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ORIGINAL ARTICLE

THE EFFICACY OF BRONCHOSCOPIC INTRATUMORAL CHEMOTHERAPY IN PALLIATION OF INOPERABLE LUNG CANCER: INITIAL EGYPTIAN EXPERIENCE

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Tumor debulking and airway re-canalization has a considerable role in increasing survival in patients with inoperable non-small cell lung cancer (NSCLC). Bronchoscopic endobronchial intratumoral chemotherapy (EITC) is a new intervention to treat airway obstruction. This work aims to determine the efficacy of EITC in palliative care for patients with inoperable NSCLC. Between April 2009 and June 2011, patients with newly diagnosed non metastatic inoperable symptomatic non-life threatening airway obstruction secondary to NSCLC were selected for tumor debulking via EITC through flexible bronchoscopy. EITC of maximum 20mL cisplatin with the concentration of 50 mg/50 mL was injected into the tumor bulk through flexible needle (weekly for 4 sessions). Patients were followed according to the symptoms, performance and functional status and endobronchial lesions changes after EITC. Fourteen male and 1 female were studied in which 7 cases had squamous cell carcinoma, 5 cases had adenocarcinoma and 3 cases had unspecified NSCLC. After 4 sessions of EITC, the involved lumen was considerably opened (> 25%) in 80% of cases in which 7 cases >50% and 5 cases showed a 25–50% luminal opening. Significant statistical improvement was found in dyspnea score, Karnofsky performance scale as well as spirometric and arterial blood gases indices after than before the 4 sessions of EITC. EITC was well tolerated by most of the patients with minimal non systemic complications. In conclusion, EITC is a promising, safe, effective and less invasive procedure for palliative treatment of obstructive non-life threatening endobronchial NSCLC lesions.

Keywords: ***Endobronchial intratumoral chemotherapy, inoperable lung cancer, bronchoscopy.***

INTRODUCTION

Endobronchial obstruction is a common complication of advanced-stage lung cancer. Patients presenting with severe bronchial obstruction are at a high risk for developing haemoptysis, post-obstructive pneumonia, or respiratory failure, this often leads to death in weeks to months.[1,2]

Multiple studies suggested that significant palliative relief of endobronchial obstruction is often possible through tumor debulking and airway re-canalization by cryotherapy, electrocautery, laser resection, brachytherapy or endobronchial stent insertion leading to restoring the airway patency, adequate air exchange, increasing survival and life expectancy in patients with inoperable lung cancer.[1,3,4]

Management of patients presenting with obstructive endobronchial malignant lesions that have a large extraluminal component or extensive submucosal involvement is not possible by the available thermic bronchoscopic interventions (e.g. laser therapy, electrocautery, cryotherapy, photodynamic therapy).[5]

Thus, new ancillary endobronchial bronchoscopic procedures are warranted in such patients.

Celikoglu et al., 2004[5] proceeded to use a new technique for which had promising clinical results which is the intratumoral chemotherapy. Intratumoral chemotherapy is a novel interventional bronchoscopy technique, which involves injection of one or several conventional cytotoxic drugs directly into the tumoral tissue through a flexible bronchoscope by means of an ordinary transbronchial aspiration biopsy needle.

The available published studies on endobronchial intratumoral chemotherapy (EITC) reported its favorable clinical outcome, cost-effectiveness and usefulness as new non systemic loco-regional chemotherapy resulting into reduction of large local tumor cell burdens.[2,5,6]

The aim of the present work was to determine the efficacy of EITC in palliative care for patients with inoperable lung cancer.

PATIENTS AND METHODS

Patients referred to Pulmonary Medicine Department, Ain Shams University hospital between April 2009 and June 2011 with newly diagnosed non metastatic inoperable symptomatic non-life threatening airway obstruction secondary to non-small cell lung cancer (NSCLC), disease verified by bronchoscopy and having at least one endobronchial tumor measuring $\geq 0.5\text{cm}$ were recruited for tumor debulking via EITC using cisplatin through flexible bronchoscopy. Patients who could not tolerate the flexible bronchoscopy, had distant metastasis or had Karnofsky scale score < 60% were excluded.

