	0.59	reported

ADT: androgen deprivation therapy; Chemo: chemotherapy; RP: radical prostatectomy; RT: radiation therapy; CRT: conformal radiation therapy; IMRT: intensity modulated radiation therapy; BT: brachytherapy; EBRT: external-beam radiation therapy; NLT: no local therapy; NA: not available; SC: survival curves; HR: Hazard ratios; LCI: lower confidential interval; UCI: upper confidential interval.

3.2. Results from network meta-analysis

3.2.1. Network structure diagrams

The present article covered ten different therapeutic regimens, such as RP, BT, CRT, IMRT, EBRT, NLT, ADT, ADT + chemo, RP/RT, BT/IMRT/CRT/EBRT. Network structure diagrams were applied to display the direct association between different treatment regimens and the thicknesses of the lines were proportional to the number of comparisons, and the diameters of the circles were proportional to the number of treatments included in this meta-analysis. All of these were presented in Fig. 2.

3.2.2. OS associated with mPCa

A total of 11 studies containing 17 direct comparisons and eight different treatments (RP, BT, CRT, IMRT, EBRT, NLT, ADT, ADT + chemo) contributed to the analysis of OS for mPCa. The efficacy of different treatments using HR and corresponding 95% CrIs was displayed in Fig. 3A and Supplement Figure 1. As indicated in the result, compared with RP, NLT and ADT had a shorter OS (HR: 2.1, 95%CI 1.5–3.3; HR: 2.0, 95%CI 1.3–3.0, respectively). Similar results could be observed in NLT or ADT vs BT (HR: 2.9, 95%CI 1.3–6.7; HR: 2.7 95%CI 1.0–7.2, separately). Besides, ADT was inferior to ADT + Chemo (HR: 1.5, 95%CI 1.1–2.2). Fig. 4A was a direct plot of rank probabilities, from which we could easily find the ranking of each therapeutic regimens. Fig. 5A was a cumulative rank plot with the surface under the cumulative ranking curve (SUCRA) of each intervention and its detailed values were presented in Table 3. Meanwhile, the higher the SUCRA value, the higher possible ranking was that of the treatment. As indicated by the results of rank probabilities and SUCRA, therapeutic regimens for mPCa from best to worst were BT, RP, IMRT, ADT + Chemo, EBRT, ADT, CRT and NLT respectively.

3.2.3. CSM associated with mPCa

Seven studies including 15 direct comparisons and seven different treatments (RP, BT, CRT, IMRT, NLT, RP/RT, BT/IMRT/CRT/EBRT) contributed to the analysis of CSM for mPCa. Managements were compared with each other independently; HRs and corresponding 95%CIs were calculated. As shown in Fig. 3B and Supplement Figure 2, compared with RP, BT or CRT or NLT or BT/IMRT/CRT/EBRT displayed a higher incidence rate of CSM (HR: 1.5, 95%CI 1.1–2.1; HR: 2.5 95%CI 1.5–4.0; HR: 2.9, 95%CI 2.3–3.6; HR: 1.8 95%CI 1.2–2.6, separately). RP/RT showed its superiority, whereas NLT presented its inferiority than BT (HR: 0.65, 95%CI 0.43–0.94; HR: 1.9 95%CI 1.4–2.4). RP/RT or IMRT was observed to have a significantly lower rate of CSM than CRT (HR: 0.41, 95%CI 0.24–0.69; HR: 0.45 95%CI 0.22–0.93, respectively). Besides, RP/RT or BT/IMRT/CRT/EBRT had a

