The Effectiveness and Safety of Metronomic Chemotherapy in Patients with Head and Neck Carcinoma: A Systematic Review and Meta-analysis

Xingli Li

Lanzhou University

Jianjian Wang

Lanzhou University

Ting Zhang

Gansu Provincial Maternity and Child-care Hospital

Jiabin Wang

Gansu Provincial Maternity and Child-care Hospital

Zhangcai Zheng

Gansu Provincial Maternity and Child-care Hospital

Cheng Wang

Gansu Provincial Maternity and Child-care Hospital

Lan Yang (✉ 16608055616@163.com)

Gansu Provincial Maternity and Child-care Hospital

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Abstract

Background: Head and neck carcinoma, usually begins in the squamous cells, not only seriously endangers the quality of life, but brings a heavy financial burden for families and countries. Metronomic chemotherapy, a frequent administration of chemotherapeutic agents at a non-toxic dose, gives an alternative low-cost and tolerated approach for patients. We conducted a systematic review to find the effectiveness and safety of metronomic chemotherapy for head and neck cancer.

Methods: We searched seven databases and Clinical.gov from the inception to July 14, 2021. The patients diagnosed head and neck cancer and older than 18 were included. Metronomic chemotherapy was defined as intervention. Randomized and non-randomized trials were all included. Quality assessment of included randomized control trials was performed using the Cochrane Risk-of-Bias criteria, cohort studies using The Newcastle-Ottawa Scale (NOS), single arm trials using the checklist recommended by The Agency for Healthcare Research and Quality (AHRQ). Studies were synthesized using a narrative approach. The indicators used for meta-analysis was hazard ratio (HR).

Results: 310 Literatures were potentially eligible from 7 databases, finally 13 records were included. Five studies were of high quality, while eight were of moderate quality. The overall effect of HR for death of five trials reported had no statistically significant (HR=0.89, 95%CI 0.71-1.10). Subgroup analysis by different design showed a statistically significant HR (0.73, 95%CI 0.60-0.90) in randomized control trials while no significant difference in subgroup of prospective study design (HR=1.23, 95%CI 0.72-2.10). As for HR for PFS, there was no significant difference in overall effect of four studies. HR for PFS was 0.84 (95%CI 0.55-1.31). Subgroup analysis of study design showed that randomized control trials produced a significant HR (0.54, 95%CI 0.45-0.64), while prospective studies did not (1.25, 95%CI 0.73, 2.14).

Conclusions: Metronomic chemotherapy has been an optimistic option for treatment for advanced head and neck cancer, especially in low income and medical resource-restricted regions.

Background

Head and neck cancer, usually begins in the squamous cells from varied anatomic subsites, is always associated with pain, dysfunction, psychosocial distress, and death[1, 2]. It was reported that head and neck cancer was the seventh most common cancer worldwide in 2020 (930,000 new cases and 470,000 deaths), accounting for almost 5% of all cancers and over 4.5% of all cancer death[3]. Though tobacco and alcohol related incidence was decreased slowly for War Against Tobacco, human papillomavirus (HPV) associated cancer is increasing[2, 4, 5].

The treatments for head and neck cancer vary depending on the anatomical location, stage of disease, prior therapeutic effects and so on, including surgery, radiation therapy, chemotherapy and targeted therapy. With improvements of standard therapies, the preservation of function has greatly enhanced while the life prolonged[4], but limitation in applicability are still big challenges. Besides, resistance to

chemotherapy, treatment-related toxicities, disease metastasis and economic burden of drugs still remain major obstacles to cancer treatment[6, 7].

Metronomic chemotherapy, defined as frequent administration of chemotherapeutic agents at a non-toxic dose without extended rest periods, was originally designed to overcome drug-resistance by shifting the therapeutic target from tumor cells to tumor endothelial cells[6, 8, 9]. The effectiveness of metronomic chemotherapy is greatly associated with its anti-cancer mechanism[9]. Therefore, it is increasingly thought as an alternative and a possible approach of low-cost and low toxicities for patients, especially in low- and middle-income regions.

