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RMAC study: A randomized study for evaluation of metronomic adjuvant chemotherapy in recurrent head and neck cancers post salvage surgical resection in those who are ineligible for re-irradiation

Vijay Patil [a], Vanita Noronha [a], Amit Joshi [a], Nandini Menon [a], Vijayalakshmi Mathrudev [a], Atanu Bhattacharjee [b], Arun Chandrasekharan [a], Dilip Vallathol [a], Hollis Dsouza [a], Sujay Srinivas [a], Tanmay Mandal [a], Pankaj Chaturvedi [c], Devendra Chaukar [c], Prathamesh Pai [c], Sudhir Nair [c], Shiva Thiagrajan [c], Sarbani Laskar [d], Kavita Nawale [a], Sachin Babanrao Dhumal [a], Rupali Tambe [a], Shripad Banavali [a], Kumar Prabhash [a,*]

[a] Department of Medical Oncology, Tata Memorial Centre, HBNI, Mumbai, India
[b] Section of Biostatistics, Centre for Cancer Epidemiology, Tata Memorial Centre, HBNI, Mumbai, India
[c] Department of Head and Neck Surgery, Tata Memorial Centre, HBNI, Mumbai, India
[d] Department of Radiation Oncology, Tata Memorial Centre, HBNI, Mumbai, India

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ABSTRACT

Background: Adjuvant re-chemoradiation after salvage surgery improves disease-free survival in recurrent head and neck cancer. However, most patients are ineligible for re-irradiation and are kept on observation. We investigated the efficacy of metronomic adjuvant chemotherapy (MAC) in this group of patients compared to observation.

Methods: This was a randomized integrated phase II/III clinical trial. Adults with recurrent head and neck cancer, who had undergone salvage surgery, but were ineligible for adjuvant re-irradiation were randomized in a 1:1 ratio to either MAC arm or observation. MAC consisted of weekly oral methotrexate (at a dose of 15 mg per square meter of body surface area) and celecoxib (at a dose of 200 mg orally twice daily) for 6 months. The primary endpoint of phase 2 was disease-free survival (DFS) while that of phase 3 was overall survival (OS). For phase 2, to detect an improvement in the hazard ratio (HR) 0.67 with MAC, with a type 1 error of 10% (1-sided), type 2 error of 30%, 105 patients were required. While for phase 3, with a target HR of 0.77, with a type 1 error of 5%, type 2 error of 20%, 318 patients were required. Here we report the results of phase 2 part of the study.

Results: At a median follow up of 30.2 months (95% confidence interval (CI), 25.3 to 35.1) the 1 year and 2-year DFS were 57.4% (95% CI, 42.8–69.5) and 37.6% (95% CI, 24.1–51) in MAC arm whereas the corresponding numbers were 62.3% (95% CI, 47.8 to 73.8) and 54.2%(95% CI, 39.8 to 66.5) in observation arm, respectively (hazard ratio for progression, 1.45; 95% CI, 0.87 to 2.47; P = 0.15). In the MAC arm, the 1 and 2 year OS was 78.7% (95% CI, 64.9 to 87.6) and 48% (95% CI, 34.1 to 62).The corresponding figures in the observation arm were 79.2% (95% CI, 65.7 to 87.9) and 65.5% (95% CI, 50.9 to 76.7) (hazard ratio for death, 1.7, 95% CI, 0.94 to 3.08; P = 0.08).

Conclusion: The adjuvant 6-month metronomic schedule was ineffective in improving outcomes in recurrent head and neck cancers post salvage surgery who are ineligible for re-radiation.

Trial registration.

Clinical trial registry of India (CTRI)- CTRI/2016/04/006872 [Registered on 26/4/2016]

* Corresponding author at: Department of Medical Oncology, Tata Memorial Centre, HBNI, Mumbai 400012, India.
E-mail address: kumarprabhashtmh@gmail.com (K. Prabhash).

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Introduction

Salvage surgery remains the cornerstone of management of recurrent head and neck cancer [1,2]. However, despite salvage resection, subsequent local and distant failures occur in 60 to 80% of patients, within 2 years of surgery [3,4]. Adjuvant re-radiotherapy with concurrent chemotherapy leads to improved disease-free survival (DFS) from 20% to 62% at 2 years when compared to observation alone [4]. However, not all patients are eligible for re-radiotherapy, either due to early failure or due to the presence of sequelae of previous radiation therapy or inability to give adequate dose due to previous total dose administered in the field of recurrence [5,6]. As a considerable proportion of patients (30 to 92%) fail within 24 months of initial radiation, patients who are eligible for re-radiation are uncommon[7–10]. At present these ineligible patients are kept under observation and the 2-year DFS in these patients is likely below 20%[3,4].

