

Limited Field Radiotherapy Concomitant with Cisplatin/Etoposide Followed by Consolidation Docetaxel for the Treatment of Inoperable Stage III Non-Small Cell Lung Cancer

EHAB MOSTAFA, M.D.*; ADEL KHATAB, M.D.**; EMAN R. AL-ADWY, M.D.** and GIHAN M. AL-ASSAL, M.D.**

The Departments of Radiation Oncology & Nuclear Medicine* and Chest**, Ain Shams University.

ABSTRACT

Purpose: To evaluate the efficacy and outcome of concomitant cisplatin/etoposide and limited field irradiation followed by consolidation docetaxel in patients with locally advanced non small cell lung cancer (NSCLC).

Patients and Methods: This is a prospective phase II study that included 32 patients with locally advanced stage III NSCLC who presented to the Radiation Oncology and Chest Departments- Ain Shams University hospitals, and Sohag Cancer Center between May 2004 and August 2006. Eligible patients were treated first with two cycles of cisplatin 50mg/m²/day on days 1, 8, 29 and 36 and etoposide 50mg/m²/day on days 1-5 and 29-33 concomitant with conventionally fractionated radiation (66Gy in 2Gy fractions) to the gross primary disease and regionally involved lymph nodes followed by 3 cycles of consolidation single agent docetaxel, 75mg/m²/3 weeks.

Results: The median follow-up duration was 13.5 months (range from 6 to 30 months). The median survival was 17.4 months and the median progression free survival was 13 months. A total of 20 patients (62.5%) had treatment failure, 47% had an in field failure, 44% had distant failure, and one patient (3%) had isolated nodal failure (INF). Neutropenia (15.5%), anemia (19%), nausea and vomiting (15.5), esophagitis (9%) and pneumonitis (3%) were the most severe, grade 3 and 4, acute toxicities recorded during concomitant chemoradiation and 3 patients (9%) had grade 3 late esophagitis. Neutropenia (35%) and anemia (17%) were the most pronounced, grade 3 and 4, toxicities during consolidation chemotherapy.

Conclusion: Concomitant chemoradiation, without elective nodal irradiation (ENI), is a promising approach for management of locally advanced NSCLC. Conformal irradiation with possible dose escalation may provide an

opportunity for more improvement of the therapeutic ratio. The addition of consolidation docetaxel is still questionable and needs more investigation.

Key Words: NSCLC – Radiation – Cisplatin – Etoposide – Docetaxel.

INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for approximately 80-85% of all cases of lung cancer. It was estimated that 45% of newly diagnosed lung cancer cases will be diagnosed as stage III world wide [1]. The majority of patients with stage III NSCLC are "unresectable". Recently, several randomized and meta-analysis studies confirmed that for unresectable locally advanced NSCLC with good performance status, concomitant radiation and 2-4 cycles of platinum based chemotherapy is now the standard treatment with median survival of 17 months and 5 year overall survival of 15% but at the risk of increased morbidity, mainly esophageal and pulmonary toxicity. There were increased rates of severe esophagitis (grade 3 or 4) in 20-30% of patients with concurrent therapy compared with thoracic radiation alone [2-6]. However, the recurring themes of dominance of distant sites of failure and significant rates of local progression support the hypothesis that the addition of systemic dose chemotherapy to concurrent chemoradiotherapy, either as induction or as consolidation chemotherapy, might further improve survival rates.

Correspondence: Dr Ehab Mostafa, Department of Radiation Oncology and Nuclear Medicine, Ain Shams University, Cairo, ehmostafa@hotmail.com

Recently, the Cancer and Leukemia Group B (CALGB) explored the induction chemotherapy strategy followed by concomitant chemoradiation [7-10]. They evaluated different platinum based induction regimens like cisplatin and vinblastine [7] or the new cytotoxic agents like cisplatin and gemcitabine, paclitaxel or vinorelbine [9] or carboplatin and paclitaxel [8,10]. The induction regimen was followed by concomitant 60-66Gy thoracic radiation (TRT) and different single or combined cytotoxic agents like cisplatin and new cytotoxic agents [9], weekly single agent carboplatin [7] or weekly carboplatin and paclitaxel [8,10]. The median survival times of ~13 to 17 months were compatible with a concomitant chemoradiotherapy effect alone [2-4]. Of note, the two paclitaxel-based arms were associated with the lowest numerical survival times. In addition, the overall rates of grade 3 esophagitis, pneumonitis and fatigue/malaise were 20.6%, 4.5% and 14.4%, respectively [6].