This study aims to systematic review the literatures available of metronomic chemotherapy used in head and neck cancer, through comparing the main outcomes like overall survival and progression free survival, to explore the effectiveness and safety of metronomic chemotherapy. We hope it can give a reference of treatment for advanced head and neck cancer.

Methods

The systematic review was reported based on Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines[10]. The protocol for this systematic review is available in PROSPERO (CRD42020207243).

Search strategy:

We searched the PubMed, Embase, Web of Science, The Cochrane Library, CNKI, WanFang and CBM databases from the inception dates to July 14, 2021, using *head and neck cancer*, *metronomic chemotherapy* and relevant words as key words. An additional file showed in more detail [see Additional file 1]. Clinical.gov was also searched to ensure all the related studies published or ongoing being included. There were no publication date restrictions, and languages were restricted into Chinese and English.

Inclusion and exclusion:

Population:

Adult patients older than 18 years and diagnosed as head and neck cancer were included. Cancers of head and neck are further categorized in the area of oral cavity, pharynx (including oropharynx and hypopharynx), larynx, paranasal sinuses and nasal cavity, salivary glands[11]. Pathologic biopsy is a confirm diagnosis of cancer. Cancers of the brain, the eye, the esophagus, and the thyroid gland, as well as those of the scalp, skin, muscles, and bones of the head and neck, which are not usually classified as head and neck cancers, were excluded from the study[1].

Intervention:

Patients received metronomic chemotherapy were defined as intervention group, whether single agent or combined agents. Therapies except metronomic chemotherapy were all regarded as control treatments, including other chemotherapies, radiotherapy or without treatment.

Type of study:

We selected literatures related to head and neck cancer with metronomic chemotherapy. Studies published or ongoing, randomized or non-randomized design were all included. It was different from our strategy registered in PROSPERO, because randomized control trials were too less. Considering the possible bias resulting from the limited literatures included, we modified our inclusion criteria of study type by including cohort studies, single arm studies and retrospective studies. Records meeting the following conditions were excluded: 1. Trials not targeted to treat, such as determining the optimal dose or qualitative studies; 2. Literatures like comments or letters[12]. If there was any disagreement, we would consult a third member (CW). The primary studies included in systematic reviews and meta-analysis were reviewed, selected and extracted using criteria above.

Risk of bias assessment:

The methodological quality of randomized control trials was assessed by 2 researchers (TZ and J.B. W) independently based on Cochrane Risk-of-Bias criteria, which graded each quality item as low risk, high risk, and unclear risk[13]. The items used to evaluate bias including the random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, blinding of outcome assessor, selective reporting and other bias[13]. The trials were graded as low quality, high quality, or moderate quality based on the following criteria: 1. Trials were considered low quality if either randomization or allocation concealment was assessed as high risk of bias, regardless of the risk of other items; 2. Trials were considered high quality when both randomization and allocation concealment were assessed as a low risk of bias, and all other items were assessed as low or unclear risk of bias; 3. Trials were considered moderate quality if they did not meet criteria of high or low risk[14].

The methodological quality of cohort studies was assessed by The Newcastle-Ottawa Scale (NOS). It awarded each item a maximum of one star in the selection and outcome categories while a maximum of two stars for comparability[15]. We considered one star as one point to quantify the outcomes for comparison.

The methodological quality of non-randomized control trials nor cohort studies was assessed using 11 items checklist recommended by The Agency for Healthcare Research and Quality (AHRQ)[16]. Each quality items were identified as yes, no, or unclear. We considered to score items answered “yes” for one

point, and items answered “no” or “unclear” for zero. The quality of studies was graded as low quality for score of 0–3, moderate quality for score from 4 to 7 and high quality for score from 8 to 11.