Metronomic chemotherapy consisting of methotrexate and celecoxib has activity in head and neck cancer[11,12]. We conducted a randomized study comparing oral metronomic chemotherapy, comprising of methotrexate and celecoxib, with intravenous cisplatin in advanced head and neck cancer patients treated with palliative intent. Oral metronomic chemotherapy led to a 33% improvement in progression-free survival (PFS) and overall survival (OS)[11]. In another matched pair analysis from Tata Memorial Hospital (TMH) Mumbai, patients with locally advanced head and neck cancers who received perioperative neoadjuvant and adjuvant metronomic chemotherapy with methotrexate and celecoxib, had a 2-year DFS of 95% as opposed to 70% for those patients who did not[13]. We investigated whether the same metronomic adjuvant chemotherapy (MAC) could improve patient outcomes in completely resected recurrent head and neck cancer subjects who are ineligible for re-radiation.

Methods

Trial design and conduct

This was a randomised parallel-group, integrated phase II/III clinical trial conducted at a premier tertiary cancer centre in India. The study protocol was approved by the Institutional Ethics Committee (IEC). All patients provided written informed consent prior to accrual in the study. The study was conducted according to the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2004, Good Clinical Practice (GCP) guidelines, the Indian Council of Medical Research (ICMR) guidelines, the schedule Y and was in compliance with applicable laws and regulations of India. The investigator complied with the study protocol, except when a protocol deviation was required to eliminate an immediate hazard to a subject. The study reports the outcomes post phase 2 part as the intervention was found to be futile.

Participants

The patients eligible for this study were adult (age $\geq$ 18 years) recurrent head and neck cancer, post salvage surgery, ineligible for re-radiation, ECOG PS 0–2 and adequate organ function. The ineligibility for re-irradiation was decided in a multidisciplinary clinic. The ineligibility for re-irradiation was considered when at least one of the following criteria was present; a short disease-free interval (relapse within 18 months of last radiation) or presence of severe late morbidity from previous radiation (example osteoradionecrosis or grade 3 lymphedema according to Common Terminology Criteria for Adverse Events (CTCAE) version 4) or coverage of planning target volume (PTV) would deliver a biologically equivalent dose in excess of 66 Gy3 to 10 cm of the spinal cord or 83.66 Gy3 to brainstem or treatment volume would require coverage of the posterior neck (level 5). Patients with prolonged QT_C interval, uncontrolled comorbidities or infection and pregnant or lactating women were excluded. Subjects should have fulfilled all of the inclusion criteria and none of the exclusion criteria to be eligible for this study (Study protocol-Supplementary appendix).

Randomization

Block randomization was done with 1:1 allocation in both arms. The randomization request was conveyed telephonically by the study coordinator to independent personnel. The randomization was performed by this personnel and was conveyed to the study coordinator telephonically. Neither the principal investigator (PI) nor the other study investigators had access to the randomization sheets.

Interventions

There were 2 arms in the study, the metronomic adjuvant chemotherapy arm (MAC) and the observation arm. Subjects in the MAC arm received weekly oral methotrexate (at a dose of 15 mg per square meter of body-surface area) and celecoxib (at a dose of 200 mg orally twice daily). A total of 6 cycles were administered, with each cycle consisting of 28 days. During treatment, subjects were assessed at the start of each cycle for the first 4 cycles. If subjects tolerated these cycles well, then they were assessed after 2 months. After completion of treatment, patients were followed up every 3 months up to 2 years. Subjects in the observation arm were assessed at monthly intervals for 4 months, then at 6 months, and then every 3 months 2 years. Patients underwent a comprehensive head and neck examination and blood tests (complete blood count, renal function, and liver function tests) at each visit. European Organization for the Research and Treatment of Cancer (EORTC) C30 and HN-35 Quality of Life (QOL) questionnaires were administered to both arms at baseline and at each visit.

Outcomes

Disease-free survival (DFS) was defined as the time from randomization until the first-day disease recurrence was documented, or until death in the absence of recurrence. OS was defined as the time from randomization until the death of the patient. Adverse events were documented in accordance with CTCAE version 4.02.