The consolidation chemotherapy approach has mainly been investigated by the Southwest Oncology Group (SWOG). Initial phase II data (SWOG 9019) using cisplatin/etoposide both during and following radiotherapy (61Gy) at systemic doses yielded a median survival of 15 months [11]. In a SWOG 9504 trial, the consolidation chemotherapy regimen was altered to single-agent docetaxel. Although the survival of 25 months was impressive, yet this was still associated with high morbidity rate, especially esophagitis, pneumonitis, and neutropenia, with poor compliance [12]. In the locally advanced multimodality protocol (LAMP) trial, patients received either induction chemotherapy followed by radiation, induction chemotherapy followed by chemoradiotherapy, or chemoradiotherapy followed by consolidation chemotherapy. Chemotherapy regimen on all three study arms was the combination of paclitaxel and carboplatin. Median survival times were 13.2, 12.7 and 16.3 months, respectively [13].

An obvious way to reduce toxicity due to radiotherapy is to reduce the volume of dose limiting organs, such as lungs and esophagus, included in the planning target volume (PTV) [14]. The policy of sparing normal tissue is discordant with the conventional irradiation of clinical and radiological uninvolved regional

lymph nodes (elective nodal irradiation, ENI). Proponents of ENI justify this practice because normal sized mediastinal nodes might harbor occult metastasis. However, several studies have been published in which it was shown that it is safe to irradiate only mediastinal lymph nodes enlarged on CT scan hence omitting elective nodal irradiation, with < 5% of patients experiencing an isolated nodal failure [2,3,14,15].

Building upon the above mentioned information, we conducted this prospective phase II study in which all the patients received concomitant chemotherapy, cisplatin/etoposide and limited field radiation to the primary tumor and grossly involved lymph nodes, i.e. selective nodal irradiation, to be followed by 3 cycles of docetaxel. The primary end points of the study were survival, progression free survival (PFS), pattern of recurrence and isolated nodal failure (INF). The second end point of the study was toxicity.

PATIENTS AND METHODS

This trial was conducted on 32 patients with locally advanced NSCLC who presented to the Radiation Oncology and Chest Departments Ain Shams University hospitals, and Sohag Cancer Center between May 2004 and August 2006. Initial evaluation included history, physical examination, complete blood count, serum chemistries, and baseline audiometry. Local and regional tumor extents were assessed by contrast enhanced computerized tomographic scan (CT scan) of the chest and upper abdomen to assess liver and adrenal glands, and fiberoptic bronchoscopic examination. Contrast CT or magnetic resonance images (MRI) of brain were essential to rule out asymptomatic brain metastasis. Bone scan was indicated only upon symptoms or when elevated alkaline phosphatase was encountered. Tumor staging was determined according to the American Joint Committee on Cancer Staging and End Result Reporting/International Union Against Cancer (AJCC/ UICC 2002) [16]. Patients eligible for this study had histologically confirmed locally advanced (T3, T4 and/or N+ M0) NSCLC. Other eligibility criteria were age of at least 18 years but not more than 70 years, performance status (PS) of ≤ 2 according to the Eastern Co-operative Oncology Group (ECOG), weight loss <10%

in the last 3 months, adequate pulmonary function test (forced expiratory volume in 1sec >1L), adequate hematologic status (leukocyte count >4000/uL, absolute neutrophil count (ANC) \geq 1500/uL, platelets \geq 100,000/uL and hemoglobin \geq 10g/dl), adequate kidney function (creatinine clearance (CrCl) \geq 60mL/min and serum creatinine level of \leq 1.5mg/dl) and adequate liver functions (bilirubin <2mg/dl, and transaminases levels < three times the upper normal limit). Exclusion criteria included mixed pathology (non small and small cell lung carcinoma) or bronchioalveolar carcinoma, T4 lesions because of malignant pleural or pericardial effusion, supraclavicular lymph node metastasis, and evidence of distant metastasis, weight loss >10%, prior malignancy, prior chemotherapy or radiotherapy to the lung or concurrent serious medical illness. All patients were required to provide written informed consent before joining the study, and the protocol was approved by the institutional ethics committee.