Data extraction:

The following information from each study was extracted by two researchers (XL and TZ) independently using a predefined electronic data extraction form: lead author, publication year, country of origin, participant characteristics (number, age, tumor location), study design, treatments (regimen including agents, dose, course/procedure, single or combination agent) and outcomes referred above. A third author (LY) checked extracted data for accuracy. Disagreements were resolved by a group consensus. If the trials had more than 2 group, we only extracted the information interested[14].

Primary and secondary outcomes:

The primary outcome was overall survival (OS), which was measured from the date of randomization or research beginning to the date of death or last follow-up. Some studies gave the overall survival rate, defined as the number of patients who were still alive when last follow-up, usually 3 or 6 months.

The secondary outcomes included progression-free survival (PFS), disease-free survival (DFS), the incidence of adverse events, toxicity, progression, and so on. PFS was measured from the date of randomization or research beginning to the date of progression. DFS was defined as time interval from date of registration till date of recurrence or death of any causes. If trials gave both intention-to-treat (ITT) and per-protocol results, we only extracted ITT results for analyses.

Data synthesis:

Studies that met the inclusion criteria were synthesized using a narrative description because of the heterogeneity in cancer location, intervention (agents, dose, course of different regimens), duration of follow-up and different effect index. Besides, we performed a meta-analysis in Stata SE15 to calculate the hazard ratio (HR) for survival and HR for PFS, and 95% CIs using the Mantel-Haenzel statistical method.

The fixed-effects model was selected first, and statistical heterogeneity between data was evaluated using I^2 statistic. If the heterogeneity was not accepted, then using random-effects model. Subgroup analysis was performed by different study designs, or different regimens. Sensitivity analysis was performed by excluding researches affected the stability of outcomes.

Results

Study selection:

The literature selection process has been shown in the flowchart (Fig.1). 310 potentially eligible studies were identified through 7 databases. Then we excluded 65 duplicates. After screening the 245 articles and trials through titles and abstracts, 80 records were remained and full texts of them were reviewed. Then 67 records including 9 comments or abstracts related to the aim of study were excluded. Finally, 13 records meeting criteria, including 3 randomized control trails[17-19], 1 cohort study[20], 4 prospective studied (3 single arm trials[21-23], 1 match pair analysis[24]) and 5 retrospective studies[25-29] were included.

Study characteristic:

The characteristic of 13 selected studies were shown in Table 1[more details see Additional file 2]. The sample size ranged from 15[23] to 422[17] participants while median age differed from 41[21] to 65[23] years. In terms of tumor location, oral cavity occupied the most proportion, and next were pharynx and larynx. Most studies reported Eastern Cooperative Oncology Group performance status score of participants, except one study that used the Karnofsky Performance Status[19] and three studies did not report which standard they used[20, 27, 28]. Four studies reported their dropout or loss data[17, 19, 21, 23], while remaining did not give the information. Of all the studies included, nine were conducted in India[17, 19, 21, 23-25, 27-29], and two in the USA[18, 26], two in China (Taiwan[20] and Hong Kong[22]).

Treatment regimens

The regimens of 13 studies were shown in Table 2[more details see Additional file 3]. The most common option was 15 mg/m² methotrexate once per week along with 200 mg celecoxib twice per day[17, 19, 24, 25, 27-29], and one study[23] added erlotinib (150 mg per day) based on the common regimen as above. Other treatments including 20 mg AT-101 per day with 75 mg/m² docetaxel per day in one study[18], and 150 mg/m² UFUR twice per day as adjuvant metronomic chemotherapy in one study[20]. In prospective studies, one study used 150 mg erlotinib per day, 200 mg celecoxib twice per day and 9 mg/m² methotrexate once per day[21]. Some used cyclophosphamide between 50 and 150 mg once daily. Besides, one retrospective analysis did not give exact dose of agents including Taxols, Platins, 5-Fluorouracil and Epidermal Growth Factor Receptor inhibitors but reported giving at approximate 50% dose of currently recommended doses[26]. Two randomized control trials used 75 mg/m² cisplatin as positive control[17, 19]. One study set two groups including 75 mg/m² docetaxel every 21 days and 75 mg/m² docetaxel pulse 40mg AT-101 twice daily for 3 days, which was different in using of AT-101 compared with metronomic group[18]. And one study did not give other therapies after surgery which defined as blank control[20].

