

Modified Docetaxel, Cisplatin, and Fluorouracil (mDCF) as a Neoadjuvant Chemotherapy for Non-metastatic Esophageal Cancer (nMEC)

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Objective: Perioperative chemotherapy can potentially downstage esophageal cancer, reducing the risk of early systemic dissemination. One recommended neoadjuvant regimen for managing gastroesophageal junction and esophageal cancer is docetaxel, cisplatin, and 5-fluorouracil (DCF). To address the high toxicity profile of DCF, modifications in dosages and treatment intervals have been studied. We integrated a modified DCF regimen (mDCF) into a multimodal treatment approach for non-metastatic esophageal cancer (nMEC). Retrospectively, we sought to describe our community experience of administering neoadjuvant mDCF to patients with nMEC.

Design: Patients diagnosed with nMEC between August 2008 and November 2017 and prescribed mDCF were identified for retrospective review. Outcomes of interest included disease-free survival (DFS), overall survival (OS), and hematologic toxicities. Analyses were performed using SAS 9.4.

Results: Thirty patients met inclusion criteria with a median age of 64.9 years; 90% were male. The 2-year and 5-year DFS was 60.8% and 41.7%, respectively, for adenocarcinoma and 71.4% and 71.4% for squamous cell carcinoma (SCC). The 2-year and 5-year OS was 64.9% and 44.5%, respectively, for adenocarcinoma and 71.4% and 71.4% for SCC. Both DFS and OS decreased with increasing disease stage, histology (adenocarcinoma versus squamous), esophageal compared to esophagogastric-junction involvement, and without surgical intervention. Frequent toxicity grades for leukopenia and thrombocytopenia were Grades I and II.

Conclusion: Using an mDCF regimen in combination with chemoradiation +/- surgical resection in a community setting appears to have an acceptable toxicity profile as well as DFS and OS outcomes compared to chemotherapeutic regimens reported in other similar studies.

Keywords: Modified docetaxel, cisplatin, and fluorouracil; Non-metastatic esophageal cancer; Disease-free survival; Overall survival; Hematologic toxicities; Community

With the lowest 5-year relative survival (19%) among all cancer types, esophageal cancer is a fatal malignancy with an estimated 16,080 deaths in the United States (US) in 2019.¹ Although it represents only 1% of all newly diagnosed cancers, esophageal cancer accounts for about 3% of all cancer deaths in the US.^{2,3} In addition to other histologic types, squamous cell carcinoma and adenocarcinoma are the most frequently diagnosed variants of esophageal cancer, representing 31.3% and 64.1% of all esophagus carcinoma, respectively.^{3,4} Although race/ethnicity plays a role in the survival of esophageal cancer, patients with esophageal squamous cell carcinoma (SCC) tend to have poorer survival rates than patients with esophageal adenocarcinoma (AC).^{5,6}

Surgery plays an essential role in controlling local/regional esophageal carcinoma and optimizing treatment outcomes; however, it has a limited impact on survival for those with advanced esophageal carcinoma.⁷⁻¹⁰ A multimodal treatment approach combining surgical and non-surgical therapies personalized to the patient's needs, disease type, and stage, has been recommended by the European Society for Medical Oncology Guidelines Committee in the management of esophageal carcinoma.⁹⁻¹¹ Perioperative chemotherapy has the potential advantage of downstaging esophageal cancer and reducing the risk of early systemic dissemination.⁹⁻¹¹ Indeed, the survival advantage of perioperative neoadjuvant strategy over surgery alone in SCC and AC was confirmed in multiple meta-analyses.¹²⁻¹⁴ Still, the optimal neoadjuvant regimen has not been well identified.