Treatment plan:

Eligible patients were treated with concomitant chemotherapy (cisplatin and etoposide) and limited field conventionally fractionated irradiation followed by consolidation chemotherapy (docetaxel).

Concomitant chemoradiation: Chemotherapy and radiotherapy began simultaneously.

1- Chemotherapy:

Cisplatin was given intravenously in a dose of 50mg/m²/day on days 1, 8, 29 and 36 and etoposide 50mg/m²/day on days 1 through 5 and 29 through 33. The chemotherapy was given at approximately 30-60 minutes before receiving radiotherapy. Normal saline (500mL) was given before and during 2 hours cisplatin infusion, during which mannitol and frusemide were also used to maintain a high urine output. Intravenous antiemetics were given before cisplatin, including ondansetron or granisetron and 8mg dexamethazone.

Complete blood picture with differential and blood chemistry, including electrolytes, were performed before each cycle of chemotherapy. Chemotherapy was administered at full calculated dose unless ANC was less than 1500/uL or platelet count was less than 100,00/uL. For

patients with Cr Cl between 40 to 60mL/min, carboplatin targeting an area under the curve (AUC) of 2mg/mL min (Calvert formula) was to be substituted for cisplatin. If the nadir of the Cr Cl was <40mL/min or the patient developed otologic grade 3 or worse toxicity, cisplatin was stopped totally. Carboplatin was to be substituted for cisplatin in case of grade \geq 2 neurologic toxicity.

2- Radiotherapy:

Radiation began using a linear accelerator (6-10MV) or Cobalt-60. The patients were treated in supine position with arms raised above head. All the patients underwent CT-based treatment planning. A CT scan of the thorax was performed that extended from the cricoid to the second lumbar vertebra with a maximal slice thickness of 5mm. Contouring of the lungs was done in every case. The tumor, lung, esophagus and spinal cord, considered to be at the inner margin of the bony spinal canal were delineated on the CT contour. The gross target volume (GTV) was defined as the primary tumor and grossly enlarged lymph nodes detected with CT scan, only mediastinal lymph nodes with a short axis diameter of \geq 1cm or clusters of lymph nodes were considered to contain tumor without confirmatory histologic finding. The PTV was generated by expansion of the GTV. The PTV was defined as the GTV with a margin of 1.5-2cm in all directions. No elective nodal irradiation was carried out. Three to four co-planner fields were used according to patient contour. The treatment continued to a total dose of 66Gy in 23 fractions at a dose of 2Gy/fraction, one fraction per day, five fractions per week. Normal tissue tolerance criteria for the heart, spinal cord, involved and uninvolved lung were mandated as follows. For the spinal cord, the maximum dose was 50Gy to any point. After the 50Gy dose was reached, the spinal cord should be shielded from direct radiation. The entire heart could not receive more than 35Gy. The lung containing the primary tumor could receive up to 25Gy, but the contralateral lung could not receive more than 5Gy.

Symptomatic treatment was started as soon as esophagitis occurred (grade 1). It Systematically combined a proton pump inhibitor, anti-infective therapy in case of clinical mycosis, and steroids and analgesics for grade 2 esophagitis. Radiation therapy interruptions or delays

were permitted only in case of severe (grade 3 or 4) neutropenia, pneumonitis or esophagitis.

Consolidative chemotherapy: Four weeks after completion of concurrent chemoradiation, the patients underwent a re-staging work up including, history, physical examination, chest X ray and CT chest and upper abdomen. Bone scan and contrasted CT or MRI brain were indicated if the patient had symptoms or signs suggestive of bone or brain metastasis. In the absence of clinical or radiological evidence of progressive disease, consolidation docetaxel started 4 to 6 weeks after chemoradiotherapy at 75mg/m² intravenously over 1 hour every 21 days for three cycles. Docetaxel was administered only if the ANC was $\geq 1500/\mu\text{L}$ and platelet count was $\geq 100,000/\mu\text{L}$. Otherwise, docetaxel was delayed for one week to allow hematological recovery.