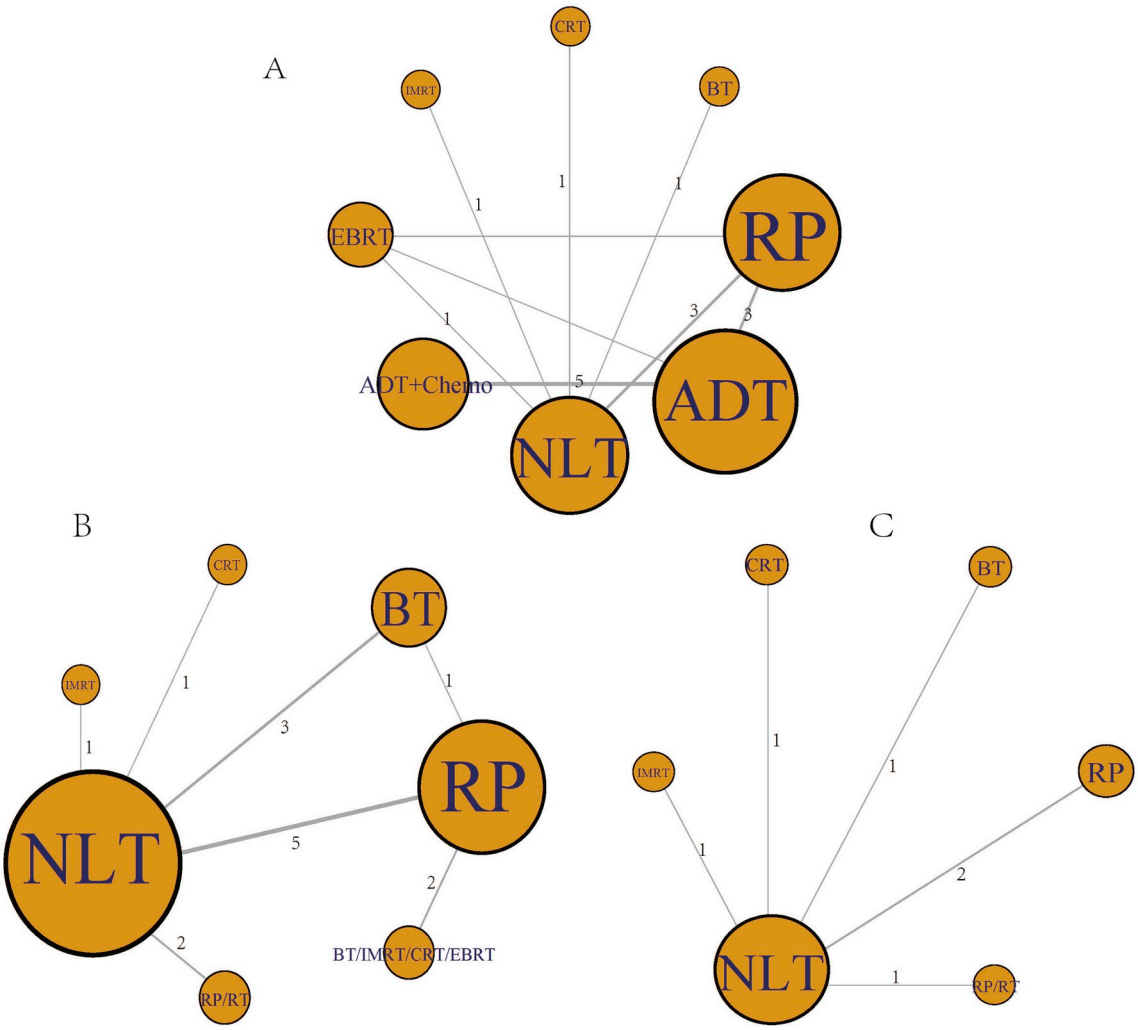

Fig. 2. Network structure diagrams. (A) Overall Survival (OS); (B) Cancer Specific Mortality (CSM); (C) All-Cause Mortality (ACM).

lower rate of CSM than NLT significantly (HR: 0.35, 95%CI 0.25–0.47; HR: 0.62 95%CI 0.40–0.97, separately). As indicated by the results of rank probabilities as well as SUCRA, RP, RP/RT, IMRT, BT, BT/IMRT/CRT/EBRT, CRT and NLT had an increasing tendency of CSM (Figs. 4B and 5B, Table 3).

3.2.4. ACM associated with mPCa

Three articles including six direct comparisons and six different treatments (RP, BT, CRT, IMRT, NLT, RP/RT) contributed to the analysis of CSM for mPCa. According to our result, subjects receiving NLT have a significantly higher incidence rate of ACM than RP (HR: 3.0 95% 1.0–8.2). No other significant results were identified about ACM (Fig. 3C; Supplement Figure 3). As indicated in the cumulative rank probability and SUCRA, therapeutic regimens for mPCa from best to worst were RP, BT, IMRT, RP/RT, CRT and NLT separately (Figs. 4C and 5C, Table 3).

3.2.5. Node-splitting method

Node-splitting method and its relative Bayesian P value were utilized to report the inconsistency of our results. When a loop connecting three arms existed, the method separated the evidence concerning certain comparison into direct and indirect evidence. Because of inconsistent loop, no comparisons were made in ACM. As presented in Fig. 6, we could easily find that all *P* values were above 0.05 and no significant differences were observed between direct and indirect evidence in CSM and OS group, indicating that our results were reliable. Besides, as displayed in Supplement Table 1, it summarized the pooled results and heterogeneity between different comparisons (Notably, when two or more comparisons were available, it would be detailed in this table).

4. Discussion

With the successful application of LT in the treatment of other metastatic malignancies and the development of surgical technology, accumulating researches had suggested that definitive LT (RP or RT) could suppress systemic disease progression and improve survival benefits of mPCa. Although the recommended therapy for mPCa was ADT with or without chemotherapy, LT had gained more and more interests. Faced with so many treatment options and the recognition of over-diagnosis and over-treatment of PCa, both clinicians and patients felt confused and the ideal therapeutic regimen remained to be completely identified. Hence, this network meta-analysis was conducted to clarify this question and it was anticipated to providing some references for clinical work.