Sample size

The study had an integrated phase II/III design. For phase 2, to detect an improvement in the hazard ratio (HR) 0.67 with MAC, with a type 1 error of 10% and type 2 error of 30%, 105 patients were required. Analysis for this part of the study was planned after the completion of enrollment and a minimum follow-up of 24 months of the last patient. If the DFS improvement was met, then the study would have entered phase 3. For phase 3, with a target HR of 0.77, type 1 error of 5%, and type 2 error of 20%, 318 patients were required.

Statistical methods

Statistical package for social sciences (SPSS) version 20 and RStudio version 3.1.2 were used for statistical analysis. Futility analysis at the end of phase 2 was performed and descriptive statistics were also performed. Continuous variables were described using median and its 95% confidence interval (CI) while nominal and ordinal variables were described in percentages. Nominal and ordinal data were compared using Fisher's exact test while continuous data were compared using Mood's median test. Median DFS and OS with its 95% Confidence interval (CI) were estimated using the Kaplan Meier method and compared using the log-rank test. Brookmeyer and Crowley method was used for the construction of the 95% CI. COX regression analysis was used for the calculation of hazard ratio (HR) with Efron's method of tie handling, with the observation arm being considered as a reference. The proportional hazard assumption was tested prior to performing the COX

regression analysis. A P-value of 0.1 was considered significant. Data was censored for analysis on 20th March 2020.

Results

Baseline characteristics

In the period from 8th June 2016 to 12th July 2018, 105 patients were recruited; 52 in the MAC arm and 53 in the observation arm. Baseline characteristics at the time of randomization were similar between both arms (Table 1). The majority of patients had a primary in oral cavity (n = 53,50.5%), with relapsed or residual (n = 89,84.5%) being the commonest indication for salvage surgery. The prior tumour (prior to recurrence for which the salvage surgery was performed) and its treatment details are provided in supplementary appendix Table 1. The details of salvage surgery and histopathological details are provided in Table 2. The reasons for ineligibility for radiation were interval of less than < 18 months from last radiation (n = 85,81%), grade 3 or above previous radiation soft tissue sequelae (n = 25,23.8%), risk of excess dose to critical organs at risk (n = 89,84.8%) and presence of posterior fossa node which couldn't be safely encompassed in radiation portal (n = 1, 1.9%) {Supplementary Appendix Table 2}.

Treatment compliance

In the metronomic arm, all patients started metronomic chemotherapy and the median time to start therapy was 29 days (Interquartile range 21–35.75) (Figure 1, Supplementary Table 3). Thirty six patients (69.2%) completed 6 cycles. The reason for not completing 6 cycles was recurrence in 12 (23%), adverse events in 2 (3.9%), and patient's choice in 2 (3.9%). The adverse events leading to permanent discontinuation were febrile neutropenia & non-neutropenic infection in 1 (1.9%) patient each. Dose reduction of methotrexate was required in 1 patient after cycle 1 in view of grade 3 mucositis with febrile neutropenia. Dose reduction of 20% (from 15 mg/m^2 weekly to 12 mg/m^2) was done in subsequent weekly doses. reduced. Dose delays were seen in 4 patients (7.7%). The reasons were mucositis and myelosuppression, dysphagia, non-neutropenic fever and logistics, in 1 patient (1.9%) each.

Table 1
Baseline Characteristics.

Variable	Metronomic adjuvant chemotherapy arm (n = 52)	Observation arm (n = 53)	P-value
Age in years			
Median	53(44.25–59)	53 (43.5–60)	0.761
(interquartile	5(9.6)	7(13.2)	
range)			
Elderly-no(%)			
Gender-no(%)			0.39
Male	47(90.4)	44(83)	
Female	5(9.6)	9(17)	
ECOG PS-no(%)			0.618
0	2(3.8)	1(1.9)	
1	50(96.2)	52(98.1)	
Habits-no(%)*			
Cigarette	6(11.5)	7(13.2)	1
Beedi	16(30.8)	14(26.4)	0.67
Smokeless tobacco	31(59.6)	38(71.7)	0.221
Alcohol	6(11.5)	7(13.2)	1
Comorbidities-no(%)			
*	12(23.1)	7(13.2)	0.214
Hypertension	5(9.6)	10(18.9)	0.265
Type 2 Diabetes	-	3(5.7)	0.243
mellitus	-	1(1.9)	1
COPD			
Ischemic heart			
disease			
Site of malignancy-			0.277
no(%)	26(50)	27(50.9)	
Oral cavity	16(30.8)	10(18.9)	
Oropharynx	6(11.5)	6(11.3)	
Hypopharynx	4(7.7)	10(18.9)	
Larynx			
Type of recurrence			
Relapse or residual	46(88.5)	43(81.1)	0.416
Second Primary	6(11.5)	10(18.9)	
Site of recurrence			
Local	26(50)	34(64.2)	0.366
Nodal	17(32.7)	12(22.6)	
Local and nodal	9(17.3)	7(13.2)	

Table 1- Baseline characteristics. ECOG PS- Eastern Cooperative Oncology Group Performance Status. COPD-Chronic obstructive pulmonary disease. *-patient may be represented under more than one subheading. Elderly is defined as 65 years or above.

