Concurrent Palliative Chemoradiotherapy versus Definitive Chemoradiotherapy in Poor Prognosis Stage III non-small-cell lung cancer

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Maha Abd-El Hady El-Khafif

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Abstract

Background: The palliative role of chemoradiation in treatment of patients with locally advanced non-small-cell lung cancer remains unresolved; Controversy remains about whether long term and high doses radiotherapy provide better results than short course schedules in treatment of inoperable stage III NSCLC and negative prognostic factors poor performance status (PS), large tumor, poor pulmonary functions and comorbidities.Hypofractionated radiotherapy can expose tumors to a high dose of radiation in a short period of time.

Methods: One hundred and ten patients with locally advanced stage III NSCLC with poor prognosyic factors were randomized to receive either definitive chemoradiation or palliative chemoradiation in cancer department of faculty of medicine of AIN SHAMS UNIVERSITY .Arm (A) patients will receive induction chemotherapy with two cycles of carboplatin(AUC6) and paclitaxel 175mg/m²) cycles every 21 day, the third cycle administrated with radiotherapy with low dose of carboplatin(AUC 2) and paclitaxel 60 mg/m² on day 1& 8 administrated concomitant with the radiotherapy 42 Gy over 15 fraction over 3 weeks .

Arm (B) patients will receive standard-dose fractionation of radiation 60Gy/6 weeks 2Gy once per day with concurrent weekly low dose of carboplatin (AUC 2) and paclitaxel 60 mg/m² followed by two cycles of full doses of carboplatin (AUC 6) /paclitaxel 175mg/ m² every 21 days.the primary end points were overall survival and progression free survival;secondary end points were health related quality of life(HRQOL) and toxicity.

Results: The median follow-up duration was 24 months in surviving patients' .Median survival and 2-year OS were in concurrent palliative chemoradiation arm 4.7 and 12.3-months respectively and was 7.3 and 17.6 in concurrent definitive chemoradiatiobn arm respectively ($p < 0.01$).

HRQOL was better in the palliative arm during the treatment but remained unchanged in both arms during the follow up visits. There were more hospital admissions related to side effects in the definitive chemoradiation arm ($p<0.05$).

Conclusions: This study confirmed that the definitive chemoradiation was superior to palliative chemoradiation arm with respect to survival.the treatment related toxicity and HRQOL were better in the palliative chemoradiation arm than the definitive arm.

List of abbreviations

Abbreviation	Full term
2DXRT	Two-dimensional external beam radiotherapy
5-FU	5-fluorouracil
AJCC	American joint committee on cancer
ALT	Serum glutamic-pyruvic transaminase (SGPT).
ANC	Absolute neutrophil count
AST	Serum glutamic-oxaloacetic transaminase (SGOT).
AUC	Area under the plasma concentration-time curve
ACTH	Adrenocorticotropic hormone
CBC	Complete blood count
CCRT	Concomitant chemoradiotherapy
CI	Confidence interval
CALGB	Cancer and leukemia group B
C-erb 2	Receptor tyrosine-protein kinase erb-2
cMyc	Chromosomal-Myelocytomatosis
CSF	Cerebro-spinal fluid
CT	Computed tomography
CTCAE	Common toxicity criteria and adverse events
CTV	Clinical target volume
CYP450	Cytochrome P450
DFS	Disease free survival
EBRT	External beam radiotherapy
EBUS	Endobronchial ultrasound
ECOG	Eastern cooperative oncology group performance status
EGF-R	Epidermal growth factor
EORTC QLQ-LC 30	European organization for research and treatment of cancer patients quality of life questionnaire for lung cancer module
EUS	Endoscopic(oesophageal ultrasound)
FEV1	Forced expiratory volume in first second
FDG	Flurodeoxyglucose