This article systematically assessed the comparative efficacy of different therapeutic regimens for patients with mPCa. A total of 55,363 cases from 17 studies were ultimately involved in our study. As

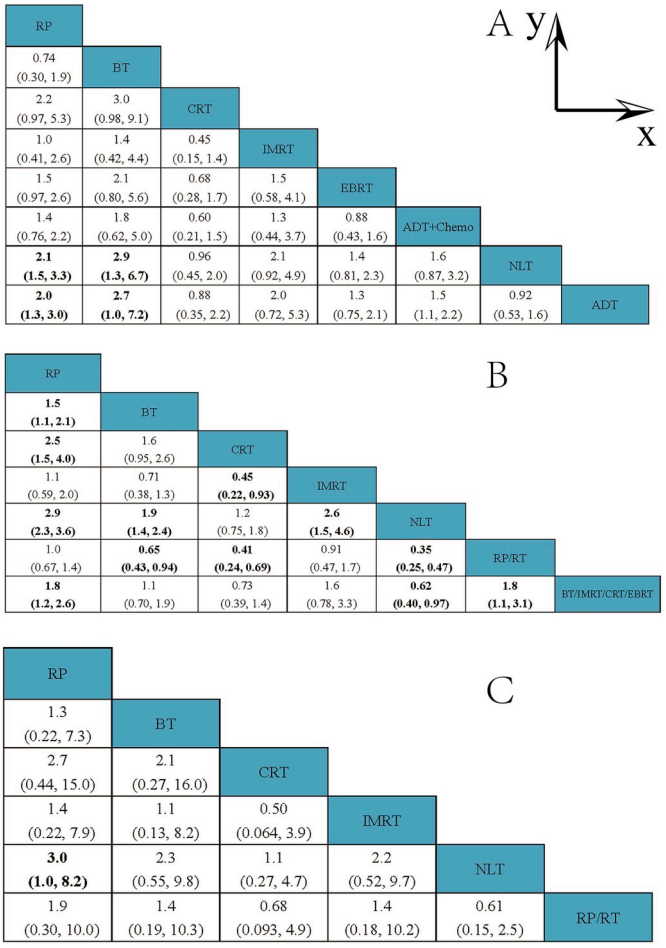

Fig. 3. The efficacy of different treatment regimens using HRs and corresponding 95% CrIs; All results were displayed as the ratio of the x axis versus y axis. (A) Overall Survival (OS); (B) Cancer Specific Mortality (CSM); (C) All-Cause Mortality (ACM).

illustrated by the results, LT (such as RP or RT) could provide a relatively more favorable survival rate than systematic therapies including NLT, ADT or ADT + Chemo. Meanwhile, BT and IMRT were among the best two therapies in the comparison of RT. Furthermore, RP had a relatively lower CSM or ACM than BT or IMRT in the comparison of LT, whereas BT showed a relatively longer OS than RP. All in all, RP, BT and IMRT were considered to be more efficient in a comprehensive comparison of three endpoints (OS, CSM or ACM).

As far as we know, this is the first and largest network meta-analysis considering the comparative efficacy of both local and systematic therapies in mPCa patients with a large scale of cases involved in the analysis. As indicated by node-splitting method, there was little inconsistency between direct and indirect evidence, suggesting relatively reliable results provided by us. Vale et al. reported in their meta-analysis that the addition of chemotherapy into ADT could improve survival, which was also confirmed in our analysis [46]. It had also been demonstrated by Botrel et al. and Ramos-Esquivel et al. [47,48]. There was also a meta-analysis revealing that LT (RT or RP) could significantly improve the OS in comparison with NLT [19]. In the same way, Wang et al. noted that no matter how RP compared with NLT or RT, it showed significant superiority in OS [20]. Above-mentioned results were in consistent with ours.

There was a network meta-analysis by Wu et al. comparing the efficacy of RT, endocrine therapy (ET) and RT + ET therapy for the treatment of advanced/metastatic PCa [49]. They found that OS achieved with RT or ET was shorter than obtained with RT + ET. The ranking of ET concerning OS was estrogen therapy, luteinizing hormone-releasing hormone agonist (LHRH-A), ADT, ADT + LHRH-A and ET + LHRH-A. Unlike them, all subjects involved in our study were patients with mPCa. We paid more attention to local therapies such as RP and RT and the comparison between local and systematic therapies.

In addition to the positive impact on the survival, LT still had some other benefits for mPCa. Due to progression of primary tumor, literature data showed that more than one third of patients without LT would present severe local complications including the number of hospitalizations, surgical procedures and consequently higher morbidity, worsening the quality of life of PCa patients [50–52]. A case-control study shed light on RP that lowered complication rates of urinary tract related to the progression of the disease, while one third of patients in the control group presented lower urinary tract obstruction, hematuria or anemia [53]. In consideration of morbidity and sequelae of LT, its indication was still limited in this scenario of no documented benefit. However, with the development of technology, including robotic surgery, and more precise modalities of radiotherapy, the morbidity was being significantly reduced.