The Research Ethics Committee (REC) at the Faculty of Medicine, Ain Shams University has approved the study (FMASU 137/2009). Informed consent was obtained from all patients enrolled.

The following variables were initially studied: age, sex, initial, new or progressive symptoms including dyspnea grade using modified medical research council (MMRC) dyspnea scale,[7] computed tomography (CT) scan, bronchoscopic evaluation, histopathology, Karnofsky index of performance status,[8] laboratory investigations (complete blood picture, kidney and liver function tests, electrolytes and bleeding profile), arterial blood gases (ABG), spirometry and the presence of distant metastasis.

All bronchoscopic procedures were carried out transnasally under topical lidocaine anesthesia, supplemental oxygen, atropine premedication, and incremental doses of midazolam sedation administered as needed using a flexible bronchoscope (FB) (Pentax EB-1830T3 video bronchoscope 6.0mm insertion tube, 2.6mm working channel, 60cm working length; Asahi Optical, Japan). Bronchoscopic examination was first performed in a standard fashion with careful inspection of the airways.

Endobronchial Intratumoral Chemotherapy procedure:

EITC was performed as previously described in detail by Celikoglu et al., 2004[5] using a flexible transbronchial aspiration needle (eXcelon®-M00564101-gauge 19, needle length 15mm, Boston Scientific Corporation, USA) which was advanced in a retracted position in its sheath through the working channel of FB. Once the tip of the sheath was approximately 2cm above the area to be injected, the needle was advanced out from its sheath. The needle was either inserted directly into the tumor itself in intraluminal exophytic tumors, obliquely in intraluminal infiltrative lesions or perpendicularly in extraluminal lesions. Once the needle was embedded in the tumor tissue, the chemotherapeutic drug was injected while moving the needle back and forth in a fanning manner with reintroduction of the needle in multiple sites of the tumor to obtain maximum dispersion of the drug.

Cisplatin was the chemotherapeutic drug solution used in a concentration of 50mg/50mL for all the cases. Maximum 20mL cisplatin was injected intratumorally per session. EITC procedure was performed weekly for 3 weeks (days 1, 8, 15 and 21) with a follow up inspection bronchoscopic study without intervention after one week.

Bronchoscopic evaluation of site, size, appearance and extent of the tumor obstruction after each session was recorded on charts of the bronchial tree using obstruction scoring system[9] Table 1 and photographic documentation was obtained before and after all treatments for further comparative assessment. Duration of bronchoscope, duration of procedure, complications during or after bronchoscope (either immediately or for the next 24 hours) either from the sedation, bronchoscope or from cisplatin were documented.

Table 1. Speiser's obstruction scoring criteria[9]

Site	>50% obstruction	<50% obstruction	<10% obstruction
Main bronchus	6	3	1
Lobar bronchus	2	1	

Atelectasis or pneumonia: An additional 2 points per lobe.

Patients' response:

Assessment of the patients' response to EITC one week after the last session was based on:

a) ***Subjective response,*** which depends on recording the changes in patients' symptoms, performance status.

b) ***Objective response,*** which depends on bronchoscopic evaluation according to Speiser's obstruction scoring criteria[9] and new Response Evaluation Criteria in Solid tumors (revised RECIST) guidelines[10] Table 2, CT scan evaluation, functional evaluation (arterial blood gases & spirometry) and laboratory investigations.

Table 2. Criteria for evaluation of therapeutic effects (revised RECIST)[10]

- ***Good response:*** more than 50% increase in caliber of the lumen.
- ***Partial response:*** 25- 50% increase in the caliber of the lumen.
- ***No response:*** less than 25% increase in the caliber of the lumen.
- ***Progressive disease:*** a 25% or more increase in the size of one or more measurable lesions or the appearance of new lesions.

c) ***Follow up duration of response before further management:*** Follow up the duration of response to initial EITC as well as the cause of death if occurred for two week after the follow up inspection bronchoscopic study and before starting conventional systemic radio and/or chemotherapy.

