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ORIGINAL ARTICLE

Single-center comparison of multiple chemotherapy regimens for concurrent chemoradiotherapy in unresectable stage III non-small-cell lung cancer

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Abstract
Purpose To date, the best chemotherapy regimen to combine with concurrent radiotherapy in stage III non-small-cell lung cancer remains undetermined. We compared the survival outcomes and toxicities in patients who were treated with etoposide–cisplatin (EP), paclitaxel–carboplatin (PC), or vinblastine–cisplatin (VP) in one large cancer referral center.
Methods We enrolled patients who received concurrent chemoradiotherapy at our university-affiliated hospital between January 1, 2009 and December 31, 2013. Demographic and clinical characteristics were identified. Progression-free survival (PFS) and overall survival (OS) between the different treatment groups were compared using Kaplan–Meier and Cox proportional hazards regression models. Treatment-related toxicities were also compared.
Results A total of 107 patients were treated with EP (31.8%), PC (32.7%) or VP (35.5%). Treatment with VP was significantly superior to PC, both in terms of median PFS [29.2 vs. 10.5 months; hazard ratio (HR) 0.43; 95% CI 0.21–0.85; $p = 0.01$] and in terms of median OS [40.7 vs. 17.8 months; (HR) 0.42; (0.21–0.84); $p = 0.01$]. However, there was no survival difference between EP and either one of the other regimens, but there was significantly more toxicities reported with the use of EP (73.5%) compared to PC (44.7%) or VP (37.1%); ($p = 0.001$). The most frequent non-hematologic toxicities for the entire cohort were esophagitis (28%), fatigue (22.4%), pneumonitis (14%), and nephrotoxicity (9.3%).
Conclusion Although the present study is limited by its small cohort and its retrospective nature, the results suggest that VP might be superior to PC and is less toxic than EP.

Keywords Stage III NSCLC · Locally advanced NSCLC · Chemotherapy · Definitive chemoradiotherapy

Introduction

Despite remarkable progress in modern-day oncology, lung cancer remains the leading cause of cancer-related mortality. non-small-cell lung cancer (NSCLC) accounts for more than 80% of lung cancer cases with approximately 20–25% of these being classified as locally advanced stage III disease [1]. Definitive radiotherapy was a standard modality for the management of patients with locally advanced NSCLC, but progress in the past two decades allowed for the inclusion of chemotherapy in the therapeutic paradigm [2, 3]. One meta-analysis initially indicated that concurrent chemoradiation and sequential chemoradiation are each superior to radiation therapy alone [4]. Concurrent chemoradiation was subsequently found to be superior to sequential chemoradiation both in terms of survival and locoregional control, due to the radio-sensitizing effect of chemotherapy [5]. The phase III RTOG 9410 study is the

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largest trial to prospectively confirm the benefit of concurrent chemoradiotherapy [6].

Although concurrent chemoradiation has been established as the standard therapeutic strategy, many questions remains unanswered in regards to the best chemotherapy regimen. Cisplatin-based chemoradiotherapy regimens have been tested in several randomized trials, and the most commonly used agents in association with cisplatin were etoposide and vinka alkaloids (vinblastine or vinorelbine) [5–8].

Since carboplatin and cisplatin are believed by to be interchangeable, the RTOG tested a weekly regimen of low-dose paclitaxel/carboplatin (PC), based on its ease of delivery and its favorable toxicity profile [9]. The efficacy results being relatively comparable to those obtained with cisplatin-based regimen, PC became a popular therapeutic alternative frequently used in combination with radiotherapy, especially in North America [9, 10]. To date, only one large study using the Department of Veterans Affairs (VA) Central Cancer Registry sought to retrospectively compare the efficacy of PC and etoposide/cisplatin (EP) [10]. No differences in survival were noted when patients were matched for prognostic variables, but the toxicity profile favored the PC regimen. Another underpowered phase II trial managed to demonstrate a survival benefit in favor of EP when prospectively comparing it to PC [11]. Considering the lack of definitive data addressing the optimal choice of chemotherapy and in an effort to offer further insight into the relative efficacy and toxicity of EP, PC, and VP, we retrospectively reviewed the outcomes of patients with stage III NSCLC treated with either regimen at our center.