Abbreviation	Full term
FLEX	First-line Erbitux in lung cancer
GI	Gastrointestinal
GTV	Gross target volume
GY	Gray unit of measuring radiotherapy
HR	Hazard ratio
HRQOL	Health related quality of life
HNSCC's	Head and neck squamous cell carcinomas
IASLC	International association for the study of lung cancer
IHC	Immunohistochemistry
LAMP	Locally advanced multimodality protocol
LDH	Lactate dehydrogenace
LDCCT	Low dose spiral chest computed tomographic
MANOVA	Mixed design analysis of variance
MDR	Multiple Drug Resistance
MMR	Mismatch repair gene
MRI	Magnetic resonance imaging
MV	Megavoltage
NCCN	National Comprehensive Cancer Network
NLST	National Lung Screening Trial
NSCLC	Non-small-cell-lung carcinoma
OM,MTS	Oral mucositis
OS	Overall survival
OSCC	Oropharyngeal squamous cell carcinomas
PET	Positron emission tomography
PFS	Progression free survival
PFs	Prognostic factors
PS	Performance status
PTV	Planned target volume
QOL	Quality of life
RCTs	Randomized controlled trials
RECIST	Response evaluation criteria in solid tumours
RNA	Ribonucleic acid
ROS	Reactive oxygen species

Abbreviation	Full term
RT	Radiotherapy
RTOG	Radiation therapy oncology group
SUV	Standardized uptake value
SPECT	Single photon emission computed tomoraphy
SPNs	Solitary pulmonary nodules
SIADH	Syndrome of inappropriate anti-diuretic hormone
SVC	Superior vena cava syndrome
SWOG	Southwest oncology group
TBNA	Transbronchial needle aspiration
TNF-α	Tumor necrosis factor-alpha
TNM	Tumor- node- metastasis classification for head and neck cancers
TLC	Total leucocytic count
TPN	Total parenteral nutrition
TP53	Tumor Protein 53
TRT	Thoracic radiotherapy
ULN	Upper limit of normal
VATS	Video-assisted thoracoscopic surgery
WBC	White blood cell count
WHO	World health organization

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Introduction

Lung cancer is one of the common malignance with high morality. 13% of all new cancer cases and 19% of cancer related deaths worldwide are due to lung cancer. The 5 year survival rate is only 15% in the developed countries and a decimal 5% in the developing countries. There is an alarming increase in the incidence of lung cancer within women and consequently it's mortality in USA, which has been attributed to rise in smoking trends in US women in 1970s ***(Malik, Raina et al., 2015).***

NSCLC accounts for 80% of lung cancer about 30% of NSCLC presents with locally advanced disease at clinical stage III. The survival of clinical stage III NSCLC patients is poor and most patients are not eligible for surgical resection. Despite established evidence-based guidelines ***(Aragoneses et al., 2012).***

Approximately 25-30% of cases with non-small cell lung cancer (NSCLC) are diagnosed with the disease in the advanced stage and 40-50% are metastatic both not eligible for surgery ***(Lester et al., 2016).***

For patients with unresectable stage IIIA and a subset of stage IIIB disease (no malignant effusion), combined modality treatment (chemotherapy and radiotherapy) are associated with better outcome than radiotherapy alone ***(O'Rourke et al., 2017).***

Concurrent radiotherapy and chemotherapy is better than sequential approach, however, at the expense of

significant toxicity ***(Pijls-Johannesma, 2016).***

Unfortunately, many patients in stage IIIA to IIIB are not candidates for definitive chemoradiotherapy because of poor performance status (PS), large tumor, poor pulmonary functions and comorbidities. Recent prospective analysis showed that most of the potential patients in stage III (~60%) are not eligible for definitive chemoradiotherapy because of the poor performance status (PS) and the weight loss ***(Werner-Wasik et al., 2015).***

These patients are treated either with palliative radiotherapy or palliative chemotherapy. In patients with large tumors, the probability of both local and distant control is low ***(Le Chevalier et al., 2014).***