RESULTS

Twenty five patients fulfilled the study inclusion criteria during the study period. Ten patients refused to participate and 15 patients participated and completed the study.

Fourteen patients were men and 1 was woman with a mean age of 55.2±7.9 years.

Bronchoscopic evaluation of the studied 15 obstructing endobronchial lesions revealed that their size ranged from 3 to 5 cm with a mean of 4.1±1.12 cm. Six and 9 of the endobronchial lesions completely and near totally obstructed the bronchus lumen respectively. Using the obstruction scoring system of endobronchial lesions previously mentioned by Speiser, 1990 [9], the obstruction score ranged from 4 to 6 with a mean of 5.2±1. The sites of the studied obstructing endobronchial lesions was 2 in left upper lobe, 2 in left lower lobe, 4 in right upper lobe, 4 in right lower lobe and 3 in right middle lobe. While, the histopathologic type of such lesions was 7 squamous cell carcinoma, 5 adenocarcinoma, and 3 unspecified NSCLC.

Comparison between the clinical, radiological and bronchoscopic evaluation before and after EITC is shown in Table 3. Clinical and radiological evaluation revealed that there was no statistically significant difference between cough and expectoration before and after EITC, while there was a highly statistically significant improvement of both MMRC dyspnea score and Karnofsky Performance Status after EITC than before EITC by using Paired t-test. There were significant statistical decrease of haemoptysis, chest pain, and post obstructive
pneumonia after EITC in addition to significant statistical improvement of lobar atelectasis after EITC than before the procedure by using McNemar's test. While, bronchoscopic evaluation revealed that there was a highly statistically significant decrease of obstruction score and size of the tumor after EITC by using Paired t-test.

(Figs. 1,2) shows an obstructing endobronchial mass before and after EITC.

Comparison between arterial blood gases, spirometry and laboratory investigations evaluation before and after EITC is illustrated in Table 4. There was a highly statistically significant difference between arterial blood gases and spirometry indices before and after EITC. While, there was no statistically significant difference between kidney function tests, liver function tests and electrolytes before and after EITC.

Bronchoscopic evaluation after EITC indicated that 7 of 15 patients had an increase in the airway lumen diameter of > 50% (good response) and 5 patients showed an improvement between 25% and 50% (partial response). While, in 3 patients the improvement was < 25% (no response) Table 5. Overall, debulking by EITC was considered clinically satisfactory (>25%) in 12 of the 15 patients (80%).

The mean total duration of FB examination (including EITC) was 20.56±4.34 (range 12-28) minutes. While, the mean EITC procedure duration was 12±3 (range 5-16) minutes. The percentage of the EITC procedure to the total time of FB examination was calculated as 70%.

All complications encountered after EITC were early Table 6. There were no late or systemic complications. All cases survived until referred to systemic chemotherapy and/or radiotherapy 2 weeks later.

Table 3. Comparison between Clinical, Radiological and Bronchoscopic evaluation before and after EITC.

	Before EITC N (%)	After EITC N (%)	P	S
Clinical				
MMRC dyspnea grade[7]*	2.60±0.507	1.67±0.724	0.001	HS
Cough & Expectoration	14 (93.3%)	13 (86.7%)	0.988	NS
Hemoptysis	5 (33.3%)	1 (6.7%)	0.045	S
Chest pain	9 (60%)	3 (20%)	0.031	S
KPS[8]*	69.3±7.03	76±9.10	0.001	HS
Radiological				
Post obstructive pneumonia	9 (60%)	3 (20%)	0.031	S
Lobar atelectasis	14 (93.3%)	7 (46.7%)	0.016	S
Bronchoscopic				
Obstruction scoring system[9]*	5.20±1.014	2.47±2.066	0.001	HS
Size of the tumor by FB*	4.1±1.12	1.50±1.03	0.001	HS

EITC= endobronchial intratumoral injection of chemotherapy, MMRC: Modified Medical Research Council. KPS: Karnofsky Performance Status, FB: fiberoptic bronchoscopy. S= Significant, NS= Non significant, HS= highly significant. Digits are presented in number (N) and percentages (%) unless otherwise illustrated. *=Mean ±SD.