Patients, materials, and methods

Setting and study population

We retrospectively reviewed the clinical records of patients diagnosed with locally advanced NSCLC at the Centre Hospitalier de l'Université de Montréal (CHUM), one of two major cancer networks in the city of Montréal, Quebec. Data available from the CHUM's medical archives was used to identify all patients who were diagnosed with unresectable stage III NSCLC between January 1, 2009 and December 31, 2013 (Fig. 1). Disease stage was determined using the seventh edition of the American Joint Commission on Cancer's staging system [12].

Patients who were treated with definitive chemoradiotherapy were included in the study. Concurrent chemoradiation therapy consisted of administering the first dose of chemotherapy on day 1 of radiation therapy. All patients who had surgery, as part of tri-modality therapy, were excluded. Patients diagnosed at the CHUM and treated elsewhere were also excluded.

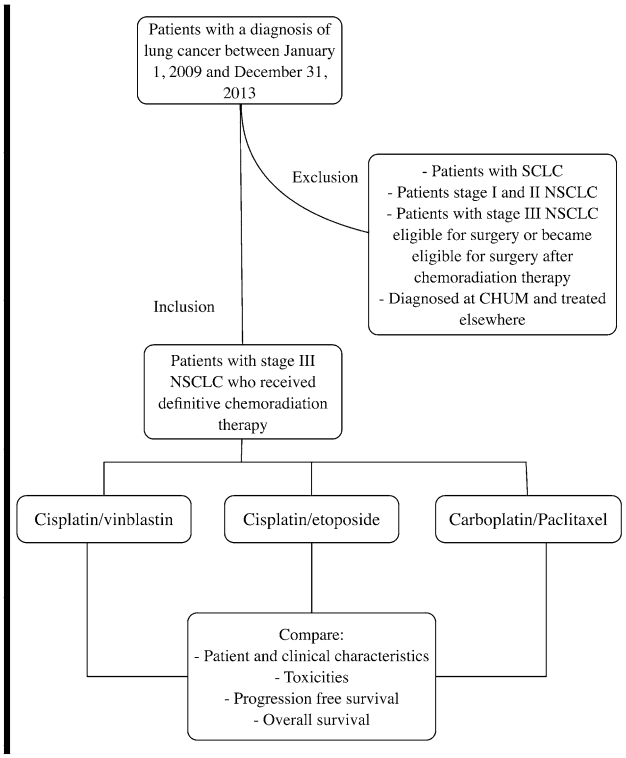

Fig. 1 Identification and inclusion/exclusion of patients with stage III non-small-cell lung cancer (NSCLC). *SCLC* small cell lung cancer, *CHUM* Centre Hospitalier de l'Université de Montréal

This study was approved by the CHUM's Institutional Review Board.

Analytical variables

The patients' clinical records were reviewed from the time of diagnosis until the first notation of death or the date of last contact. We retained information relating to the age at diagnosis, gender, histology, tumor (T) and nodal (N) stage, comorbidities, tobacco consumption, dose of radiation therapy, and lines of therapy administered subsequent to progression. Performance status was measured according to the ECOG classification which ranges from grade 0 (fully active) to grade 5 (dead). Patients were categorized into different treatment arms depending on which chemotherapy regimen was administered concurrently with radiotherapy (EP, VP, PC). The chemotherapy regimen each patient received was usually determined by the attending physician's preference.

Treatment-related toxicities were documented.

Overall survival (OS) was defined as the time from treatment initiation until death or loss of follow-up. Progression-free survival (PFS) was defined as the time from treatment initiation until first objective tumor progression, loss of follow-up, or death.