Primary and secondary outcomes

As shown in Table 2[more details see Additional file 3], only two studies reported OS and PFS[17, 19] in three randomized control trials. Swiecicki et al.[18] stopped trial due to futility pooled data of two groups together for analysis. Instead of giving index of two group, they reported OS and PFS. The cohort study[20] only gave outcome of survival rate (SR) of two groups. Three prospective studies reported Median OS[21, 22, 24]. One study did not calculate median OS for less deaths at median follow-up[23]. Three studies reported median PFS[21-23]. The matched pair analysis[24] showed a benefit for cetuximab-based chemotherapy in terms of superior median PFS and OS. There were four literatures in five retrospective studies reported the median OS [25-27, 29]. One retrospective matched-pair study only reported the estimated two-year DFS[28]. Median PFS of three studies was reported respectively[25, 26, 29]. There was one study using DFS as outcome[27].

We calculated overall effect of HR for death regardless of study design of five trials reported[17, 19-21, 24], which showed the result of no statistically significant HR (0.89, 95%CI/0.71-1.10). Heterogeneity test showed a significant difference ($I^2=76.1$, $P=0.002$). Subgroup analysis performed by different design showed a homogeneity ($I^2=0$, $P=0.342$) and a statistically significant HR (0.73, 95%CI/0.60-0.90) in randomized control trials. Subgroup of prospective study design was of significant heterogeneity ($I^2=79.3$, $P=0.028$), and with no significant difference in HR (1.23, 95%CI/0.72-2.10) (Fig.2).

As for HR for PFS, there was no significant difference in overall effect of four studies[17, 19, 21, 24], that HR for PFS was 0.84 (95%CI/0.55-1.31), the test for heterogeneity gave a significant result ($I^2=93.9$, $P<0.001$). Subgroup analysis of type of design showed that randomized control trials[17, 19] with homogeneity ($I^2=0$, $P=0.351$) produced a significant HR (0.54, 95%CI/0.45-0.64), while prospective studies did not (1.25, 95%CI/0.73, 2.14). The heterogeneity between groups was of significant difference ($P=0.004$) (Fig.3).

Considering the confounding of single arm study and analysis of database, we excluded these two studies[21, 24]. Sensitivity analysis showed a significantly difference in HR for death in remaining studies (HR=0.75, 95%CI/0.64-0.88) (Fig.4).

Risk of bias assessment:

Three randomized control trials were open label designed, none of them were double-blind. Considering it would not affect our outcomes, we assessed these related items for low risk. One trial described random sequence generation and allocation concealment, three trials reported complete outcome. One trial[17] was high quality, two[18, 19] were moderate quality. The cohort study[20] with no details of loss was high quality with a score of 8. Regarding the remaining studies, two got 10 points, one for 8 points, four for 7, one for 6 and 5 respectively. Thus, three[21, 23, 24] were high quality and six[22, 25-29] were moderate quality. The results were showed in Table 1[more details see Additional file 2].

Discussion

The result of this systematic review and meta-analysis showed that the effectiveness of metronomic chemotherapy still needs more and further studies to be identified. Though studies included gave a positive conclusion or point of view [17, 19–21, 25, 26, 28, 29], there were studies with high quality giving opposite conclusion or suggestion for further studies [23, 24]. A match-paired analysis of data showed a negative outcome but proved that metronomic chemotherapy caused less and lighter adverse events [24]. According to the result of meta-analysis, two randomized control trials [17, 19] with great homogeneity showed that metronomic chemotherapy was associated with better PFS, OS and fewer adverse events, which was consistent with other researches [8, 30, 31]. Actually, the continuous administration of low-dose drugs allows prolonged duration of treatment, while minimizing the risk of adverse effects [32]. Regarding its low-cost and well-tolerated [33–35], metronomic chemotherapy has been endorsed as an alternative option for patients with advanced head and neck cancer, which was in line with the current treatment recommendations for cancer patients of maintaining their quality of life [32, 36].