Notably, not all the patients could benefit from LT. Fossati et al. and Loppenberg et al. clarified that the potential benefits of LT depended greatly on baseline characteristics and patients with less aggressive tumors and good general health [37,54]. As indicated by this, do not rush to receive any treatment and a comprehensive assessment of their own situation might be helpful for patients. As for clinicians, we should make appropriate choices, based on the individual conditions of patients.

Nonetheless, several limitations should be mentioned in this study. Firstly, since various protocols were applied by eligible studies, significant heterogeneity might be elicited. Secondly, some variants such as age, ethnicity, tumor grade and general health may mislead the results. Due to lack of original data, subgroup analysis was not carried out. Further stratified analyses based on a larger set of samples were recommended. Thirdly, management for mPCa compared in this article was incomplete. For example, except ADT, other ET such as estrogen therapy and LHRH-A weren't involved. Last but not least, some articles enrolled in this network meta-analysis were retrospective cohort studies and they could not have a clear impact on group baseline features as RCTs did. Moreover, the retrospective cohort study and RCTs had a different level of evidence, which could not provide the same statistical power. Upcoming prospective RCTs were required to provide more available data.

5. Conclusions

Taken together, our results shed light on LT (including RP or RT) that could provide a relatively favorable survival rate, in comparison with systematic therapies (such as NLT, ADT and ADT + Chemo). In a comprehensive comparison of three clinical endpoints (OS, CSM or ACM), RP had a relatively lower CSM or ACM than RT, whereas BT was superior to RP for OS. In addition, RP, BT and IMRT were considered to be more efficient. Hopefully, this article was anticipated to providing some evidence for clinicians in the selection of appropriate treatments for patients with mPCa. Subsequent prospective RCTs were required to provide more high-quality data to elaborate our findings.

Data statement

All the data (pooled hazard ratios with corresponding 95% credible intervals of OS, CSM or ACM) used to support the findings of this study are included within the article. Please contact author for data requests.

We certify that the submission is an original work and this paper has not been published elsewhere in whole or in part. All authors have read and approved the content, and agree to submit it for consideration for