Table 2
Salvage surgery and histopathological details.

Variable	Metronomic adjuvant chemotherapy arm (n = 52)	Observation arm (n = 53)	P-value
Surgery type-no(%)			1.0
Open	50(96.2)	51(96.2)	
Robotic	2(3.8)	2(3.8)	
Margin status-no(%)			0.25
Negative	42(80.8)	44(83)	
Close	9(17.3)	5(9.4)	
Positive	1(1.9)	4(7.5)	
Number of lymph nodes dissected			0.773
Median (Interquartile range)	17.5(10.25–26.5)	17(6.5–25.5)	
Pathological T			0.277
grouping-no(%)	17(32.7)	12(22.6)	
T0	4(7.7)	9(17)	
T1	9(17.3)	5(9.4)	
T2	4(7.7)	8(15.1)	
T3	18(34.6)	18(34)	
T4a	-	1(1.9)	
T4b			
Pathological N			0.581
grouping-no(%)	22(42.3)	30(56.6)	
N0	18(34.6)	12(22.6)	
N1	2(3.8)	3(5.7)	
N2a	7(13.5)	7(13.2)	
N2b	2(3.8)	1(1.9)	
N2c	1(1.9)	-	
N3			
Stage grouping-no(%)			0.123
I	1(1.9)	6(11.3)	
II	7(13.5)	2(3.8)	
III	17(32.7)	14(26.4)	
IVA	26(50)	29(54.7)	
IVB	1(1.9)	2(3.8)	
Perinodal extension-no			0.548
(%)	21(40.4)	18(34)	
Yes	31(59.6)	35(66)	
No			
Adverse events-no(%)			
Poor differentiation	21(40.4)	24(45.3)	0.695
Lymphovascular	5(9.6)	6(11.3)	1
emboli	20(38.5)	18(34)	0.687
Perineural invasion	11(21.2)	8(15.1)	0.457
Depth of invasion >			
1 cm			

Table 2- Salvage surgery and histopathological details. *-All stagings are in accordance with the 7th AJCC-UICC edition of TNM staging. UICC- Union for International Cancer Control AJCC-American Joint Committee on Cancer.

Adverse event rate

Acute adverse events were available in all patients (Table 3). The rate of any grade mucositis (25% versus 3.8%), odynophagia (25% versus 7.5%), dysphagia (32.7% versus 13.2%), hyponatremia (30.8% versus 7.5%), hypomagnesemia (9.6% versus 0%) and anemia (61.5% versus