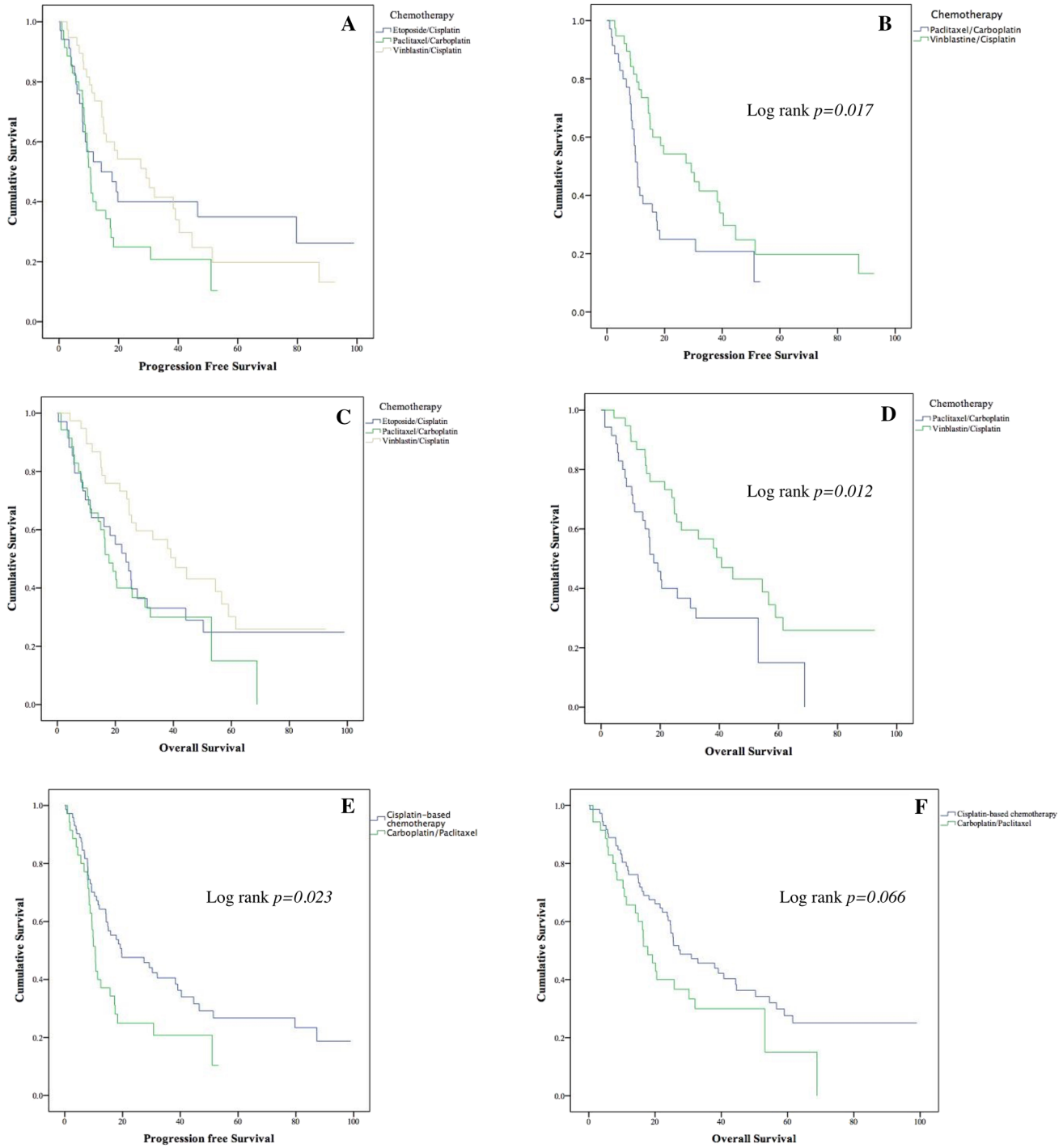

Fig. 2 **a** Progression-free survival of all three groups; **b** progression-free survival of PC and VP groups; **c** overall survival of all three groups; **d** overall survival of PC and VP groups; **e** progression-free survival of cisplatin-based regimen versus PC; **f** progression-free survival of cisplatin-based regimen versus PC. *PC* paclitaxel/carboplatin, *VP* vinblastin/cisplatin

Laboratory findings at diagnosis included hemoglobin, albumin, and creatinine level (Fig. 2).

Treatment considerations

The PC group received carboplatin [area under the curve (AUC) 2] and paclitaxel (45 mg/m^2) administered on days 1, 8, 15, 22, 28, and 35 ± 42 over a period of 6–7 weeks. The EP group received 50 mg/m^2 of cisplatin administered on days 1, 8, 29, and 36, and 50 mg/m^2/day of etoposide delivered on days 1–5 and 29–33. The VP group received 100 mg/m^2 of cisplatin on days 1 and 29 and 5 mg/m^2 of vinblastine on days 1, 8, 15, 22, and 29. Participants received up to 60–66 Gy of cumulative concurrent radiotherapy doses administered in conventional daily fractions of 1.8–2.0 Gy.