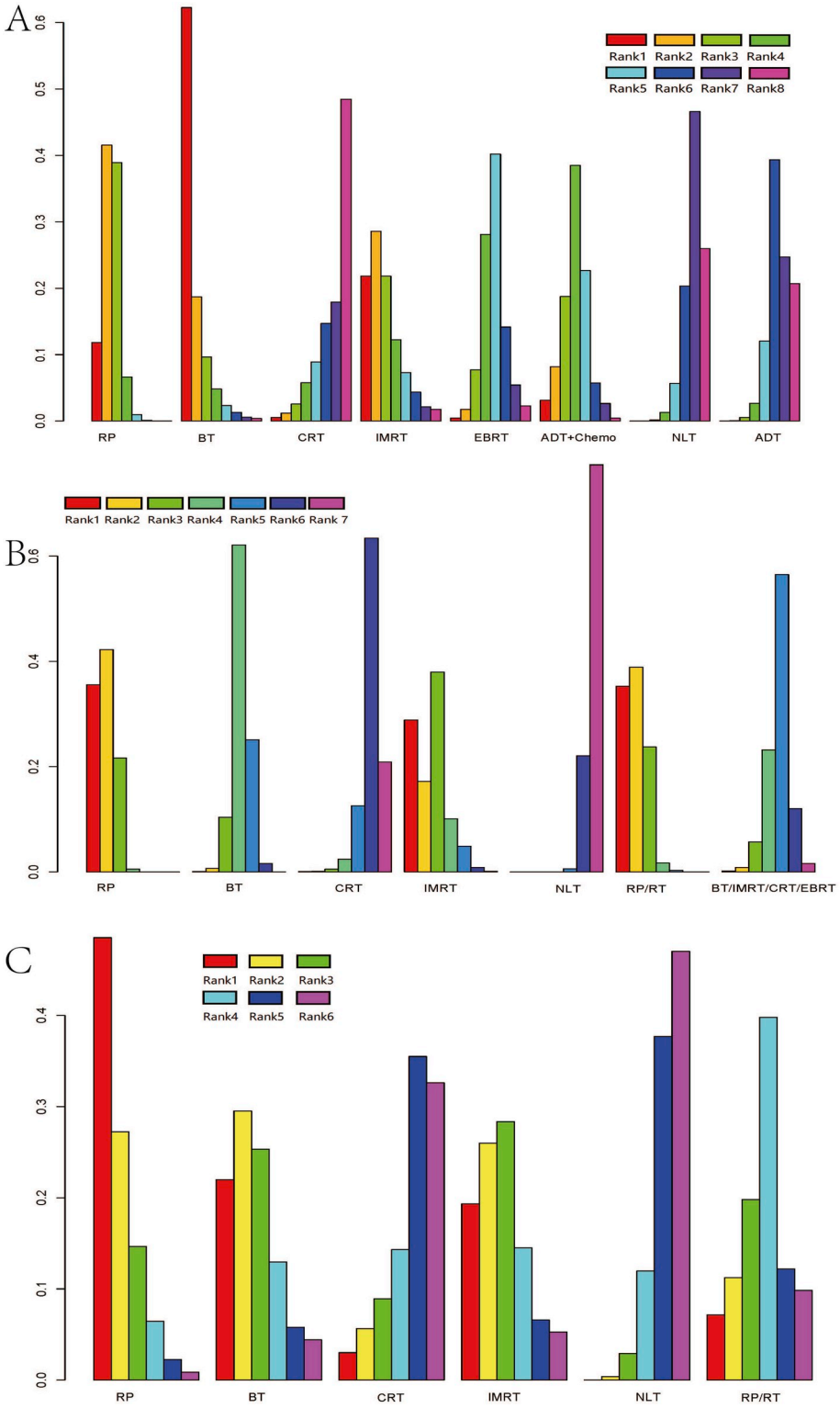

Fig. 4. Rank of the efficacy of different treatment regimens; (A) Overall Survival (OS); (B) Cancer Specific Mortality (CSM); (C) All-Cause Mortality (ACM).

publication in your journal. There are no ethical/legal conflicts involved in the article.

Ethical approval

Not applicable.

Sources of funding

This article was funded by Medical key talent of Jiangsu Province: ZDRCA2016009 and the National Natural Science Foundation of China [grant number: 81871151].

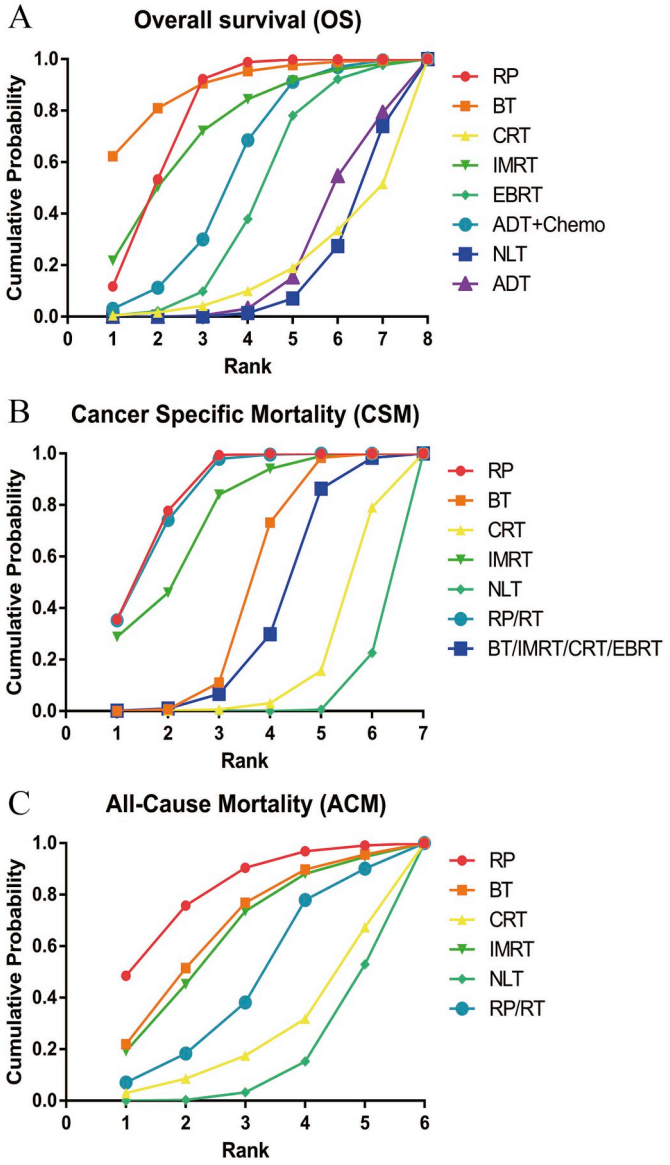

Fig. 5. Cumulative rank plot with the surface under the cumulative ranking curve (SUCRA) of each intervention for effective outcomes; (A) Overall Survival (OS); (B) Cancer Specific Mortality (CSM); (C) All-Cause Mortality (ACM).

Author contribution

M.G, YM.W, NH.S: Protocol/project development;
JD.X, YC.W: Data collection or management;
Y.T, X.Z, XH.M: Data analysis;
QJ.Z, H.C, Y.W: Manuscript writing/editing.