Table 4. Comparison between Arterial blood gases, Spirometry and Laboratory investigations evaluation before and after EITC.

	Before EITC Mean±SD	After EITC Mean±SD	P	S
Arterial blood gases*				
PH	7.39±0.028	7.41±0.035	0.001	HS
PaO_2 mmHg	68.53±4.83	74.07±6.45	0.001	HS
$PaCO_2$ mmHg	38.53±5.26	36.00±4.45	0.003	HS
SaO_2 %	93.13±2.13	94.67±2.44	0.001	HS
Spirometry				
FEV_1% predicted	52.93±17.45	61.87±14.643	0.001	HS
FVC% predicted	61.73±12.635	70.60±11.469	0.001	HS
Laboratory				
Serum creatinine (mg/dL)	1.01±0.24	1.06±0.19	0.532	NS
Blood urea nitrogen (mg/dL)	21.2±11.66	22.06±6.86	0.807	NS
Serum sodium(mEq/L)	136.46±6.04	136.33±3.59	0.943	NS
Serum potassium (mEq/L)	3.91±0.65	4.06±0.53	0.494	NS
AST (IU/L)	25.4±11.91	23.66±12.97	0.704	NS
ALT(IU/L)	21.26±9.17	21.8±8.06	0.865	NS

EITC= endobronchial intratumoral injection of chemotherapy, Paco2= partial pressure of CO_2 in the blood, Pao_2= partial pressure of oxygen in the blood, SaO_2 = O_2 saturation, *arterial blood gases on room air. FEV_1 = forced expiratory volume in the first second, FVC = forced vital capacity. AST= Aspartate aminotransferase, ALT= Alanine aminotransferase. S= Significant, NS= Non significant, HS= highly significant.

Table 5. Treatment response after EITC.

Total objective response	N	%
No response	3	20.0
Partial response	5	33.3
Good response	7	46.7

Evaluation of response was according to new Response. Evaluation Criteria in Solid tumors (RECIST).[10]

Table 6. Early complications after EITC.

	N
Fever one day after bronchoscope	3
Newly developed/ progressed dyspnea	4
Newly developed/ progressed chest pain	2
Newly developed/ progressed cough	8
Newly developed/ progressed haemoptysis	2
Hypoxia	2
Tachycardia	1
Nausea	1

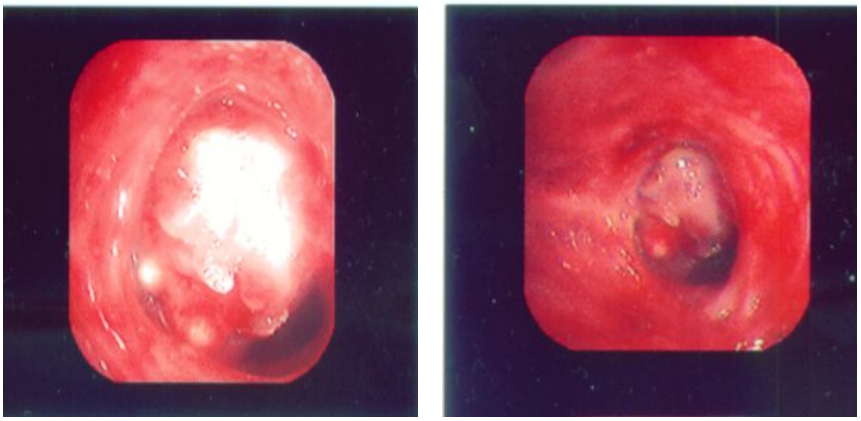

Fig 1. Endobronchial mass before and after EITC.