Statistical methods

SPSS 21.0 software was used for statistical analysis. Descriptive statistics were used to describe the patterns of treatment delivery. Multivariate analysis was assessed using a binary logistic regression [Method Enter]. Survival time was calculated in months and defined as the time from study entry until death or loss of follow-up. Survival curves were plotted using Kaplan–Meier methods and the log-rank test was applied. Survival analysis was performed using Cox proportional hazards model and hazard ratios (HR) were calculated. All statistical tests were conducted at the 5% level, and 95% confidence intervals (CI).

Results

Characteristics of the study cohort

Patient characteristics are described in Table 1. In total, 125 eligible cases treated at the CHUM during the predesignated period fulfilled the inclusion criteria, and 107 were included in the final analysis after rigorous assessment for missing variables and exclusion/inclusion criteria.

Median age at diagnosis was 62 (±8.6) years for the entire cohort, and patients in the VP arm had the lowest median age (57 ± 7) whereas patients in the PC arm had the highest median age (66 ± 9.8). Female patients comprised 45.7% of the study population. Most patients (98.1%) had an ECOG-PS of 0–1. Adenocarcinoma (50.5%), was the most frequent histologic subtype. Most patients had stage IIIA disease (70.1%) (Table 2).

Adverse events and toxicity

Treatment-related toxicities are listed in Table 3. Patients in the PE arm had significantly more acute toxicities (73.5%) than patients in the PC (44.7%) and the VP (39.4%) arms ($p = 0.006$). Esophagitis and pneumonitis were most prevalent in the PE arm (44.1 and 20.6%, respectively). Nephrotoxicity only occurred in cisplatin-containing arms. Only one treatment-related death was noted in the PE arm. Dose reductions were common among patients experiencing treatment-related toxicities in the entire cohort (EP = 58.9%; PC = 37.1%; VP = 52%).[1]

Survival analysis

Survival was analyzed after a median follow-up time of 58.7 months for living patients. Results of median OS and median PFS for each of the treatment arms is listed in Table 3. Patients in the VP arm had a significant PFS and OS advantage in comparison with the PC arm [hazard ratio (HR) 0.43; 95% CI 0.21–0.85; $p = 0.015$ and (HR) 0.42; (0.21–0.84); $p = 0.015$, respectively]. There were no statistical differences in survival between the EP arm and each of the two other treatment arms. When both cisplatin-based regimens (EP + VP) were compared to PC, a PFS advantage was noted in favor of the cisplatin-based chemotherapy [19.6 vs. 10.5 months; (HR) = 0.46; 95% CI (0.26–0.81); $p = 0.008$]. Of note, only five patients were lost to follow-up (one patient in the EP arm and two patients in each of the other arms).

In a multivariate analysis, using Cox regression model, baseline hemoglobin [≥12 g/dL (HR) 0.96; (0.95–0.98); $p = 0.003$] was the only variable other than treatment arm with statistically significant impact on OS. Other covariate included age, sex, ECOG, baseline albumin, baseline creatinine, histology, TNM stage, T stage, and N stage.

Pulmonary progression was most common in all treatment arms, and cerebral metastasis accounted for more than 30% of first site of progressive disease (Table 4).

Discussion

Our retrospective analysis is the first to compare the three most commonly used chemoradiotherapy regimens in patients with unresectable stage III NSCLC. OS and PFS favored VP over PC, whereas no survival difference was shown between EP and either regimen. Additionally, PFS favored cisplatin-based chemotherapy regimens over PC. Nevertheless, EP was associated with the highest rate of treatment-related toxicities and the only treatment-related death in the cohort, which

[1] Dose reductions in this arm are superior to the reported toxicities because vinblastine doses on days 8;15 and 22 tend to be omitted when the patient experiences asymptomatic hematologic toxicities. Tests are usually conducted at outpatient facility and results are sent directly to the pharmacy where a decision is made in regards to the upcoming dose depending on the complete blood count.