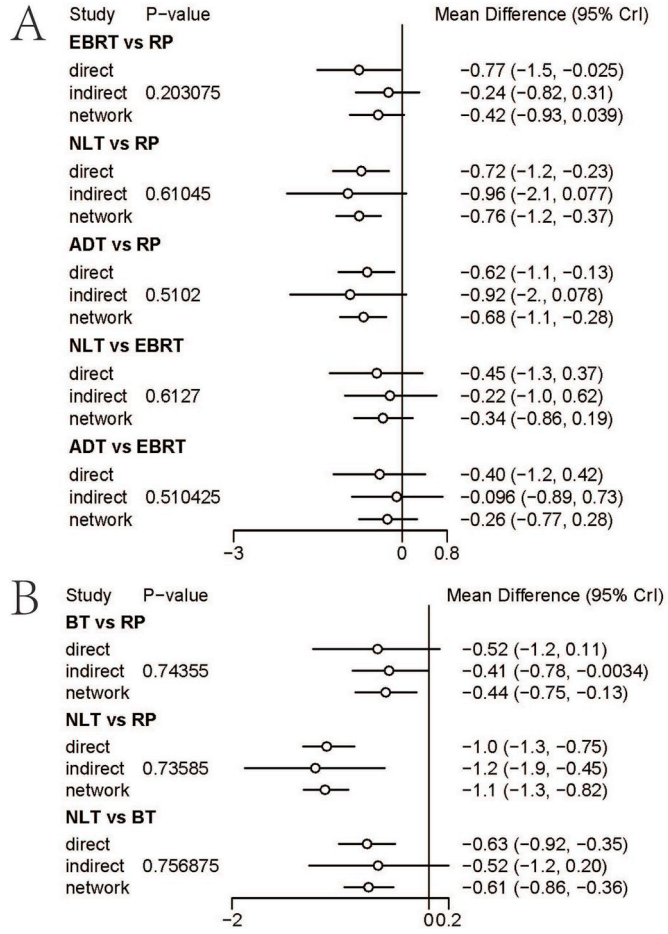

Fig. 6. Node-splitting method in comparison between direct and indirect evidence; (A) Overall Survival (OS); (B) Cancer Specific Mortality (CSM).

Conflicts of interest

None declared.

Unique identifying number

This network meta-analysis was registered in *PROSPERO* and the unique identifying number of the study was CRD42018093864.

Guarantor

The corresponding author (NH.S) accepted full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Table 3
The SUCRA probabilities of different therapeutic regimens for metastatic prostate cancer on clinical outcomes.

Intervention	RP	BT	CRT	IMRT	EBRT	ADT + Chemo	NLT	ADT
OS	60.02%	64.44%	17.04%	55.40%	36.84%	44.91%	16.02%	20.31%
Intervention	RP	BT	CRT	IMRT	NLT	RP/RT	BT/IMRT/CRT/EBRT	–
CSM	54.49%	33.35%	14.89%	48.75%	7.33%	53.94%	27.25%	–
Intervention	RP	BT	CRT	IMRT	NLT	RP/RT	–	–
ACM	43.65%	37.47%	17.70%	36.15%	12.20%	27.82%	–	–

SUCRA: the value of surface under the cumulative ranking curve (The higher the SUCRA value was, the higher possible ranking of the treatment was.); ADT: androgen deprivation therapy; Chemo: chemotherapy; RP: radical prostatectomy; RT: radiation therapy; CRT: conformal radiation therapy; IMRT: intensity modulated radiation therapy; BT: brachytherapy; EBRT: external-beam radiation therapy; NLT: no local therapy; OS: Overall survival; CSM: Cancer specific mortality; ACM: All-cause mortality.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.04.006.