Follow-up:

The patients were followed up 8 weeks after the end of the consolidation chemotherapy and later, every 3 month during the first two years then twice a year afterward. During each visit, the patients underwent complete history and physical examination, plain chest x-ray and abdominal ultrasonography. CT scan of the chest was done at 3 and 6 months after treatment and then every 6 months during the first 2 years, then annually or whenever indicated, upon suspected local or regional recurrences as indicated by chest x ray or symptoms. Other investigations like bone scan or contrasted CT or MRI brain was indicated whenever needed i.e. appearance of symptoms or signs.

Evaluation criteria:

Radiological evaluation was carried out after concomitant chemoradiation and at the end of the treatment, after consolidation chemotherapy. Radiological tumor response was evaluated according to the WHO criteria [17], complete response (CR), and partial response (PR), stable (SD) or progressive disease (PD). Objective response included those who had complete and partial response. Local tumor control was defined according to the criteria of Green et al. [18]. Residual radiographic abnormalities, assessed by chest CT at 3 and 6 months after completion of radiation, then remained stable for an additional 6 months or

more, were qualified as controlled local disease.

Morbidity of treatment:

Chemotherapy-related toxicities were recorded according to the National Cancer Institute Common Toxicity Criteria version 2.0 [19]. Acute (≤ 90 days) and chronic or late (>90 days) radiation related toxicities were graded according to the acute and chronic Radiation Morbidity Scoring Criteria of the Radiation Therapy Oncology Group (RTOG) [20]. Acute radiation pneumonitis was classified according to SWOG toxicity criteria, which defines grade 1 (mild) toxicity when radiographic (chest X ray or CT scan) changes appear and clinical symptoms exist, but do not require steroids; grade 2 (moderate) toxicity when steroids are required; grade 3 (severe) toxicity when oxygen is needed; grade 4 (life threatening) toxicity when assisted ventilation is necessary; and grade 5 toxicity when the treatment is fatal. Late radiation pneumonitis was recorded according to the RTOG scale.

Survival and patterns of failure:

Major end points of the study were the pattern of recurrence, isolated nodal failure, median survival, median progression free survival and toxicity. INF was defined as recurrence in the regional nodes outside of the clinical target volume, in the absence of local in-field failure. INF were recorded even if a distant metastasis had been the first site of failure. The 2-year survival and 2-year progression free survival (PFS) were estimated using the Kaplan-Meier method. Survival was estimated from the date of first treatment day to death or last follow-up visit. PFS was estimated from the date of first treatment day to first evidence of disease progression.

RESULTS

The present study included 32 patients with pathologically proven locally advanced NSCLC. The demographic baseline patients and disease characteristics including age, sex, ECOG performance status, degree of weight loss, pathology; T stage, N stage and overall TNM stage of the treated patients are detailed in Table (1). The median age was 51.3 years old (range from 39-70 years) and 25 patients were males. Twenty six patients had good performance status (ECOG

0 and 1). Forty percent of patients had <5% loss of body weight and 60% had weight loss of 5-10%. According to the WHO classification, squamous cell carcinoma pathology predominated in our patients, representing 53% of the patient sample. Twelve patients had stage IIIA and 20 patients had stage IIIB. Two patients had T2 N1 tumor and were medically inoperable, 19 patients had T3 disease and 11 patients had T4 disease. N2 (ipsilateral mediastinal lymph node involvement) and N3 disease (contralateral mediastinal lymph node involvement) had been recorded in 17 (53%) and 13 (41%) of patients, respectively.

Response:

All patients had bidimensionally measurable disease on computerized tomography (CT) scan at study entry. Table (2) shows the details of response after concomitant chemoradiation and at the end of the treatment. After concomitant chemoradiation, 17 patients (53%) achieved objective response {CR 2 patients (6%) and PR 15 patients (47%)}. Twelve patients (37.5%) had stable disease and 3 patients (9%) had progressive disease. At the end of treatment, 19 patients (59%) achieved objective response, {CR 3 patients (9%) and PR 16 patients (50%)}. The two patients who originally had small volume disease T2N1 achieved complete response. The local control, according to the Green et al. criteria [18], was assessed in 28 patients. Four patients who progressed during the treatment were excluded. Of the assessable 28 patients, 16 patients remained radiologically stable and were qualified as controlled local disease.