Subgroup analysis showed that two randomized control trials [17, 19] of great homogeneity showed a statistically significant HR for death (0.73, 95% CI 0.60–0.90). Except for their similar design, they had same regimen of 15 mg/m² methotrexate once per week along with 200 mg celecoxib twice per day. A match pair analysis of a prospectively maintained database with same regimen showed an opposite outcome (HR = 1.72, 95% CI 1.05–2.86), which demonstrated cetuximab-based chemotherapy led to a significant improvement in OS in comparison to metronomic chemotherapy, but with more adverse events including severe toxicity [24]. However, the subgroup analysis of same regimen [17, 19, 24] appeared a heterogeneity ($I^2 = 81.1$, $P = 0.005$) with no significant difference in HR (0.91, 95% CI 0.55–1.50). Besides, the sensitivity analysis showed a homogeneity ($I^2 = 0$, $P = 0.599$) and significant outcomes of remaining three studies [17, 19, 20]. Therefore, we thought study design was primary origin of heterogeneity, and more high-quality randomized control trials were needed to identify the effectiveness of this combination of agents in metronomic chemotherapy. The HR for PFS had a same trend with HR for survival.

In order to explore the effectiveness and application of metronomic chemotherapy, some trials registered in Clinical.gov were ongoing, one is a single arm study to explore the safety and efficiency of metronomic capecitabine plus camrelizumab (NCT04510818), and another is about metronomic chemotherapy plus immunotherapy for head and neck cancer (NCT03518606). These results may give new evidence.

To our knowledge, this is the first systematic review and meta-analysis about metronomic chemotherapy for head and neck cancer. Actually, there were some literatures like reviews or letters of metronomic chemotherapy for head and neck cancer published [37, 38], but they did not give a definite inclusion and exclusion, or lacking meta-analysis of outcomes, which demonstrated in our literatures. However, we should acknowledge there were still limitations. Considering seven databases we searched and languages restricted into Chinese and English, we may omit some studies related. Besides, the number of researches in this field was too less to conclude definitely, especially much less lack of high-quality evidence like randomized control trials. Limited by reports of original researches, the indicators for meta-analysis we chose were only HR for death and HR for PFS, which may greatly reduce the credibility of analysis.

Metronomic chemotherapy, as a cost-effective treatment with low toxicity and benefit for improving quality of life, has been an optimistic option for treatment for advanced head and neck cancer, especially in low income and medical resource-restricted regions. However, as referred before, more high-quality randomized control trials should be conducted to give more evidence of its effectiveness. Moreover, considering the maintenance of quality of life functionally and psychologically, the aggressive intent therapy is not always in line with patients' will[39]. Thus, metronomic chemotherapy may be a good choice for patients for its tolerance and low toxicity.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XL and JW designed the work and substantively revised it. XL and TZ extracted and analyzed the data. TZ and J.B. W assessed the risk of bias. ZZ gave good guidance about cancer and treatment. CW and LY did quality control through the study. All authors read and approved the final manuscript.