In the last few decades, the first line treatment for esophageal cancer has consisted of two to three neoadjuvant chemotherapeutic agents with or without concurrent radiotherapy.¹²⁻¹⁴ The most frequently seen combination of neoadjuvant chemotherapy has been the combination of cisplatin and 5-fluorouracil (CF). However, the dosage, cycle, and interval of administration of the CF regimen has varied in clinical trials.¹²⁻¹⁴ The combination of docetaxel, cisplatin, and 5-fluorouracil (DCF) are frequently utilized in advanced esophageal SCC and AC. Ferri and colleagues¹⁵ conducted a phase II multicenter trial studying the effectiveness and toxicity of perioperative DCF (three 3-week cycles DCF [docetaxel 75 mg/m² on day 1, cisplatin 75 mg/m² on day 1, 5-FU 750 mg/m² for 120 hours] before and after surgery) for locally advanced esophageal and gastric adenocarcinoma. The findings of their study supported that not only is the DCF regimen the first line treatment for advanced gastric adenocarcinoma, but it is also a tolerable and effective neoadjuvant regimen for the management of gastroesophageal junction and esophageal cancer.^{15,16} Additionally, two 3-week DCF cycles have shown great effectiveness in managing advanced, metastatic, or recurrent esophageal squamous cell carcinoma when concurrently administered with radiotherapy.^{17,18} However, a major concern related to DCF was raised due to the significant severe adverse events (Grade III/IV adverse event of 70%), especially neutropenia (about 80%).^{16,17}

Due to the relatively high toxicity profile of DCF, some clinicians have explored the option of modifying the dosage and/or frequency of this chemotherapy regimen with the hopes of maintaining effectiveness while decreasing the toxicity. A modified weekly DCF (docetaxel 35 mg/m² and cisplatin 25 mg/m² on days 1, 8, 15, 29, 36, 43, 50, and 57; 5-FU 180 mg/m² on days 1-21 and 5-FU 150 mg/m² on days 29-63) added to 50 Gy radiotherapy described by Pasini and colleagues^{19,20} showed a better pathological complete remission and lower rates of severe adverse events (Grade III/IV neutropenia: 13.5%; Grade III/IV nonhematological toxicity: 32.4%). Shah and colleagues²¹ have also described another modified DCF (mDCF) regimen (docetaxel 40 mg/m² on day 1, cisplatin 40 mg/m² on day 3, 5-FU 2000 mg/m² on days 1-2, leucovorin 400 mg/m² on day 1) provided every 2 weeks with/without bevacizumab, which was found to extend survival with a lower toxicity profile (Grade III/IV neutropenia 50-60%) in contrast to two 3-week DCF cycles in the management of metastatic gastroesophageal adenocarcinoma.^{21,22} Our institution also adopted an mDCF regimen and integrated its use into our multimodal treatment approach for patients with non-metastatic esophageal cancer (nMEC). Our mDCF regimen was similar to that described by Shah et al^{21,22} with two important differences: (1) cisplatin is administered on day 1 in our regimen but not on day 2 or day 3 as presented in Shah's trials; and (2) leucovorin and granulocyte colony-stimulating factors are provided. With a decade of experience utilizing the mDCF regimen in conjunction with radiation +/- surgery for patients with nMEC, we sought to describe our experience of administering neoadjuvant mDCF to patients with nMEC in a real-world setting.

Methods

Patients

From our electronic health records, we identified all esophageal carcinoma cases histologically diagnosed and managed within our health network between August 1, 2008 and November 30, 2017 (N=115). Only records from adult patients (≥18 years of age) who received mDCF for nMEC were considered for analysis. Imaging studies such as endoscopic ultrasound (EUS), computed tomography (CT), positron emission tomography (PET) scans, and pathology reports were further used to ascertain the stage of the esophageal tumors. Individuals who did not receive mDCF (N =74), had metastatic disease (N =9), or withdrew further treatment (N =2) were excluded from our final sample (N =30).

A retrospective chart review of the 30 cases was performed with corresponding analysis of disease-free survival (DFS), overall survival (OS), and toxicities. The analysis was conducted from the time of esophageal cancer diagnosis to time of death or disease progression/recurrence. Furthermore, we manually abstracted data on patient demographics (age and gender), tumor features (histology, grade, and stage), other concurrent treatments, hematologic toxicities, and post-treatment status. This study was approved by the Marshfield Clinic Research Institute institutional review board (IRB-18-297).