Survival and progression free survival:

The median follow-up duration was 13.5 months (range from 6 to 30 months). The actuarial 2 year survival was 56.3% with 95% CI 39.1 to 73.4 (Fig. 1). The actuarial 2 year PFS was 40.6% with 95% CI 23.6 to 57.6 (Fig. 2). The median survival was 17.4 months and the median PFS was 13 months. The one and 2 year survival for patients receiving consolidation docetaxel (23 patients) were 54.6% and 50%, respectively, compared to 55.6% and 18%, respectively, for patients not receiving docetaxel (9 patients), the differences were not statistically significant ($p=0.293$) (Fig. 3).

Pattern of treatment failure:

The details of patterns of failure are shown in Table (3). A total of 20 patients (62.5%) had treatment failure, 15 patients (47%) had an in field failure, 5 patients (16%) had exclusively in field failure, and 10 patients (32%) had in field and distant failure. Two patients had nodal failure, one patient (3%) had isolated nodal failure, and one patient (3%) had nodal failure (outside GTV), local failure and distant metastasis. Fourteen patients (44%) developed distant metastasis, 3 of them (9%) had distant metastasis without evident locoregional disease progression. The most common sites of distant metastasis were brain (8 patients), liver (4 patients) and bone (4 patients). Two patients had multiple site distant metastases. All patients who did not receive consolidation chemotherapy developed distant metastasis. Ten of the failed patients received second line chemotherapy. Those who had brain or bone metastasis received palliative irradiation. Otherwise, best supportive care was offered for patients with poor general condition.

Treatment compliance:

Twenty five (78%) patients completed the planned chemoradiation course. Seven patients received one cycle of chemotherapy only during radiation. Six of these 7 patients received <66Gy radiation, 4 patients received 60Gy and 2 patients received 50Gy and 56Gy, respectively. The patients did not complete the planned treatment course for the following reasons: Acute severe (G3/4) toxicity in 4 patients, and disease progression in 3 patients. Three patients (9%) received carboplatin instead of cisplatin; 2 patients experienced severe vomiting during the first cycle of chemotherapy and one patient had low creatinine clearance on the time due for the second cycle. The median overall treatment time for radiotherapy was 50 days (range from 32 to 60 days).

Twenty three patients (72%) received consolidative docetaxel. The reasons for not receiving consolidation chemotherapy were progressive disease on re-assessment in 3 patients, severe side effects in 4 patients and patient refusal in two patients. Of 23 patients who were candidates for docetaxel, 19 patients received 3 cycles, while 4 patients received 1-2 cycles of chemotherapy due to residual unresolved neutropenia during consolidation.

Toxicity:

Acute toxicity is shown in Table (4). All the patients experienced mild to moderate degree (grade 1/2) of dysphagia during concomitant chemoradiation. Seven patients (22%) developed grade 3 or 4 toxicity during concomitant chemoradiation (Table 4-A). Grade 3 and 4 anemia, neutropenia, vomiting, and esophagitis, the most severe toxicities during concomitant chemoradiotherapy, developed in 19%, 15.5%, 15.5% and 9% of patients, respectively. One patient (3%) developed febrile neutropenia. According to SWOG criteria of pneumonitis, 2 patients (6%) developed grade 2 pneumonitis that required corticosteroid therapy and one patient developed grade 3 pneumonitis that necessitated

hospital admission. One patient died from severe chest infection (pneumonia). Three patients (9%) had grade 3 late radiation esophagitis. No cardiac or spinal cord complications had been reported.

During consolidation chemotherapy, 9 out of 23 patients (39%) who received docetaxel, developed grade 3 or 4 toxicity (Table 4-B). Myelosuppression, especially neutropenia, was common. Eight patients (35%) developed grade 3/4 neutropenia, 3 of them (13%) developed febrile neutropenia. Grade 3/4 anemia and thrombocytopenia were recorded in 17% and 9% of patients respectively. Two patients (9%) developed grade 3 fluid retention that necessitated diuretic therapy.