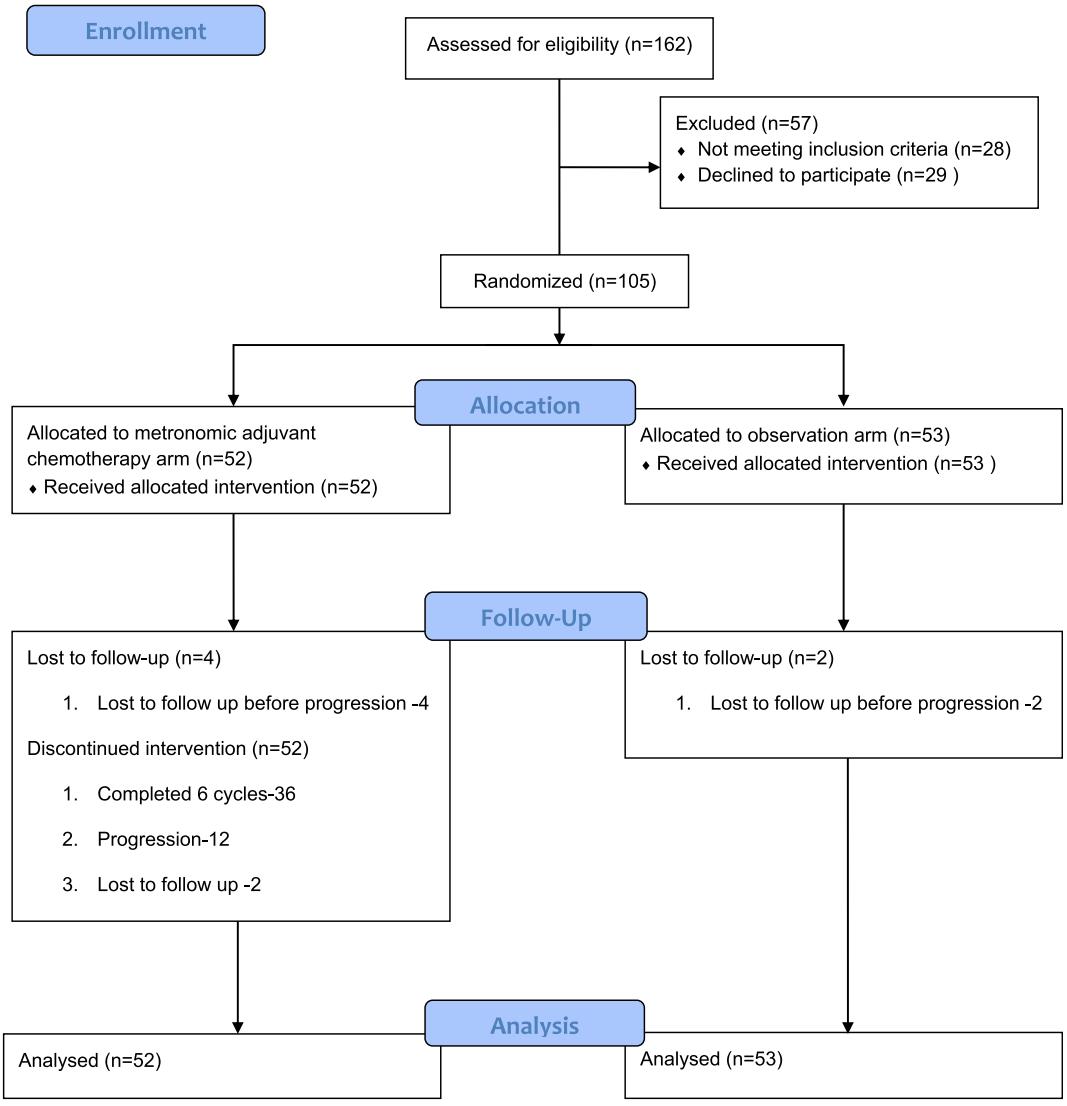

Fig. 1. Consort Diagram.

26.4%) were higher in the MAC arm. Late adverse events were defined as those occurring 90 days after randomization and were captured in 36 patients in both arms.. In the MAC arm, 12 of 52 patients progressed prior to the occurrence of late adverse events and data was unavailable in 4 patients. In the observation arm, out of 53 patients, 12 patients progressed prior to the occurrence of late adverse events and data was unavailable in 5 patients. Incidence of any grade dysphagia was seen in 21 (58.3%) versus 11(30.6%) in the MAC and observation arm, respectively (P = 0.032).

Outcomes

Disease-free survival

At a median follow up of 30.2 months (95% CI, 25.3–35.1), there were 33 and 25 events for DFS in the MAC and observation arm, respectively. The median DFS was 14.5 months (95% CI, 9.67–24.3) versus not reached (95% CI, 9.33-NA) in the MAC and observation arm, respectively (P = 0.15). The 1 year and 2-year DFS was 57.4% (95% CI, 42.8–69.5) and 37.6% (95% CI, 24.1–51) in MAC arm whereas the corresponding numbers were 62.3% (95% CI, 47.8–73.8) and 54.2% (95 %CI 39.8–66.5) in observation arm, respectively (Figure 2). The hazard ratio with the observation arm as reference was 1.45 (95% CI, 0.87–2.47, P = 0.15). The impact of various prognostic factors on DFS is shown in the Supplementary Appendix Table 4.

In the MAC arm, there were 33 events (63.5%). These were failures in 26 patients (50%), second primary in 2 patients (3.8%), death due to unknown cause in 4 patients (7.7%) and death due to chronic comorbidity in 1 (1.9%) patient. The pattern of failures was local failure in 9 (17.3%), nodal failure in 8 (15.4%), local & nodal failure in 4 (7.7%), distant failure in 4(7.7%), local & distant in 1 (1.9%) and failure at local, nodal & distant in 1(1.9%) patient.

In the observation arm, there were 25 events (47.2%). These were failures in 20 patients (37.7%), second primary in 4 patients (7.5%) and death due to unknown cause in 1 (1.9%) patient. The pattern of failures was local failure in 13 (24.5%), nodal failure in 2 (3.8%), local & nodal failure in 5 (9.4%), distant failure in 2 (3.8%), nodal & distant in 1 (1.9%) and failure at local,nodal & distant in 1(1.9%) patient.