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References

1. Institution NC. Head and Neck Cancers. <https://www.cancer.gov/types/head-and-neck>. 2017; Accessed October 3, 2020.
2. Chow LQM. Head and Neck Cancer. *N Engl J Med*. 2020; 382(1):60–72. <https://doi.org/10.1056/NEJMra1715715>.
3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021; 71(3):209–249. <https://doi.org/10.3322/caac.21660>.
4. Marur S, Forastiere AA. Head and Neck Squamous Cell Carcinoma: Update on Epidemiology, Diagnosis, and Treatment. *Mayo Clin Proc*. 2016; 91(3):386–396. doi:10.1016/j.mayocp.2015.12.017
5. Gillison ML, Chaturvedi AK, Anderson WF, Fakhry C. Epidemiology of Human Papillomavirus–Positive Head and Neck Squamous Cell Carcinoma. *Journal of Clinical Oncology*. 2015; 33(29):3235–3242. doi:10.1200/JCO.2015.61.6995.
6. Woo IS, Jung YH. Metronomic chemotherapy in metastatic colorectal cancer. *Cancer Lett*. 2017; 400:319–324. doi:10.1016/j.canlet.2017.02.034.
7. Patterson RH, Fischman VG, Wasserman I, Siu J, Shrimel MG, Fagan JJ, Koch W, Alkire BC. Global Burden of Head and Neck Cancer: Economic Consequences, Health, and the Role of Surgery. *Otolaryngol Head Neck Surg*. 2020; 162(3):296–303. <https://doi.org/10.1177/0194599819897265>.
8. Cazzaniga ME, Dionisio MR, Riva F. Metronomic chemotherapy for advanced breast cancer patients. *Cancer Letters* (2016). <http://dx.doi.org/10.1016/j.canlet.2016.12.019>.
9. Chen Y-L, Chang M-C, Cheng W-F. Metronomic chemotherapy and immunotherapy in cancer treatment. *Cancer Letters* (2017). doi:10.1016/j.canlet.2017.01.040.
10. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021; 372:n71. <http://dx.doi.org/10.1136/bmj.n71>.
11. David G. Pfister MSS, MD; David Adelstein, MD; Douglas Adkins, MD. Head and Neck Cancers, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2020 Jul;18(7):873–898. doi:10.6004/jnccn.2020.0031.
12. Bressan V, Stevanin S, Bianchi M, Aleo G, Bagnasco A, Sasso L. The effects of swallowing disorders, dysgeusia, oral mucositis and xerostomia on nutritional status, oral intake and weight loss in head and neck cancer patients: A systematic review. *Cancer Treatment Reviews*. 2016; 45:105–119. doi:10.1016/j.ctrv.2016.03.006.
13. Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA

- (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane 2021. Available from .
14. Zhao JG, Zeng XT, Wang J, Liu L. Association Between Calcium or Vitamin D Supplementation and Fracture Incidence in Community-Dwelling Older Adults: A Systematic Review and Meta-analysis. *JAMA*. 2017; 318(24):2466–2482. doi:10.1001/jama.2017.19344.
 15. GA Wells BS, D O'Connell, J Peterson, V Welch, M Losos, P Tugwell. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohrica/programs/clinical_epidemiology/oxford.asp. 2020. Accessed October 10, 2020.
 16. Rostom A DC, Cranney A, et al. Celiac Disease. Rockville (MD): Agency for Healthcare Research and Quality (US). Evidence Reports/Technology Assessments, No. 104. 2004 Sep. Available from <https://www.ncbi.nlm.nih.gov/books/NBK35156/>.
 17. Patil V, Noronha V, Dhumal SB, Joshi A, Menon N, Bhattacharjee A, Kulkarni S, Ankathi SK, Mahajan A, Sable N et al. Low-cost oral metronomic chemotherapy versus intravenous cisplatin in patients with recurrent, metastatic, inoperable head and neck carcinoma: an open-label, parallel-group, non-inferiority, randomised, phase 3 trial. *The Lancet Global health*. 2020; 8:e1213-e1222. doi:10.1016/s2214-109x(20)30275-8.
 18. Swiecicki PL, Bellile E, Sacco AG, Pearson AT, Taylor JMG, Jackson TL, Chepeha DB, Spector ME, Shuman A, Malloy K et al. A phase II trial of the BCL-2 homolog domain 3 mimetic AT-101 in combination with docetaxel for recurrent, locally advanced, or metastatic head and neck cancer. *Investigational New Drugs*. 2016; 34:481–489. doi:10.1007/s10637-016-0364-5.
 19. Patil VM, Noronha V, Joshi A, Muddu VK, Dhumal S, Bhosale B, Arya S, Juvekar S, Banavali S, D'Cruz A et al. A prospective randomized phase II study comparing metronomic chemotherapy with chemotherapy (single agent cisplatin), in patients with metastatic, relapsed or inoperable squamous cell carcinoma of head and neck. *Oral Oncology*. 2015; 51(3):279–286. <http://dx.doi.org/10.1016/j.oraloncology.2014.12.002>.
 20. Lin J-S, Cheng C-Y, Liu C-J. Oral uracil and tegafur as postoperative adjuvant metronomic chemotherapy in patients with advanced oral squamous cell carcinoma. *Journal of Dental Sciences*. 2015; 10(4). <http://dx.doi.org/10.1016/j.jds.2015.03.004>.
 21. Patil VM, Noronha V, Joshi A, Dhumal S, Mahimkar M, Bhattacharjee A, Gota V, Pandey M, Menon N, Mahajan A et al. Phase I/II Study of Palliative Triple Metronomic Chemotherapy in Platinum-Refractory/Early-Failure Oral Cancer. *Journal of clinical oncology*. 2019; 37(32):3032–3041. <https://doi.org/10.1200/JCO.19.01076>.
 22. Lee VH, Kwong DL, Lam KO, Lai YC, Li Y, Tong CC, Ho PP, Chan WL, Wong LS, Leung DK et al. Metronomic oral cyclophosphamide as third-line systemic treatment or beyond in patients with inoperable locoregionally advanced recurrent or metastatic nasopharyngeal carcinoma. *Medicine*. 2017; 96(15):e6518. <http://dx.doi.org/10.1097/MD.00000000000006518>.
 23. Patil VM, Chakraborty S, Jithin T, Sajith Babu TP, Babu S, Kumar S, Biji M, Bhattacharjee A, Balasubramanian S. An audit of the results of a triplet metronomic chemotherapy regimen