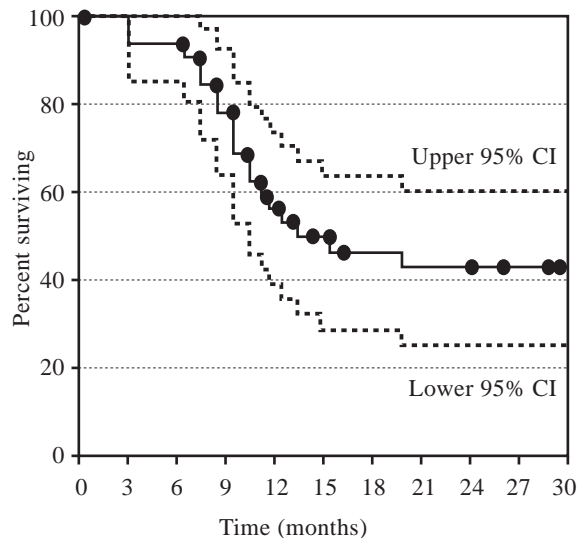


Fig. (1): Actuarial survival.

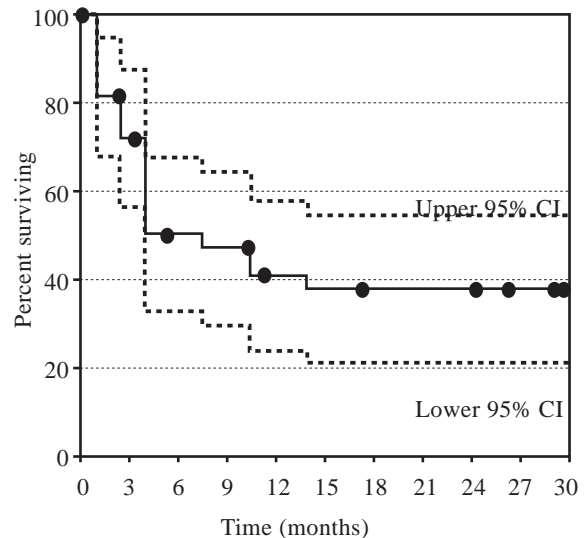


Fig. (2): Actuarial progression free survival.

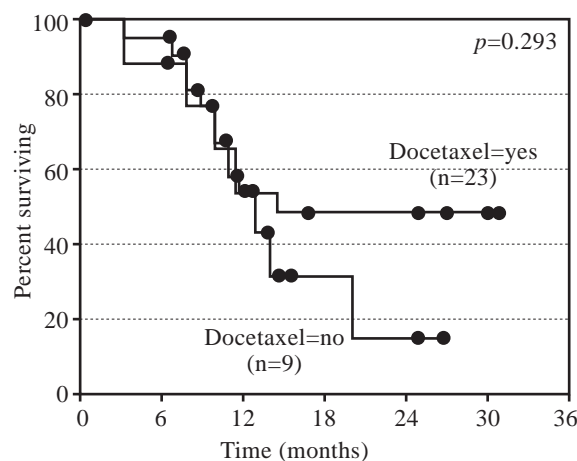


Fig. (3): Actuarial survival of patients receiving and not receiving consolidation docetaxel.

Table (1): Patients and disease characteristics.

No. of patients	32
<i>Age (year):</i>	
Median	51.3±8.5
Range	39-70
Sex (M/F)	25/7
<i>Performance status (ECOG):</i>	
0	6 (19%)
1	20 (62%)
2	6 (19%)
<i>Weight loss:</i>	
<5%	13 (40%)
5-10%	19 (60%)
<i>WHO classification:</i>	
Squamous cell carcinoma	16 (53%)
Adenocarcinoma	7 (20%)
Large cell carcinoma	9 (27%)
<i>AJCC staging system:</i>	
Stage IIIA	12 (37.5%)
Stage IIIB	20 (62.5%)
<i>Tumor (T) lymph node (N) M0:</i>	
T2N1	2 (6%)
T3N2	10 (31%)
T3N3	9 (28%)
T4N2	7 (22%)
T4N3	4 (13%)

Table (2): Clinical response after induction chemotherapy and at the end of treatment.

Response	No. of patients (%)	
	After concomitant chemoradiation	After consolidation chemotherapy
Complete response (CR)	2/32 (6%)	2/32 (9%)
Partial response (PR)	15/32 (47%)	16/32 (50%)
Stable disease (SD)	12/32 (37.5%)	9/32 (28%)
Progressive disease (PD)	3/32 (9%)	4/32 (12.5%)

Table (3): Pattern of treatment failure.