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2018, Ca - Cancer J. Clin. 68 (2018) 7–30.
[2] A.B. Weiner, R.S. Matulewicz, S.E. Eggener, E.M. Schaeffer, Increasing Incidence of Metastatic Prostate Cancer in the United States (2004-2013), Prostate Cancer & Prostatic Diseases, 2016.
[3] K. Yasuhide, N. Mikio, Prostate-specific antigen-based population screening for prostate cancer: current status in Japan and future perspective in Asia, Asian J. Androl. 17 (2015) 475–480.
[4] F.H. Schroder, Prostate cancer around the world. An overview, Urol. Oncol. 28 (2010) 663–667.
[5] M. Hussain, C.M. Tangen, D.L. Berry, et al., Intermittent versus continuous androgen deprivation in prostate cancer, N. Engl. J. Med. 368 (2013) 1314–1325.
[6] D.A. Loblaw, K.S. Virgo, R. Nam, et al., Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline, J. Clin. Oncol. : Off. J. Am. Soc. Clin. Oncol. 25 (2007) 1596–1605.
[7] J.L. Mohler, A.J. Armstrong, R.R. Bahnson, et al., Prostate cancer, version 3.2012 featured updates to the NCCN Guidelines, J. Natl. Compr. Cancer Netw. 10 (2012) 1081–1087.
[8] R.E. Bristow, R.S. Tomacruz, D.K. Armstrong, et al., Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis, J. Clin. Oncol. Offic. J. Am. Soc. Clin. Oncol. 20 (2002) 1248.
[9] A. Bamias, K. Tzannis, A. Papatsoris, et al., Prognostic significance of cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma treated with first-line sunitinib: a European multiinstitutional study, Clin. Genitourin. Cancer 12 (2014) 373–383.
[10] D. You, I.G. Jeong, C. Song, et al., Analysis of pre-operative variables for identifying patients who might benefit from upfront cytoreductive nephrectomy for metastatic renal cell carcinoma in the targeted therapy era, Jpn. J. Clin. Oncol. 45 (2015) 96–102.
[11] F. Roviello, S. Caruso, D. Marrelli, et al., Treatment of peritoneal carcinomatosis with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: state of the art and future developments, Anaesthesia 20 (2011) 211–233.
[12] O. Glehen, F. Mohamed, F.N. Gilly, Peritoneal carcinomatosis from digestive tract cancer: new management by cytoreductive surgery and intraperitoneal chemohyperthermia, Lancet Oncol. 5 (2004) 219.
[13] S.R. Leyhbannurah, S. Gazdovich, L. Budäus, et al., Local therapy improves survival in metastatic prostate cancer, Eur. Urol. 72 (2017) 118–124.
[14] M. Moschini, A. Morlacco, E. Kwon, et al., Treatment of M1a/M1b prostate cancer with or without radical prostatectomy at diagnosis, Prostate Cancer Prostatic Dis. (2017) 117–121.
[15] P. Sooriakumaran, J. Karnes, C. Stief, et al., A multi-institutional analysis of perioperative outcomes in 106 men who underwent radical prostatectomy for distant metastatic prostate cancer at presentation, Eur. Urol. 69 (2015) 788.
[16] R. Satkunasivam, A.E. Kim, M. Desai, et al., Radical prostatectomy or external beam radiation therapy vs No local therapy for survival benefit in metastatic prostate cancer: a SEER-medicare analysis, J. Urol. 194 (2015) 378–385.
[17] P. Dell'Oglio, A. Stabile, G. Gandaglia, et al., New surgical approaches for clinically high-risk or metastatic prostate cancer, Expert Rev. Anticancer Ther. 17 (2017) 1013–1031.
[18] R. Satkunasivam, A.E. Kim, M. Desai, et al., Radical prostatectomy or external beam radiation therapy vs No local therapy for survival benefit in metastatic prostate cancer: a SEER-medicare analysis, J. Urol. 194 (2015) 378.
[19] A. Carneiro, W. Baccaglini, F.P.A. Glina, et al., Impact of local treatment on overall survival of patients with metastatic prostate cancer: systematic review and meta-analysis, Int. Braz. J. Urol. Off. J. Braz. Soc. Urol. 43 (2016).
[20] Y. Wang, Z. Qin, Y. Wang, et al., The role of radical prostatectomy for the treatment of metastatic prostate cancer: a systematic review and meta-analysis, Biosci. Rep. (2018) 38.
[21] V. Fadda, D. Maratea, S. Trippoli, A. Messori, Network meta-analysis. Results can be summarised in a simple figure, Bmj 342 (2011) d1555.
[22] T.L., Network meta-analysis for indirect treatment comparisons, Stat. Med. 21 (2010) 2313–2324.
[23] P.R. Williamson, C.T. Smith, J.L. Hutton, A.G. Marson, Aggregate data meta-analysis with time-to-event outcomes, Stat. Med. 21 (2002) 3337–3351.
[24] J.F. Tierney, L.A. Stewart, D. Ghersi, et al., Practical methods for incorporating summary time-to-event data into meta-analysis, Trials 8 (2007) 16.
[25] A. Stang, Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses, Eur. J. Epidemiol. 25 (2010) 603–605.
[26] M. Egger, S.G. Davey, M. Schneider, C. Minder, Bias in meta-analysis detected by a simple, graphical test, BMJ 315 (1997) 629–634.
[27] G.V. Valkenhoef, J. Kuiper, Gemtc: Network Meta-Analysis Using Bayesian Methods, John Wiley & Sons, Ltd, 2016.
[28] H.Y. Wu, J.W. Huang, H.J. Lin, et al., Comparative effectiveness of renin-angiotensin system blockers and other antihypertensive drugs in patients with diabetes: systematic review and bayesian network meta-analysis, Bmj 347 (2013) f6008.