Overall survival

At the time of data censoring, there were 45 deaths, 27 in MAC and 18 in the observation arm. The median OS in the MAC arm was 24 months (95% CI, 18.2-NA) while it was not reached (95% CI, NA to NA) in the observation arm (P = 0.08) (Figure 3). In the MAC arm the 1 and 2 year OS was 78.7% (95% CI, 64.9 to 87.6) and 48% (95% CI 34.1 to 62) while in the observation arm, they were 79.2% (95% CI, 65.7 to 87.9) and 65.5% (95% CI, 50.9 to 76.7). The hazard ratio with the observation

Table 3
Adverse events.

Acute adverse events	Metronomic adjuvant chemotherapy arm (n = 52)		Observation arm (n = 53)		P-value	
	Any grade	Grade 3 or above	Any grade	Grade 3 or above	Any grade	Grade 3 or above
Mucositis	13 (25)	1(1.9)	2(3.8)	–	0.002	0.495
Odynophagia	13 (25)	5(9.6)	4(7.5)	1(1.9)	0.018	0.113
Dysphagia	17 (32.7)	7 (13.5)	7 (13.2)	2(3.8)	0.021	0.093
Weight Loss	7 (13.5)	–	3(5.7)	–	0.201	–
Hyponatremia	16 (30.8)	3(5.8)	4(7.5)	–	0.003	0.118
Hypokalemia	1(1.9)	–	–	–	0.495	–
Hypomagnesemia	5(9.6)	–	–	–	0.027	–
SGOT rise	2(3.8)	–	–	–	0.243	–
SGPT rise	4(7.7)	–	–	–	0.057	–
Anemia	32 (61.5)	1(1.9)	14 (26.4)	–	0.000	0.495
Neutropenia	2(3.8)	2(3.8)	2(3.8)	–	1	0.243
Thrombocytopenia	2(3.8)	2(3.8)	–	–	0.243	0.243
Late adverse events	Metronomic adjuvant chemotherapy arm (n = 36)		Observation arm (n = 36)		P-value	
	Any grade	Grade 3 or above	Any grade	Grade 3 or above	Any grade	Grade 3 or above
Xerostomia	26 (72.2)	–	26 (72.2)	–	1	–
Hyperpigmentation	23 (63.9)	–	23 (63.9)	–	1	–
Skin thickening	25 (69.4)	12 (33.3)	30 (83.3)	18(50)	0.267	0.232
Lymphedema	25 (69.4)	12 (33.3)	29 (80.6)	17 (47.2)	0.415	0.337
Dysphagia	21 (58.3)	4 (11.1)	11 (30.6)	5 (13.9)	0.032	1
Dysguesia	17 (47.2)	–	18 (50)	1(2.8)	1	1
Hypothyroidism	16 (44.4)	–	17 (47.2)	–	1	–
Creatinine rise	1(2.8)	–	1(2.8)	–	1	–

Table 3- Table depicting acute and late adverse events. Late adverse events were captured in 36 patients in both arms and were defined as occurring 90 days after randomisation. In the metronomic arm out of 52 patients, 12 patients progressed prior to occurrence of late adverse events and data was unavailable in 4 patients. In the observation arm out of 53 patients, 12 patients progressed prior to occurrence of late adverse events and data was unavailable in 5 patients. SGOT-Serum glutamic oxaloacetic transaminase. SGPT-Serum glutamic pyruvic transaminase.

arm as reference was 1.7 (95% CI, 0.94–3.08, P = 0.08). The impact of various prognostic factors on OS is shown in the Supplementary Appendix Table 5.

The cause of death in the MAC arm was disease-related in 22 (42.3%), unknown causes in 4 (7.7%) and due to chronic comorbidity in 1 (1.9%) patient. In the observation arm, 17 (32.1%) deaths were disease-related while 1 (1.9%) death was due to an unknown cause.

Discussion

This is the first randomised phase 2 data exploring the use of post-operative metronomic therapy in recurrent head and neck cancer who have undergone salvage resection, have high-risk features but are ineligible for re-radiation. The study proves that the metronomic schedule of weekly methotrexate (at a dose of 15 mg per square meter of body surface area) with twice-daily oral celecoxib 200 mg for 6 months failed to improve disease-free survival over observation alone. As a matter of fact, there was a negative trend towards higher relapse and deaths in the MAC arm. Hence, administration of this schedule in clinical practice as adjuvant therapy in post salvage surgery settings cannot be recommended.