Palliative radiotherapy alone is often used to treat symptomatic patients who have limited expected survival time and/or intolerance to combined chemotherapy and radical RT regimens however patients with locally advanced NSCLC not eligible for radical chemo-radiotherapy but with relatively fair PS could be treated more aggressively by receiving higher –dose thoracic radiotherapy schedules as 42Gy/15 fractions rather than the short course radiotherapy schedules ***(Fournel et al., 2005& Corner et al., 2009).***

Controversy remains about whether long term and high doses radiotherapy provide better results than short course schedules ***(Davidoff et al., 2016).***

Recent reviews have shown that slightly hypofractionated radiotherapy regimen in advanced NCSLC patients as 42Gy/15 fractions had median survival data at least comparable to the normofractionated regimen 50Gy/25 fractions ***(Wagner et al., 2016).***

Aim of Work

The main purpose of this study was to compare concurrent palliative chemo radiation to definitive concurrent chemo radiotherapy in stage III non-small-cell lung cancer patients with poor prognostic factors (poor performance status, large tumor, poor pulmonary function, large lymph nodes and comorbidities). The primary end points are overall survival and progression free survival; secondary end points were health-related quality of life (HRQOL) and toxicity.

Epidemiology and risk factors of lung cancer

The estimate of cancer incidence in Egypt was 113.1/100, 000 of total population in 2012, and 114. 98 /100, 000 of total population in 2013 according to results of the National Population-Based Cancer Registry Program of Egypt in 2008–2011***(Ibrahim et al., 2014).***

Lung cancer incidence in Egypt is expected to almost double in the next two decades, being 456, 000 new cases in 2010 to nearly 861, 000 in 2030, which is the highest relative increase among all WHO regions ***(El-Attar et al., 2014).***

The above estimates are based only on the effect of population growth and ageing, but the additional effect of increasing exposures to cancer risk factors, such as smoking, unhealthy diet, physical inactivity and environmental pollution, will lead to an even bigger rise in the burden of cancer ***(Abou-Zeid et al., 2015).***

Lung cancer rate was 6.7 % of all types of malignancy in males while it is 5 % of all types of malignancy in females. Lung cancer rate in both sexes was 7.5% ***(Sherif, Ibrahim, 2014).***

Worldwide Lung cancer is among the most deadly cancers for both men and women ***(Kim et al., 2008).*** Its death rate exceeds that of the three most common cancers (colon, breast, and pancreatic) combined ***(Corner et al.,***

2009). Over half of patients diagnosed with lung cancer die within one year of diagnosis and the 5-year survival are around 17.8% ***(Gore et al., 2012).***

There are two main subtypes of lung cancer, small-cell lung carcinoma and non-small-cell lung carcinoma (NSCLC), accounting for 15% and 85% of all lung cancer, respectively ***(Kim et al., 2008).*** NSCLC is further classified into three types: squamous-cell carcinoma, adenocarcinoma, and large-cell carcinoma.

Adenocarcinoma is the most common form of NSCLC, accounts for about 50 % of NSCLC and 38 % of newly diagnosed lung cancers smokers and nonsmokers in men and women regardless of their age ***(Albain et al., 2009).*** Compared to other types of lung cancer, adenocarcinoma tends to grow slower and has a greater chance of being found before it has spread outside of the lungs ***(Nagai et al., 2008).***

Squamous-cell carcinoma comprises 25–30% of all lung cancer cases. It arises from early versions of squamous cells in the airway epithelial cells in the bronchial tubes in the center of the lungs. This subtype of NSCLC is strongly correlated with cigarette smoking ***(Lee et al., 2012).***

Large cell (undifferentiated) carcinoma accounts for 5–10% of lung cancers. This type of carcinoma shows no evidence of squamous or glandular maturation and as a result is often diagnosed by default through exclusion of other possibilities. Large cell carcinoma tumors are strongly associated with smoking ***(Scalliet et al., 2008).***