Treatment description

All patients received an mDCF regimen consisting of docetaxel 40 mg/m² IV infusion (day 1), cisplatin 40 mg/m² IV (day 1), 5-fluorouracil 400 mg/m² IV (day 1), 5-fluorouracil 1000 mg/m² continuous IV infusion over 48 hours (days 1 and 2), and leucovorin 400 mg/m² (day 1). The functional status of each patient before treatment initiation was assessed using the Eastern Cooperative Oncology Group (ECOG) performance status scale.²³ The mDCF regimen was administered every 2 weeks with standard premedication and antiemetic treatment for a total of four to six cycles. Chemoradiation was subsequently administered with weekly doses of carboplatin and paclitaxel as radiosensitizers along with either external beam radiation or brachytherapy. Chemoradiotherapy was followed by an esophagectomy if the tumor was considered resectable. Additional medications given during the course of chemotherapy include leucovorin and granulocyte colony stimulating factors (G-CSF) such as pegfilgrastim. Hematologic toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).²⁴ Specifically, we assessed for hematological toxicities such as anemia, leukopenia, neutropenia, and thrombocytopenia.

Statistical analyses

Descriptive statistics were performed to assess patient and tumor characteristics at baseline, concurrent treatments with multimodal therapy, and hematologic toxicities. Kaplan-Meier curves were generated for analysis of DFS and OS. The DFS and OS functions were examined for each group in these variables: histology, stage, gastroesophageal junction involvement, and surgical treatment. DFS was measured from the date of diagnosis to disease recurrence/progression, whereas OS was measured from the date of diagnosis to death. Statistical analysis was performed using SAS 9.4 (SAS Institute, INC., Cary, NC, USA).

Results

Patient characteristics

Patient and tumor characteristics for our cohort are shown in Table 1. The majority of patients were men (90%) with a median age of 64.9 years (interquartile range 61.4-72.6 years). Approximately one-third of the patients had no previous history of smoking. All patients had an ECOG performance status of <2 at baseline. The esophageal tumors diagnosed among these patients were mostly adenocarcinoma type (76.7%), with esophagogastric junction (GEJ) involvement (40%) being less frequent in the total population.

Treatment and efficacy

Table 2 describes the mDCF treatment and subsequent multimodal therapies used for these patients. All patients received radiation therapy except for two: an individual with inflammatory bowel disease (preempting radiation treatment) and another that died as a result of dehydration and cardiac complication after the fourth mDCF cycle. The majority of patients (63.3%) underwent esophagectomy.

Table 1. Patient Characteristics (N = 30)

Characteristic	n	%
Age at diagnosis		
Median: 64.9 years		
IQR: 61.4 – 72.6 years		
Gender		
Male	27	90.0
Female	3	10.0
Smoking		
Current	8	26.7
Former	12	40.0
Never	10	33.3
ECOG performance status		
0	28	93.3
1	2	6.7
Histology		
Squamous	7	23.3
Adenocarcinoma	23	76.7
Tumor site		
Esophageal	18	60.0
Esophagogastric junction involvement	12	40.0
Pathology reports		
Tumor stage		
T1	1	3.3
T2	4	13.3
T3	23	76.7
T4	2	6.7
Nodal status		
N0	12	40.0
N1	16	53.3
N2	2	6.7
Tumor size (cm²)		
<4	11	36.7
5-6	9	30.0
7-10	8	26.7
>10	3	10.0
Grade		
I	1	3.3
II	15	50.0
III	14	46.7
Stage		
I	3	10.0
II	14	46.7
III	13	43.3
Other non-esophageal cancer		
Yes	9	30.0
No	21	70.0

IQR, Interquartile Range (Q1-Q3); ECOG, Eastern Cooperative Oncology Group; mDCF, modified docetaxel, cisplatin and fluorouracil.

Table 2. Neoadjuvant Treatment and Patient Status following mDCF Therapy (N =30)

Characteristic	n	%
mDCF cycle		
Median: 6		
IQR: 4 - 6		
Radiation		
Yes	28	93.3
No	2	6.7
Surgical resection		
Yes	19	63.3
No	11	36.7
Recurrence		
Yes	9	30.0
No	21	70.0
Post-treatment Status		
Alive	16	53.3
Dead	14	46.7
Recurrence	9	30.0
Not cancer related	5	16.7

mDCF, modified docetaxel, cisplatin and fluorouracil; IQR, Interquartile Range (Q1-Q3).