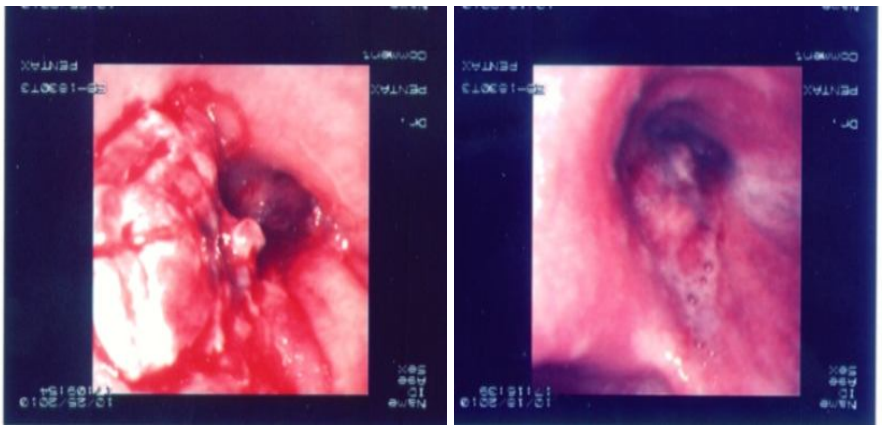

Fig 2. Endobronchial mass before and after EITC.

Case Report: A 55 years old male patient, cigarette smoker 60 packs / year presented clinically with productive cough, dyspnea on mild exertion of 2 months duration and symptoms of post obstructive pneumonia of 1 week duration. Radiologically the C.T scan showed a large tumor mass 4x5 cm in right upper lobe with subsequent consolidation.

Bronchoscopic bronchial biopsy was performed from an exophytic endobronchial tumor mass completely obstructing posterior segment of right upper lobe (Fig. 3a). Pathological examination revealed infiltrating adenocarcinoma grade II. The clinical stage was IIa. The patient was inoperable because of limited cardio-respiratory reserve.

Four sessions of EITC for the endobronchial mass one week apart were done followed by improvement of dyspnea grade from grade III to grade II, KPS from 70% to 80% and resolution of post obstructive pneumonia. Also there was decrease in the size of tumor mass to measure 2x2 cm radiologically. Follow up observational bronchoscopy one week after 4th session of EITC revealed decrease of size of endobronchial tumor mass (from 4 cm to 1 cm) (Fig. 3b) with good treatment response. No complications occurred during or after FOB.

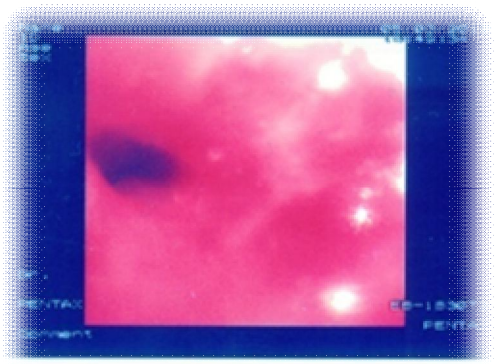

Fig 3a. Tumor mass obstructing posterior segment of right upper lobe.

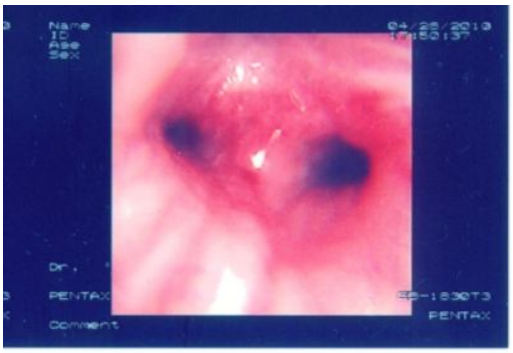

Fig 3b. Posterior segment of right upper lobe after EITC.