The above-mentioned schedule of metronomic chemotherapy has a proven advantage over intravenous chemotherapy schedules in palliative settings[11] where there was an improvement in progression-free survival and overall survival. This was achieved at a low rate of adverse events and with improvement in quality of life scores. [11,14] With these encouraging results, the schedule was tried as an adjuvant in post salvage resection patients who are at high risk of failure. However, it was not successful and this highlights an important aspect that results in a palliative setting does not necessarily translate into benefit the adjuvant setting. Multiple examples of other such scenarios are available like the FOLFIRI regimen in colon cancer[15], tyrosine kinase inhibitors in drug-sensitive EGFR mutated lung cancer[16] and antiangiogenic therapy in the colon[17], lung[18], renal clear cell carcinoma[19] and breast cancer[20]. Hence, formal testing of regimens that are successful in a palliative setting is necessary in an adjuvant setting prior to their routine recommendation.

There can be multiple clinical reasons for this failure. Patients selected were those who were ineligible for re-radiation with multiple patients having short disease-free intervals (>50% below 1 year). In the palliative setting two-drug, metronomic schedules are effective in patients with longer disease-free intervals.[11] It had limited action in patients with failures below 6 months[21]. Triple metronomic schedule consisting of methotrexate, celecoxib and erlotinib has activity in these patients[12] and should be considered for further adjuvant studies in this setting of low disease-free interval. The dose of methotrexate was 15 mg per square meter of body surface area. This dose was chosen as it is approximately 1/3rd of the maximum tolerable dose of weekly methotrexate schedules of 40 mg per $m^{2.}$ [11] However, we have shown that a dose of 9 mg per square meter of body surface area of methotrexate has more activity and has higher anti-angiogenic potential[12] and is considered to be the optimal biological dose of methotrexate. Future studies should consider this dose of methotrexate for metronomic action. The 2 drug schedule was administered for 6 months. The failure rates in head and neck cancer are high till 18 months[7,8]. Thus, an appropriate schedule could be up to 18 months. Such long adjuvant schedules have shown activity in ovarian cancer with bevacizumab[22] and with hormone blockade in hormone-positive breast cancer.[23,24].

There may be added biological reasons for these results. The local milieu is important for the action of metronomic chemotherapy[25,26]. A similar phenomenon is seen with checkpoint inhibitors, where studies with Nivolumab in glioma as adjuvant therapy have failed.[27,28] However, when administered as neoadjuvant therapy it has shown promise[29]. It seems that exposure to the local milieu is proposed as the reason for the same.[30] One of the mechanisms of metronomic action is via immunomodulation and hence the absence of local milieu will hamper this action and its impact on lymphocytes may have led to worse outcomes.[25,26] This is further strengthened by the fact that in phase 2 randomised study reported by Nair et al, administration of metronomic schedules prior to surgery in resectable oral cancer was associated with improvement in outcomes[31]. A large phase 3 study from Tata Memorial Center addressing this issue is ongoing and has both neoadjuvant and adjuvant components (CTRI/2015/01/005405). Also, the phenomenon of angiogenic switch occurs in hours following surgery. [32–35] The metronomic schedules in the current study started weeks after surgery. It is possible that the efficacy would have been different if these schedules would have been given preoperatively and continued in the immediate postoperative period. The addition of metronomic had detrimental effects on OS and this may be also due to the added toxicity of celecoxib and methotrexate may have led to an increased risk of death due to aspiration pneumonia and cardiac events.