Failure	No (%)
None	12 (37.5%)
<i>In field:</i>	
• Exclusively in field	5 (16%)
• In field and distant	10 (32%)
Isolated nodal failure only	1 (3%)
Nodal failure (outside GTV) with local and distant failure	1 (3%)
Distant metastasis only	3 (9%)

Table (4-A): Severe acute toxicity during chemoradiation (32 patients).

Toxicity	Grade 3	Grade 4	Total
Neutropenia	4 (12.5%)	1 (3%)	5 (15.5%)
Anemia	6 (19%)	0	6 (19%)
Nausea/vomiting	4 (12.5%)	1 (3%)	5 (15.5%)
Esophagitis	3 (9%)	0	3 (9%)
Pneumonitis (SWOG criteria)	1 (3%)	0	1 (3%)

Table (4-B): Severe acute toxicity during consolidation chemotherapy (23 patients).

Toxicity	Grade 3	Grade 4	Total
Neutropenia	5 (22%)	3 (13%)	8 (35%)
Anemia	4 (17%)	0	4 (17%)
Platelets	2 (9%)	0	2 (9%)
Fluid retention	2 (9%)	0	2 (9%)

DISCUSSION

The results of the present study revealed that the concomitant cisplatin/etoposide and limited volume irradiation without ENI followed by 3 cycles docetaxel can be safely administered with median survival and PFS of 17.4 months and 13 months, respectively. These figures were compared favorably with the results of other series of concomitant chemoradiation [2-4] and series of concomitant chemotherapy and standard field radiation followed by consolidation chemotherapy that reported median survival of 15-16.3 months [11,13,21]. Additionally, although no difference had been noticed in one year

survival rates between the group of patients who received docetaxel compared to patients who did not receive consolidation chemotherapy (54.6% and 55.6% respectively), yet there was a trend for better 2 year survival for patients who received consolidation docetaxel (50% versus 18% respectively) but the difference was not statistically significant. Two important studies evaluated the role of consolidation docetaxel. SWOG 9504 reported an impressive median survival of 25 months after treatment with concomitant cisplatin/etoposide and standard field radiation followed by 3 cycles of consolidation single agent docetaxel [12]. It must be pointed out that the final analysis of SWOG 9504 included only 83 of 98 patients registered. Furthermore, eligibility criteria differed from those used in stage III trials in that pathologically proven stage III disease was required. This may have led to inclusion of patients with less bulky disease. On the contrary, Hanna et al. [22] from NCI Canada, compared concomitant chemo radiation followed by consolidation docetaxel (SWOG 9504 design) with concomitant chemo radiation alone. In the latter study, PFS for doc etaxel arm was 12.3 months versus 12.9 months for no docetaxel arm and the median survival times were 21.6 and 24.2 months, respectively.

Furthermore, in the current study, 9% and 50% of patients developed CR and PR respectively at the end of the treatment. Patients with small volume disease T2N1 achieved CR. These figures compared favorably with other trials of concomitant chemoradiation followed by consolidation chemotherapy where CR ranged from 2-7% and PR ranged from 49%-59% [12,13,21,23] according to the Green et al. criteria, 16 of 28 patients assessed for local control remained radiologically stable for 6 months and were qualified as locally controlled disease. However, Arrigada and his colleagues found that with the standard radiation therapy practice (60-66Gy), in field sterilization and pathological local control only occurred in 8-15% of patients [24]. Martel et al. [25] proposed that to achieve a 50% tumor control probability with ultimate survival benefit, it is estimated that doses of 84Gy may be necessary. Unfortunately, the dose limiting constraint for the esophagus, lung and spinal cord prohibit this dose escalation with the standard radiation fields.

Several investigators addressed the issue of selective mediastinal lymph node irradiation, i.e. eliminating ENI from the radiation field with reported incidence of in field failure between 15 to 28% and INF rate of 0-6.3% [14,26-29]. In the present study, the incidence of INF was 3% but in field failure was 47%. The improved failure figures in later trials may be in part due to the capability for radiation dose escalation, through 3-dimensional conformal irradiation (3D-CRT) as a more limited radiation field had been utilized with better therapeutic ratio. The low incidence of INF could be explained by the following factors; first, the incidental dose to the uninvolved lymph nodes in mediastinum hilum, paratracheal and subcarinal regions approach 40-50Gy [25,29]; second, the increased role of cytotoxic chemotherapy in the management of locally advanced NSCLC might control these occult mediastinal diseases; third, since the patient population tended to have a more advanced disease, these patients were at higher risk for local failure or distant metastasis that would mask elective nodal failure or would have died before their elective nodal failure became clinically evident.