- incorporating a tyrosine kinase inhibitor in recurrent/metastatic head and neck cancers patients. *South Asian J Cancer*. 2016 Apr-Jun; 5(2):48–51. doi:10.4103/2278-330X.181624.
24. VM Patil, V Noronha, A Joshi et al. Comparison of paclitaxel-cetuximab chemotherapy versus metronomic chemotherapy consisting of methotrexate and celecoxib as palliative chemotherapy in head and neck cancers. *Indian journal of cancer*. 2017; 54(1):20–24. doi:10.4103/ijc.IJC_160_17.
 25. VM Patil, V Noronha, A Joshi et al. Retrospective analysis of palliative metronomic chemotherapy in head and neck cancer. *Indian journal of cancer*. 2017; 54(1):25–29. doi:10.4103/ijc.IJC_161_17.
 26. Bishnoi R, Shah C, Bejjanki H, Bennett JA, Reisman DN. An alternative approach with a low dose and prolonged chemotherapy for palliative treatment of locally advanced, metastatic or recurrent squamous cell head and neck cancer. *Applied Cancer Research* (2017) 37:43. doi:10.1186/s41241-017-0049-1.
 27. Avinash Pandey, A. Desai, V. Ostwal, V. Patil, A. Kulkarni, et al. Outcome of operable oral cavity cancer and impact of maintenance metronomic chemotherapy: A retrospective study from rural India. *South Asian J Cancer*. 2016 Apr-Jun; 5(2): 52–55. doi:10.4103/2278-330X.181625.
 28. Pai PS, Vaidya AD, Prabhash K, Banavali SD. Oral metronomic scheduling of anticancer therapy-based treatment compared to existing standard of care in locally advanced oral squamous cell cancers: A matched-pair analysis. *Indian Journal of Cancer*. 2013, 50(2):135–141. doi:10.4103/0019-509X.117024.
 29. Patil V, Noronha V, D'Cruz A K, Banavali SD, Prabhash K. Metronomic chemotherapy in advanced oral cancers. *J Cancer Res Ther*. 2012; 8 Suppl 1:S106-110. doi:10.4103/0973-1482.92223.
 30. Chen JH, Huang WY, Ho CL, Chao TY, Lee JC. Evaluation of oral tegafur-uracil as metronomic therapy following concurrent chemoradiotherapy in patients with non-distant metastatic TNM stage IV nasopharyngeal carcinoma. *Head and Neck*. 2019;41:3775–3782. doi:10.1002/hed.25904.
 31. Patil VM, Noronh V, Joshi A, Karpe A, Talreja V, Chandrasekharan A, Dhumal S, Prabhash K. Metronomic palliative chemotherapy in maxillary sinus tumor. *South Asian Journal of Cancer*. 2016; 5(2):56–58. doi:10.4103/2278-330X.181626.
 32. Rangarajan V, Agrawal A, Purandare N, Shah S, Banavali S. Response assessment with FDG PET/CT in metronomic therapy. *Eur J Nucl Med Mol Imaging*. 2012; 39 (Suppl 2):S155–S303. doi:10.1007/s00259-012-2221-x.
 33. Chubenko VA, Zagorskaya LA, Chubenko VS, Moiseenko FV, Abduloeva NK, Zhabina AS, Kramchaninov MM, Shelekhova KV, Meldo AA, Zikov EM et al. METRONOMIC CHEMOTHERAPY: EFFICACY IN REAL CLINICAL PRACTICE. *Practical oncology*. 2019; 20(4):289–298. doi:10.31917/2004289.
 34. Bansal B, Sultania M, Deo S, Shukla N, Sharma A, Sahoo R, Bhaskar S. Metronomic chemotherapy in borderline operable oral cavity squamous cell carcinoma - a pilot study. *Radiotherapy and Oncology*. 2019; 132:47. doi:10.1016/S0167-8140(19)30257-9.
 35. Caballero M, Sosa AE, Tagliapietra A, Grau JJ. Metastatic adenoid cystic carcinoma of the salivary gland responding to cetuximab plus weekly paclitaxel after no response to weekly paclitaxel alone.

- Head and Neck. 2013; 35(2):E52-E54. doi:10.1002/hed.21870.
36. Gourd E. Metronomic chemotherapy option for advanced oral cancer. *Lancet Oncology*. 2019; 20(11):E614-E614. [https://doi.org/10.1016/S1470-2045\(19\)30623-0](https://doi.org/10.1016/S1470-2045(19)30623-0).
37. De Felice F, Musio D, Tombolini V. Head and neck cancer: metronomic chemotherapy. *BMC Cancer* (2015) 15:677. doi:10.1186/s12885-015-1705-z.
38. De Felice F BI, Musella A, Musio D, Tombolini V. Metronomic chemotherapy in head and neck cancer. *Cancer Letters*. (2016), 400:219–222. doi:10.1016/j.canlet.2016.10.047.
39. Sklan A, Collingridge D: Treating head and neck cancer: for better or for worse? *The Lancet Oncology*. 2017; 18(5):570–571. [http://dx.doi.org/10.1016/S1470-2045\(17\)30269-3](http://dx.doi.org/10.1016/S1470-2045(17)30269-3).

Figures

Figure 1

The systematic review flow diagram.

Figure 2

Subgroup analysis in study design of HR for death

Figure 3

Subgroup analysis in study design of HR for PFS

Figure 4

Sensitivity analysis of metronomic chemotherapy for head and neck cancer

Supplementary Files

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- [Additionalfile1.PubMedSearchHistory.csv](#)
- [Additionalfile2Table1.Characteristicsoftheincludedstudies..xls](#)
- [Additionalfile3Table2.Findingsoftheincludingstudies..xls](#)