Table 1 Patient characteristics

	Etoposide/cisplatin 31.7% ($n = 34$)	Paclitaxel/carboplatin 32.7% ($n = 35$)	Cisplatin/vinblastine 35.5% ($n = 38$)	Total $n = 107$
Median age (years)	64 (±7.6)	66 (±9.8)	57 (±7.0)	62 (±8.6)
Sex (F)	38.2 (13)	48.6 (17)	50 (19)	45.7 (49)
ECOG				
ECOG 0	32.4 (11)	34.3 (12)	52.6 (20)	40.2 (43)
ECOG 1	61.8 (21)	65.7 (23)	47.4 (18)	57.9 (62)
ECOG 2	5.9 (2)	–	–	1.9 (2)
Comorbidities				
COPD	33.3%	41.2%	38.5%	–
Cardiac	45.8%	41.2%	30.7%	–
Peripheral vascular disease	20.9%	11.8%	23.1%	–
Nephropathy	0	5.9%	7.7%	–
Lines of therapy after progression				
No further therapy	52.4 (11)	28.6 (6)	19 (4)	–
One line	46.4 (13)	35.7 (10)	17.9 (5)	–
Two or more lines	51.3 (15)	14.8 (4)	29.6 (8)	–
Morphology				
Adenocarcinoma	38.2 (13)	42.9 (15)	68.4 (26)	50.5 (54)
Squamous cell Carcinoma	38.2 (13)	37.1 (13)	23.7 (9)	32.7 (35)
Poorly differentiated Carcinoma	23.6 (8)	20 (7)	7.9 (3)	16.8 (18)
Stage TNM				
IIIA	64.7 (22)	62.9 (22)	81.6 (31)	70.1 (75)
IIIB	35.3 (12)	37.1 (13)	18.4 (7)	29.9 (32)
Stage T				
T1	17.6 (6)	22.9 (8)	13.2 (5)	17.8 (19)
T2	26.5 (9)	25.7 (9)	42.1 (16)	31.8 (34)
T3	17.6 (6)	35 (7)	18.4 (7)	18.7 (20)
T4	38.2 (13)	32.4 (11)	26.3 (10)	31.8 (34)
Stage N				
N0	5.9 (2)	8.6 (3)	7.9 (3)	7.5 (8)
N1	11.8 (4)	5.7 (2)	7.9 (3)	8.4 (9)
N2	64.7 (22)	68.6 (24)	76.3 (29)	70.1 (75)
N3	17.6 (6)	17.1 (6)	7.9 (3)	14.0 (15)

COPD chronic obstructive pulmonary disease

Table 2 Treatment-related toxicities

	Etoposide/cisplatin [% (*n*)]	Paclitaxel/carboplatin [% (*n*)]	Cisplatin/vinblastine [% (*n*)]	Total [% (*n*)]
Esophagitis	44.1 (15)	22.9 (8)	18.4 (7)	28 (30)
Fatigue	35.3 (12)	11.4 (4)	21.0 (8)	22.4 (24)
Pneumonitis	20.6 (7)	14.3 (5)	7.9 (3)	14 (15)
Nephrotoxicity	11.8 (4)	0 (0)	15.8 (6)	9.3 (10)
Ototoxicity	14.7 (5)	0 (0)	2.6 (1)	5.6 (6)
Febrile neutropenia	8.8 (3)	0 (0)	15.8 (6)	8.4 (9)
Neuropathy	8.8 (3)	2.9 (1)	0 (0)	3.7 (4)
Death	2.9 (1)	0 (0)	0 (0)	0.9 (1)

Table 3 Survival analysis

	Overall survival (months)	95% CI	Three-year survival (%)	Progression-free survival (months)	95% CI
Etoposide/cisplatin	23.6	15.6–31.7	23.5	14.1	1.1–27.2
Vinblastine/cisplatin	40.7	26.4–55.0	47	29.2	13.4–44.7
Cisplatin-based regimens	27.5	14.7–40.3	36.1	19.6	5.5–33.8
Carboplatin/paclitaxel	17.8	13.2–22.4	20	10.5	9.1–12.0
Entire cohort	25.3	20.6–30.0		15.7	10.6–20.8

Table 4 Pattern of progression

	Etoposide/cisplatin [% (*n*)]	Carboplatin/paclitaxel [% (*n*)]	Vinblastin/cisplatin [% (*n*)]	Total [% (*n*)]
Pulmonary progression	68.4 (13)	57.1 (16)	53.9 (14)	58.9 (43)
Cerebral metastasis	26.3 (5)	35.7 (10)	30.7 (8)	31.5 (23)
Other systemic metastasis	5.3 (1)	7.2 (2)	15.4 (4)	9.6 (7)

might have mitigated the overall efficacy of this regimen. Such results are consistent with the large VA retrospective analysis, demonstrating no survival differences between the PC and EP group but indicating higher rates of hospitalization, outpatient visits, and infectious/renal complications for patients receiving the EP combination [10].