Figure 1 depicts the DFS and OS curves. The survival curves for DFS and OS were close to each other, with only one patient surviving with recurrent disease. Mean DFS was found to be 54.7±7.7 months, and median OS was 56.7±7.8 months for our cohort (squamous cell carcinoma: 76.5 months, adenocarcinoma: 44.4 months). All patients with stage I esophageal cancer were

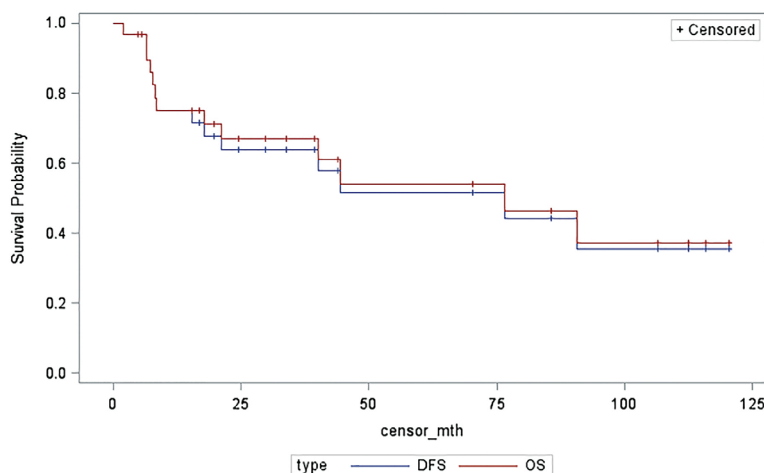
recurrence-free and alive at the end of both the second and fifth years following initial diagnosis (Table 3). Both DFS and OS decreased with increasing disease stage, histology (adenocarcinoma versus squamous), tumor location (esophageal versus GEJ involvement), and without surgical intervention. The DFS and OS mirrored each other at all-time points of follow-up in stage II, esophageal squamous cell carcinoma (SCC), GEJ involvement, and non-resected esophageal cancers, while the DFS and OS remained the same at 2-year and 5-year follow-up in esophageal SCC (71.4%). Among the patients who did not have surgical resection (11), one underwent surgery as the study was completed; five could not have surgery due to the location of the tumor; three had adverse event(s) (two with debilitation, and one with hypotension 1), and two had no residual tumor following neoadjuvant mDCF and/or chemoradiotherapy.

Hematologic toxicities

As demonstrated in Table 4, Grade III or IV hematologic toxicities were less frequently seen compared to Grade I and II toxicities, with anemia and neutropenia being the least common higher-grade toxicities at 13.3% and 13.4%, respectively. The number and frequency of hematological toxicities were proportional between nMEC subtypes.

Discussion

Our retrospective examination of the rates of OS, DFS, and hematologic toxicities of mDCF in conjunction with radiotherapy +/- surgical resection used to treat nMEC in a community setting further emphasizes the promise of this regimen’s use as a neoadjuvant treatment when incorporated in multimodal therapy for nMEC, especially for patients with AC of nMEC.



# at risk	Baseline	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years	10 years	11 years	12 years
Type													
DFS	30	21	17	13	12	8	8	8	6	5	4	3	1
OS	30	21	17	13	12	8	8	8	6	5	4	3	1

Figure 1. Comparison of DFS and OS following mDCF therapy for esophageal cancer. Note. mDCF, modified docetaxel, cisplatin, and fluorouracil; DFS, Disease-free survival; OS, Overall survival.

Examining the nMEC subpopulation of patients diagnosed with AC in our study, the 5-year OS was comparable to that reported by several prior studies using alternate chemotherapeutic regimens. The most frequently mentioned neoadjuvant chemotherapy is CF (cisplatin + 5-fluorouracil), while, in fact, multiple combinations and times of administration (prior-and/or post-surgery) of neoadjuvant chemotherapy were proposed and studied in the last decades to identify the best treatment in patients with localized nMEC.²⁵⁻³⁰ The neoadjuvant ECX (epirubicin 50 mg/m², cisplatin 60 mg/m², and capecitabine 1250 mg/m²; median survival: 26.1 months) and neoadjuvant CF (cisplatin 80 mg/m² and fluorouracil 1000 mg/m²; median survival: 23.4 months) were compared in the OE05 trial conducted in England.²⁹ Patients with surgically

Table 3. Disease-Free and Overall Survival following mDCF Therapy According to Tumor Features and Surgical Treatment (N =30)