Additionally, we recorded that 44% of patients had developed distant metastasis. In SWOG trial, the incidence of distant metastasis rate was 65% [11,12]. Fournel et al. [21] reported in their trial of concomitant cisplatin/etoposide with standard 66Gy radiation followed by consolidation cisplatin and vinorelbine that the distant failure rate was 34%. On the other side, in selective mediastinal lymph node irradiation trials, the incidence of distant metastasis ranged from 23 to 35% [14,26-29]. The relatively lower incidence of distant metastasis of selective nodal irradiation trials may reflect the fact that, not only chemotherapy can play a role in controlling distant metastasis but also achieving higher local control rate through dose escalation may play an important role as uncontrolled disease is often the direct cause of death due to local effects within the lung and mediastinum and may serve as a focus for distant metastasis.

The toxicity in the current study was moderate and manageable, 78% of patients completed the planned chemoradiation course. Grade 3/4 pneumonitis and acute esophagitis were recorded in 3% and 9% of patients, respectively, in addition to 9% who developed G3 late esoph-

agitis. In SWOG 9504 trial, 88% of patients completed the planned chemoradiation course, 17% of patients developed grade 3/4 esophagitis and 7% of patients had grade 3 to 5 pneumonitis and 3 patients got late pulmonary complications and died [12]. In a similarly designed arm in LAMP trial, 74% of patients completed the planned chemoradiation schedule and pneumonitis and esophagitis were recorded in 16% and 28%, respectively [13]. In Fournel et al. trial, the incidence of severe esophagitis was 32% and severe pneumonitis was 5% [21]. Hanna et al. [22] reported, in their trial G3/4 febrile neutropenia in 9.8% of patients and esophagitis in 17.2%. Recently, after the introduction of 3D-CRT, the incidence of \geq grade 2 pneumonitis is 36% if the lung volume that received more than 20Gy (V_{20}) exceeds 40% of lung volume. In addition, other investigators [30,31] reported that esophageal circumference treated with more than 45-50Gy was significantly associated with late esophagitis especially if the length of esophagus in the field exceed 9.5cm. In dose escalating trials with limited volume irradiation, the investigators reported lower incidence of acute esophagitis (1-2%) and pneumonitis (2-5%), although a higher radiation dose was delivered to the target volume, up to 87.8Gy using 3D-CRT [14,27,28]. The relatively higher morbidity during chemoradiation in the present study compared to the later dose escalating trials may be explained by the fact that our PTV was exclusively CT-based treatment planning which might overestimate the PTV compared to CT and PET scan based planning. In addition, the patients in these trials received neoadjuvant chemotherapy and not concurrent chemoradiation.

Docetaxel was selected for consolidation because of its high level of activity in the primary treatment of metastatic NSCLC, its activity in second-line therapy, and molecular mechanisms of p53-independent apoptosis favoring administration before the emergence of clinical drug resistance [32]. During consolidation phase, 72% of patients received docetaxel but only 59% of patients completed the planned 3 cycles of chemotherapy. This is compared favorably to other similarly designed trials where the 54 to 78% of patients received the planned consolidation chemotherapy [12,13,21,23]. In the present study, grade 3 or 4 neutropenia was most prominent, and was recorded in 35% of patients and

febrile neutropenia was reported in 13% of patients. However, this was favorably compared to 57% incidence of grade 4 neutropenia and 9% incidence of febrile neutropenia recorded in SWOG 9405 [12]. We limited the dose of docetaxel to 75mg/m² as grade 4 neutropenia was most prominent in SWOG 9504 trial after escalating the docetaxel dose to 100mg/m². In Hanna et al. trial [22], 8.2% of patients developed febrile neutropenia in consolidation docetaxel arm and 5.5% of patients died due to docetaxel.

Conclusion: Concomitant chemoradiation, without ENI, is a promising approach for management of locally advanced NSCLC. Conformal irradiation with possible dose escalation may provide an opportunity for more improvement of the therapeutic ratio. The addition of consolidation docetaxel is still questionable and needs more investigation.

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