DISCUSSION

This initial study highlighted the efficacy and safety of bronchoscopic EITC with an overall yield of clinically satisfactory tumor debulking of endobronchial obstructing lesions in 80% of studied cases with significant improvement of dyspnea score, Karnofsky performance scale as well as spirometric and arterial blood gas indices for palliative treatment of endobronchial malignant NSCLC.

Choosing non metastatic patients for this study was ethically based as newly diagnosed metastatic patients must start conventional systemic chemotherapy and / or radiotherapy once diagnosed. Also to make sure that response of treatment would be attributed to EITC alone not to systemic chemotherapy and / or radiotherapy.

All previous intratumoral injection studied in literature[6,11,12] found that combination of multi drugs gave the same effect as cisplatin alone with no recorded resistance to cisplatin; thus it was chosen for EITC in the current study.

There are several potential advantages for direct intratumoral drug injection, including assured precision in the local delivery of drugs, complete perfusion of drug within and around the lesion, higher tumor tissue concentrations than is achievable by conventional systemic chemotherapy, little or no systemic toxic side effects and much less costs than other interventional bronchoscopic techniques. One of the additional unique advantages of EITC over other thermic bronchoscopic interventions (e.g. laser therapy, electrocautery, cryotherapy, photodynamic therapy) is effective and favorable application in lesions that have a large extraluminal component, extensive submucosal involvement and long tapering lesions. Unfortunately, such lesions are not favorable by any thermic bronchoscopic interventions.[5]

The advantages of other interventional bronchoscopic procedures over EITC that it enables rapid and urgent removal of tumor obstruction e.g. mechanical debulking / resection, (Nd-YAG) laser resection, electrocautery in case of life-threatening obstruction. Also in non-life threatening obstruction thermic interventions as laser and electrocautery debulk tumor most commonly

in one session not like the four sessions of EITC, although each session time is much shorter if compared to other bronchoscopic intervention, but has prolonged cumulative time of therapy over the four sessions. On the other hand, thermic bronchoscopic interventions usually require rigid bronchoscopy with risk of general anesthesia, need more experience and more costly equipment with subsequent increase expenses and risk on the patients.[5]

All bronchoscopic (whether laser therapy, electrocautery, cryotherapy or EITC) and non-bronchoscopic interventions (whether radiotherapy or systemic chemotherapy) should supplement each other and not compete one other.[5]

Assessment of the patients' response was based mainly on subjective and objective responses. As regards the subjective response in the current study, a highly significant improvement of dyspnea grade in 80% of the 15 patients included in current study as compared by using MMRC dyspnea grade before and after EITC within 4 weeks. While there were a significant improvement of chest pain, post obstructive pneumonia and haemoptysis in 66.6%, 66.6% and 80% respectively of the 15 cases involved in current study after 4 sessions of EITC than before. These results were in partial agreement with previous studies on EITC.[6,11,12]

Celikoglu et al,[11] recorded improvement of stridor, dyspnea, post-obstructive pneumonia symptoms and haemoptysis in 87%, 90%, 80% and 90% respectively of 93 patients involved in that study after 4 sessions of EITC within 2 weeks with combination of 5 anti-cancer drugs with multiple areas of involvement such as trachea, carina, main bronchi and lobar bronchi, whereas the current study involved only lobar bronchi with 4 sessions of EITC with cisplatin within 4 weeks.

In study by Celikoglu and Celikoglu,[12] out of the 65 patients entered in that study stridor, dyspnea, post obstructive pneumonia symptoms and haemoptysis were improved in 81%, 77%, 63% and 87% respectively of the 65 patients involved in that study in response to EITC treatment of trachea, carina, main bronchi, or lobar bronchi after 3-4 sessions by 5-FU within 2 weeks.