One possible reason for the superiority of cisplatin-based regimens, and in particular the VP regimen, might be associated with cisplatin's potentially superior radio-sensitizing ability when administered with concurrent radiation therapy [13]. The belief in these preclinical data was reinforced by older phase III trials failing to demonstrate the efficacy of single-agent carboplatin as a radio-sensitizer in stage III NSCLC when single-agent cisplatin had succeeded [14–17]. However, a recent phase III Japanese trial evaluated low-dose carboplatin administered at a dose of 30 mg/m^2 per day, 5 days a week for 20 days, concurrently with radiation therapy in patients older that 70 years [18]. This trial demonstrated an OS benefit in favor of the concurrent arm (22.4 vs. 16.9; HR 0.68; 95.4% CI 0.47–0.98; $p = 0.0179$), thereby confirming the role of carboplatin as an adequate radio-sensitizer and providing clinical benefit to older patients who might have been subject to greater cisplatin-related toxicities and complications.

Another possible explanation for the survival difference might be due to a slight imbalance in the treatment arms which could have favored the VP group where younger age, a better ECOG performance status, and higher rates of stage IIIA disease were noted.

Despite the caveats of cross-trial comparison, OS and PFS results for the PC and EP groups are somewhat comparable to the numbers obtained in large landmark trials evaluating these regimens [6, 8]. On the other hand, the survival values obtained with the VP regimen are significantly superior to what is described in the preexisting literature, which might reflect an impact of the selection bias in this subgroup [7]. Despite this bias, these results also reflect encouraging contemporary survival rates (47% 3-year survival), undoubtably enhanced by the advances in radiation delivery techniques and supportive care measures.

The toxicity profile of VP, being significantly better than EP, could have also contributed to the observed survival benefit. Although VP was never directly compared to PC, one phase III study compared PC to a more toxic and outdated regimen consisting of mitomycin/vindestine/cisplatin [19]. There was no difference in median survival time between both treatment arms but the cisplatin-based regimen caused significantly more grade 3/4 neutropenia, febrile neutropenia and gastrointestinal disorder. Additionally, non-inferiority of the experimental arm was not achieved according to the predesignated endpoints [19].

Finally, the described pattern of progression, with more than one-third of patients presenting cerebral relapse, reflects the vulnerability of the central nervous system to micrometastatic disease and underlines a considerable issue related to initial treatment failure. Unfortunately, phase III data did not demonstrate any survival advantage associated with prophylactic cranial irradiation in this context, despite a decrease in the rate of brain metastasis [20]. Therefore, such an approach is not supported at the present time. Improved techniques in the delivery of prophylactic radiation to the brain (e.g., hippocampal sparing techniques) may be useful in this regard.

The present study is certainly limited by its small sample size and its retrospective nature requiring a review of individual patient files, which might have been subject to inaccurate and/or incomplete data recording, especially in terms of lower grade treatment-related toxicities. Furthermore, our physicians' preferences for PC in older patients with more comorbidities possibly skewed the results in

favor of the VP regimen. Additionally, the chemotherapy doses in the PC regimen are believed to be insufficient to treat systemic disease, which is why two consolidation cycles with higher doses of PC are commonly administered, but patients in our cohort did not receive these two cycles since their overall general status might not have allowed it once concurrent chemoradiation was over [21].

Due to its limitation, our study does not allow for the drawing of definite conclusion in regards to the optimal choice of chemotherapy to combine with radiotherapy. Also, it is still unclear which agent is better suited to be coupled with cisplatin in terms of efficacy, but vinka alkaloids appear to be associated with fewer toxicities. In patients unable to tolerate cisplatin-based therapy due to comorbidities or reduced performance status, PC is often considered as a reasonable and less toxic alternative.

Compliance with ethical standards

Conflict of interest Samer Tabchi and Marie-Pierre Campeau declare that they have no competing interests. Normand Blais reports personal fees from Merck, Pfizer, AstraZeneca, Bristol Myers Squibb, outside the submitted work. Mustapha Tehfe reports personal fees from Lilly, Amgen, and Celegene outside the submitted work.

Ethical approval This study was approved by the CHUM's Institutional Review Board. No procedures were undertaken in this retrospective analysis.

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