[29] A. Gelman, D.B. Rubin, Inference from iterative simulation using multiple sequences, Stat. Sci. 7 (1992) 457–472.
[30] S. Dias, N.J. Welton, D.M. Caldwell, A.E. Ades, Checking consistency in mixed treatment comparison meta-analysis, Stat. Med. 29 (2010) 932–944.
[31] S.R. Leyh-Bannurah, S. Gazdovich, L. Budã¤Us, et al., Local therapy improves survival in metastatic prostate cancer, Eur. Urol. 72 (2017) 118–124.
[32] P. Sooriakumaran, T. Nyberg, O. Akre, et al., Survival among men at high risk of disseminated prostate cancer receiving initial locally directed radical treatment or initial androgen deprivation therapy, Eur. Urol. 72 (2017) 345–351.
[33] R.J. Rulach, S. Mckay, S. Neilson, et al., Real-world uptake, safety profile and outcomes of docetaxel in newly diagnosed metastatic prostate cancer, BJU Int. 121 (2018) 268–274.
[34] R.R. Parikh, J. Byun, S. Goyal, I.Y. Kim, Local therapy improves overall survival in patients with newly diagnosed metastatic prostate cancer, Prostate 96 (2017) S183–S184.
[35] C.J. Sweeney, Y.H. Chen, M. Carducci, et al., Chemohormonal therapy in metastatic hormone-sensitive prostate cancer, N. Engl. J. Med. 373 (2015) 737.
[36] C.G. Rusthoven, B.L. Jones, T.W. Flaig, et al., Improved survival with prostate radiation in addition to androgen deprivation therapy for men with newly diagnosed metastatic prostate cancer, J. Clin. Oncol. 34 (2016) 2835–2842.
[37] B. Löppenberg, D. Dalela, P. Karabon, et al., The impact of local treatment on overall survival in patients with metastatic prostate cancer on diagnosis: a national cancer data base analysis, Eur. Urol. 72 (2016) 14.
[38] S.H. Culp, P.F. Schellhammer, M.B. Williams, Might men diagnosed with metastatic prostate cancer benefit from definitive treatment of the primary tumor? A SEER-based study, Eur. Urol. 65 (2014) 1058–1066.
[39] S. Antwi, T.M. Everson, Prognostic impact of definitive local therapy of the primary tumor in men with metastatic prostate cancer at diagnosis: a population-based, propensity score analysis, Cancer Epidemiol. 38 (2014) 435–441.
[40] Y.H. Shao, S. Kim, D.F. Moore, et al., Cancer-specific survival after metastasis following primary radical prostatectomy compared with radiation therapy in prostate cancer patients: results of a population-based, propensity score-matched analysis, Eur. Urol. 65 (2014) 693.
[41] C. Gratzke, J. Engel, C.G. Stief, Role of radical prostatectomy in metastatic prostate cancer: data from the munich cancer registry, Eur. Urol. 66 (2014) 602–603.
[42] G. Gravis, K. Fizazi, F. Joly, et al., Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial, Lancet Oncol. 14 (2013) 149–158.
[43] R.E. Millikan, S. Wen, L.C. Pagliaro, et al., Phase III trial of androgen ablation with or without three cycles of systemic chemotherapy for advanced prostate cancer, J. Clin. Oncol. 26 (2008) 5936–5942.
[44] I.M. Thompson, C. Tangen, J. Basler, E.D. Crawford, Impact of previous local treatment for prostate cancer on subsequent metastatic disease, J. Urol. 168 (2002) 1008–1012.
[45] G.P. Murphy, S. Beckley, M.F. Brady, et al., Treatment of newly diagnosed metastatic prostate cancer patients with chemotherapy agents in combination with hormones versus hormones alone, Cancer 51 (1983) 1264–1272.
[46] C.L. Vale, S. Burdett, L.H. Rydzewska, et al., Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data, Lancet Oncol. 17 (2016) 243.
[47] T.E.A. Botrel, O. Clark, A.C.L. Pompeo, et al., Efficacy and safety of combined androgen deprivation therapy (ADT) and docetaxel compared with ADT alone for metastatic hormone-naive prostate cancer: a systematic review and meta-analysis, PLoS One 11 (2016) e0157660.
[48] A. Ramosesquivel, C. Fernández, Z. Zeledón, Androgen-deprivation therapy plus chemotherapy in metastatic hormone-sensitive prostate cancer. A systematic review and meta-analysis of randomized clinical trials, Urol. Oncol. Semin. Orig. Invest. 34 (2016) 335.e339-335.e319.
[49] J. Wu, W.K. Chen, W. Zhang, et al., Network meta-analysis of the efficacy and adverse effects of several treatments for advanced/metastatic prostate cancer, Oncotarget 8 (2017) 59709.
[50] B. Alemayehu, E. Buysman, D. Parry, et al., Economic burden and healthcare utilization associated with castration-resistant prostate cancer in a commercial and Medicare Advantage US patient population, J. Med. Econ. 13 (2010) 351–361.
[51] A.C. Won, H. Gurney, G. Marx, et al., Primary treatment of the prostate improves local palliation in men who ultimately develop castrate-resistant prostate cancer, BJU Int. 112 (2013) E250–E255.
[52] G. Aus, J. Hugosson, L. Norlén, Need for hospital care and palliative treatment for prostate cancer treated with noncurative intent, J. Urol. 154 (1995) 466–469.
[53] A. Heidenreich, D. Pfister, D. Porres, Cytoreductive radical prostatectomy in patients with prostate cancer and low volume skeletal metastases: results of a feasibility and case-control study, Eur. Urol. 193 (2015) 832.
[54] S.R. Leyh-Bannurah, S. Gazdovich, L. Budaus, et al., Local therapy improves survival in metastatic prostate cancer, Eur. Urol. 72 (2017) 118–124.