As regards the subjective response in study by Jabbardarjani et al,[6] which involved 100 patients, improvement of dyspnea and haemoptysis occurred in 36% and 80% of the 100 patients included in that study respectively, while chest pain was not improved at all after 4 sessions of EITC by cisplatin within 4 weeks with the concentration of 50mg/100mL which was the difference from the current study that used cisplatin by concentration of 50mg/50mL, with total dose of 20mL cisplatin in both studies. Also the above mentioned study6 involved a metastatic disease that may contribute to the low percentage of improvement.

The difference between the results of the current study and those of the above listed ones may be due to the difference in the site of the tumor peripheral or central, the number of patients enrolled in each study, difference in size, stage or type of the tumor, presence of metastasis.

It is noted that haemoptysis was the most common symptom to improve after treatment due to the haemostatic effect of EITC probably due to vasoconstriction of small vessels in or around the tumor growth due to the reaction with very high concentrations of the cytotoxic drug; a probable oligemia caused by the compression of small vessels in the tumor due to the additional volume of injected aliquot of drug solution into a restricted space and intravascular formation of thromboses in the tumor vessels.[5]

Productive cough was not improved significantly in either current study or other studies[6,11,12] even with improvement of other symptoms because of the chronicity of the symptom due to that most of patients had chronic obstructive pulmonary disease, so EITC did not improve cough and expectoration significantly.

Considering KPS, it had highly significantly increased after (76±9.10) than before (69.3±7.03) EITC. The improvement may be attributed to one or more of the following factors, improvement of symptoms such as (dyspnea, haemoptysis, chest pain and cough), improvement of arterial blood gases and spirometry after relief of the endobronchial obstruction and its consequences e.g. atelectasis and post-obstructive pneumonia. In the other hand, Jabbardarjani et al,6 showed less improvement (52%) than the current study. This may be due to the difference in the number of patients enrolled in each study, difference in sites involved, size or stage of the tumor, presence of metastasis, or due to post procedural complications.

FVC improved significantly in 77% of patients and FEV_1 improved significantly in 60% of patients after end of sessions. This is in agreement with Celikoglu et al,[11] Celikoglu and Celikoglu.12 They recorded improvement in spirometric data of FVC and FEV_1 of 80% and 72% respectively. This high percentage may be due to the fact that most of the patients had tumors in the trachea and main bronchi. The relatively high percentage of improvement of FVC and FEV_1 in the current study may be attributed to improvement of obstruction, post obstructive pneumonia and stoppage of haemoptysis after EITC

In the present study, PaO_2 and $PaCO_2$ improved significantly in 70% of patients after end of sessions for both parameters of arterial blood gases. This is in agreement with Celikoglu et al,[11] Celikoglu and Celikoglu.[12] The improvement in PaO2 and normalizing PaCO2 may be attributed to improvement of the lobar

atelectasis, thus decreasing the shunt effect of these unventilated and hypoventilated lung units which acted as a potentially reversible shunt, hence improve ventilation/perfusion (V/Q) ratio.[5]

As regard bronchoscopically visible tumors, reduction in tumor size was noticed in 12 patients (80%) with subsequent variable improvement in post-obstructive pneumonia and atelectasis in 10 patients of them. These results were in agreement with previous studies on EITC.[6,11,12]

Complete resolution of lobar atelectasis occurred in 50% of patients, while 50% showed no resolution of atelectasis after end of sessions in the current study, while in Celikoglu et al,11 atelectasis was resolved completely in 51.5%, 17% showed partial resolution of atelectasis, and 31.5% showed no resolution of atelectasis. In Celikoglu and Celikoglu,12 50% of patients with obstruction showed complete resolution of atelectasis, while 20% showed partial resolution of atelectasis and 30% showed no resolution after end of sessions. While In Jabbardarjani et al,6 52% of patients showed complete resolution, 28% of patients showed partial resolution of lobar atelectasis and 20% showed no response.