Variable	Disease-Free Survival			Overall Survival		
	2-year, %	3-year, %	5-year, %	2-year, %	3-year, %	5-year, %
Stage						
I	100.0	100.0	100.0	100.0	100.0	100.0
II	68.8	68.8	51.6	68.8	68.8	51.6
III	50.0	50.0	37.5	57.1	57.1	42.9
Histology						
Adenocarcinoma	60.8	60.8	41.7	64.9	64.9	44.5
Squamous	71.4	71.4	71.4	71.4	71.4	71.4
Location						
Esophageal	66.7	66.7	57.1	72.2	72.2	61.9
GEJ involvement	60.0	60.0	45.0	60.0	60.0	45.0
Surgical resection						
Yes	65.3	65.3	54.4	69.9	69.9	58.3
No	60.6	60.6	48.5	60.6	60.6	48.5
Overall	63.9	63.9	51.6	67.0	67.0	54.2

GEJ, Gastroesophageal junction; mDCF, modified docetaxel, cisplatin, and fluorouracil.

resectable nMEC AC had a better median survival with neoadjuvant ECX (26.1 months) than those with neoadjuvant CF (23.4 months).²⁹ However, Grade III/IV neutropenia rate was higher with ECX (23%) than CF (17%).²⁹ Our study, on the other hand, shows a promising profile in both safety and survival outcome: 13% Grade III/IV neutropenia and 44 months median survival time in the nMEC AC subgroup. A similar median survival time in the CROSS trial has been observed in neoadjuvant chemoradiotherapy comprising taxane + platinum and radiation (41.4 Gy).^{28,30} In the CROSS trial, patients with resectable nMEC were treated either with surgery only or neoadjuvant chemoradiotherapy followed by surgery; the

neoadjuvant chemoradiotherapy comprised five cycles of neoadjuvant PC (paclitaxel 50 mg/m², carboplatin AUC 2 mg/mL per min on day 1, 8, 15, 22 and 29) concurrent with radiotherapy (23 fractions of 1.8 Gy starting on the first day of the first chemotherapy, 5 days per week in weeks 1, 2, 3, and 4, then 3 days in week 5).^{28,30} Findings in the CROSS trial showed patients treated with neoadjuvant chemoradiotherapy demonstrated better survival outcomes (median survival time: 43.2 vs. 24.0 months) compared to those treated with surgery only, and neoadjuvant chemoradiotherapy (taxane + platinum+ radiation) was associated with less severe adverse events (Grade III/IV neutropenia: 2%, Grade III/IV leukopenia: 6%, Grade III/

Table 4. Hematologic Toxicities During mDCF Treatment (N =30)

Toxicity Type	Grade ^a				
	1 N (%)	2 N (%)	3 N (%)	4 N (%)	3/4 N (%)
Anemia	15 (50.0)	11 (36.7)	4 (13.3)	0 (0.0)	4 (13.3)
Squamous cell carcinoma (N=7)	5 (71.4)	2 (28.6)	0 (0.0)	0 (0.0)	
Adenocarcinoma (N=23)	10 (43.5)	9 (39.1)	4 (17.4)	0 (0.0)	
Leukopenia	14 (46.7)	3 (10.0)	11 (36.7)	2 (6.7)	13 (43.4)
Squamous cell carcinoma (N=7)	4 (57.1)	0 (0.0)	2 (28.6)	1 (14.3)	
Adenocarcinoma (N=23)	10 (43.5)	3 (13.0)	9 (39.1)	1 (4.4)	
Neutropenia	15 (50.0)	11 (36.7)	2 (6.7)	2 (6.7)	4 (13.3)
Squamous cell carcinoma (N=7)	4 (57.1)	2 (28.6)	0 (0.0)	1 (14.3)	
Adenocarcinoma (N=23)	11 (47.8)	9 (39.1)	2 (8.7)	1 (4.4)	
Thrombocytopenia	19 (63.3)	6 (20.9)	5 (16.7)	0 (0.0)	5 (16.7)
Squamous cell carcinoma (N=7)	5 (71.4)	2 (28.8)	0 (0.0)	0 (0.0)	
Adenocarcinoma (N=23)	14 (60.9)	4 (17.4)	5 (21.7)	0 (0.0)	

^aGrading was defined using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. (Finnigan 2018)

IV thrombocytopenia: 1%) than neoadjuvant mDCF (taxane + platinum + 5-FU) in our study (neutropenia: 13%, leukopenia: 43%, thrombocytopenia: 17%).³⁰ With all evidence from these different studies, we summarized that the combination of taxane and platinum might be a better mainstay of neoadjuvant for nMEC AC than CF (cisplatin and platinum), because less severe adverse events were observed. However, different compounds under the same category might have different safety profiles, and so further studies focused on neoadjuvant chemotherapy with taxane and platinum are encouraged.