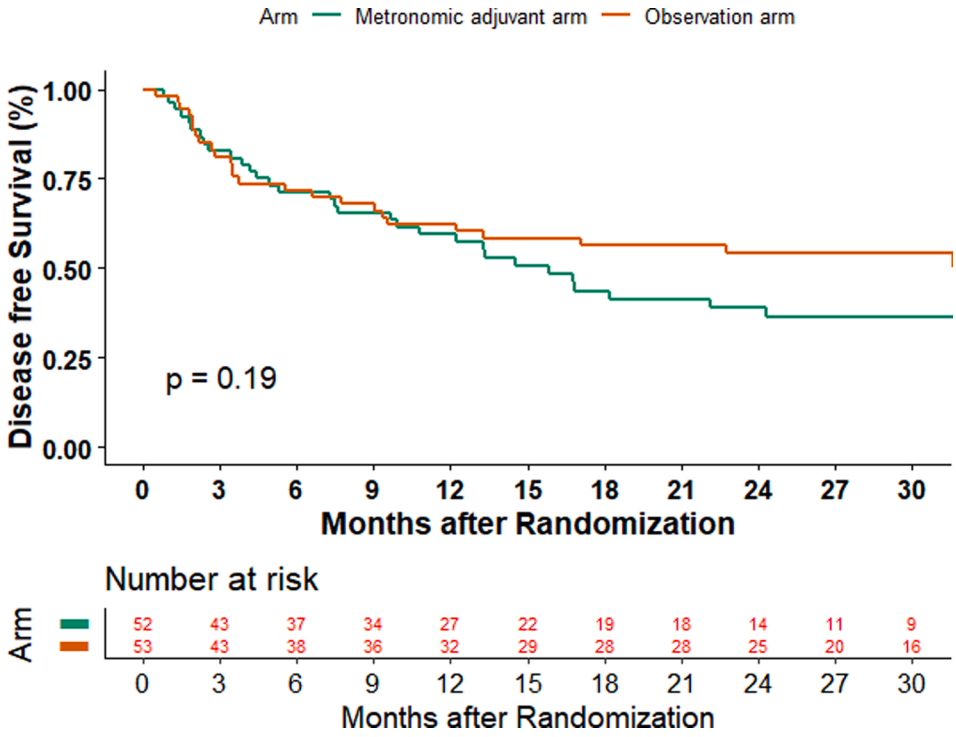

Fig. 2. Disease free survival graph.

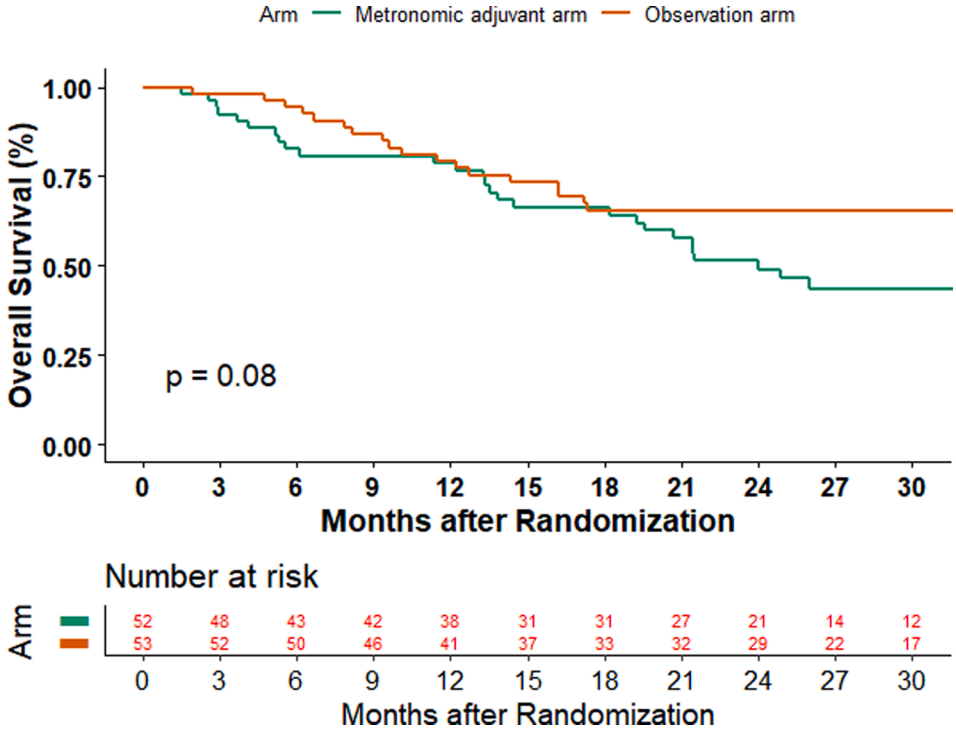

Fig. 3. Overall survival graph.

The study has its strengths and limitations. The strength of this study was that it was a randomised study that was adequately powered, studied an unaddressed issue in literature and had mature results with a median follow up of>2 years. It was a single centre study, predominantly done in oral cancer settings and the surgery was performed by the expert head and neck surgeons, with an envious low rate of margin positivity. The margin positive rate in T3-T4 head and neck cancers in the Western world is in the range of to 32.4%[36,37] while those in our study were only 4.76% (n = 5) patients.

Conclusion

The adjuvant 6-month metronomic schedule was ineffective in improving outcomes in recurrent head and neck cancers post salvage

surgery who are ineligible for re-radiation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2022.105816.

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