Although the low percentage of resolution in the present study, obstruction score was improved due to improvement of lobar atelectasis and post obstructive pneumonia.

As regards the total objective response, good response was achieved in 7 patients (46.7%), partial response in 5 patients (33.3%), and no response in 3 patients (20%) Table 5. These results were in agreement with previous studies on EITC.[6,11,12]

Celikoglu et al,[11] who reported 93 cases who were treated by EITC by (fluorouracil, mitomycin, methotrexate, bleomycin and mitoxantrone), recorded good response of 39 patients (42%), partial response in 42 patients (45%) and no response in 12 patients (13%). While Celikoglu and Celikoglu, 12 who reported 65 cases who were treated by EITC by (5-fluorouracil), recorded good response of 34 patients (52.3%), partial response in 23 patients (35.3%) and no response in 12 patients (12.4%). Also Jabbardarjani et al, 6 who studied 100 cases who were treated by EITC by (cisplatin) showed good response of 52 patients (52%), partial response in 28 patients (28%) and no response in 20 patients (20%).

The slight difference between the results of the current study and the other studies regarding the objective response may be due to the difference in the number of enrolled patients in each study, the fact that other studies may have chemotherapy and/or radiotherapy before start of EITC and difference in size, stage or type of the tumor.

As regards the complications in current study, they were early transient and non-repetitive side effects which may occur intraoperative or in the first 24 hours of postoperative period Table 6. There were no late or systemic complications after the end of sessions of EITC.

Dyspnea, hypoxia and subsequent tachycardia were due to necrotic tumor residues and secretions after EITC. The debridement with forceps and suction at the same session or the next session was easily done to re-establish airway patency along with corticosteroids administered intravenously. Hypoxemia was treated via supplemental oxygen during and after end of session and was gradually improved. Intraoperative bleeding was due to vascularity of the tumor and stopped due to haemostatic effect of EITC with no need for diluted adrenaline or systemic haemostatic measures.

These results were not in agreement with previous studies on EITC.[6,11,12] Celikoglu et al,[11] and Celikoglu and Celikoglu,12 showed only transient fever in 8.6% and 30.7% occurring 6-24 h after injection, respectively. While Jabbardarjani et al, 6 reported bleeding (9%), hypoxia (12%), tachycardia (35%), hypertensive crisis (3%), and chest pain (27%). The difference between the current study and the above listed ones as regards the complications of EITC may be due to the difference in the number of enrolled patients in each study, difference in the anti-cancer drugs or difference in the stage or size of the tumor.

Considering the overall follow up duration of response, all patients were followed up for the next 2 weeks after the last bronchoscope. It was observed for only 2 weeks after the end of EITC sessions, this is because the long-term systemic effects of EITC therapy are still unclear and because the initiation of radiation and/or systemic chemotherapy occur shortly (2 weeks) after relieve of bronchial obstruction by EITC with its subsequent major effects on the survival duration.

As regards the limitations of the current study, the highly conservative attitudes among clinical oncologists and pulmonologists led to involvement of few cases in this study. The number of clinical studies to date are limited, the short-term results obtained over a period of only few weeks after intratumoural treatment, and whether long-term patient survival is significantly improved is difficult to answer because the severity of symptoms in these patients did not allow placebo-controlled or double-blind clinical trials and follow-up. Also deficient follow up of treated cases with EITC after conventional systemic chemotherapy and/ or radiotherapy and if it added to treatment by EITC.

Future research in this filed could include larger number of patients with longer periods of follow up, combining and comparing EITC with other interventional therapeutic

bronchoscopic procedures and /or with conventional systemic chemo-radiotherapy.

In conclusion, EITC is a promising, safe, relatively cheap, effective and less invasive procedure for palliative treatment of endobronchial malignant NSCLC through local delivery of chemotherapy with subsequent improvement of airway obstruction, hemoptysis and post obstructive pneumonia.

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