Studies have shown the effectiveness of mDCF in patients with nMEC AC, while providers need to pay more attention to the dosage of mDCF, interval among cycle, and administration time. A multicenter phase II trial of perioperative DCF combined with surgical resection for advanced nMEC patients reported a 3-year OS of 60% with 14-22% Grade III/IV neutropenia.¹⁵ In our study, not only did nMEC AC patients treated with neoadjuvant mDCF have good survival outcomes (3-year and 5-year OS of 64.9% and 44.5%), but patients also suffered less from severe neutropenia (13%). However, one should be aware of the differences that exist between the two studies, making it hard to perform a comparative effectiveness study. For example, all patients in Ferri's study had an advanced nMEC diagnosis and were treated with perioperative mDCF + surgery. Only 63% of our patients had surgery after the four to six cycle adjuvant mDCF.¹⁵ Examined closely, the dosages of modified DCF and interval of the cycle were different between the two studies. Three 3-week cycles mDCF (docetaxel 75 mg/m² on day 1, cisplatin 75 mg/m² on day 1, 5-FU 750 mg/m² for 120 hours) were provided before and after surgery in Ferri's, while four 6-week mDCF (docetaxel 40 mg/m² on day 1, cisplatin 40 mg/m² on day 1, 5-FU 400 mg/m² for 48 hours, leucovorin 400 mg/m² on day 1) were administrated before chemoradiotherapy + surgery. The dosage of individual compounds and interval between cycles play an essential role in the effectiveness and toxicity of mDCF as well. Simply put, both studies have shown that mDCF has a greater potential for better outcomes in patients with local and local-advanced nMEC AC, but further studies with more rigid study design and head-to-head comparisons to address confounding factors are needed.

The mDCF regimen also demonstrates promising results for locally advanced esophageal SCC compared to the parent DCF regimen. In a 2012 study by Katada and colleagues,³¹ the preoperative administration of DCF demonstrated better OS and DFS compared to CF for the treatment of locally advanced, resectable esophageal SCC. The DCF regimen in Katada's study included docetaxel 70-75 mg/m² (day 1), cisplatin 70-75 mg/m² (day 1), and 5-fluorouracil 750 mg/m² IV infusion (day 1-5) and was repeated twice every 3 weeks. The 2-year OS and DFS of study subjects were 93% and 68%, respectively. The Grade III/IV hematological toxicities were a major concern, with 87% of patients experiencing

leukopenia, and 92% experiencing neutropenia.³¹ The 2-year OS and DFS of our mDCF regimen was 71.4% with lower rates of Grade III/IV hematological toxicity (43% leukopenia and 14% neutropenia). Higher dosages of DCF seem to correlate with better survival outcomes, yet the high rates of serious adverse events are often negatively associated with disease-related quality of life. While a direct comparison to patients in the Katada study³¹ is difficult, especially in light of racial/ethnic differences (Japanese vs. Americans), sample size, and the addition of chemoradiation in our study, the relatively favorable DFS and OS of the mDCF regimen with much lower rates of toxicity suggests that minor adjustments in DCF dosages may be a promising treatment option for patients with locally advanced SCC of the esophagus. Again, further studies are needed for direct comparisons in this SCC subpopulation.

A few limitations to our study should be addressed. First, as this was a retrospective study, we were limited by factors inherent to this study design, such as less strict inclusion and exclusion criteria and certain essential information missing in the charts. Data were collected for routine clinical care rather than for research purposes, and no control group was used for comparison. When we reviewed and obtained patient information for analysis (such as DFS), we might not have captured all disease-related information if not explicitly documented in the EHR, resulting in slight differences in DFS and OS. Lastly, our study population was relatively small and homogeneous concerning race/ethnicity (approximately 90% non-Hispanic Whites vs. 77% of the general US population), which limits the generalizability of our results.

Conclusion

Our results suggest that mDCF as part of a multimodal treatment regimen for nMEC is an effective and tolerable neoadjuvant chemotherapy regimen used in a community setting. Further studies are needed for direct comparisons.

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