Incidence of silent brain metastasis in patients with non-small cell lung cancer

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Abstract

Background:

Brain is one of the common sites of metastasis in patients with lung cancer. This is more likely to be present in cases with small cell lung cancer (SCLC) than those with non-small cell lung cancer (NSCLC).

Objective:

To estimate the incidence of silent brain metastasis in patients with NSCLC (clinically stages II, III and IV at presentation).Patients and methods: A prospective study was conducted during the period from July 2012 to January 2016 for 942 patients presented in Sohag University Clinical Oncology Department, Sohag Cancer Center and Sohag Health Insurance. All of them had histopathological prove of NSCLC and contrast-enhanced conventional magnetic resonance imaging (MRI) of the brain was done for all patients at presentation.

Results:

Seventy-six percent of patients were male. Seventy-eight percent of patients were in the age group of 40-60 years. 362 patients (38.4%) had brain metastasis at time of their presentation. All those diagnosed to have brain metastasis received palliative whole brain irradiation and 20 patients received further local treatment directed to the metastatic brain deposits. Surgical resection of brain metastasis was done for 8 patients and conformal radiotherapy boost for 12 patients.

Conclusion:

NSCLC is one of the common causes of brain metastasis. Presentation with silent brain metastasis is not an uncommon occurrence. So MRI brain should be routinely used for the evaluation of patients with NSCLC even in the absence of symptoms or signs of brain metastasis which help to start brain directed therapy earlier.

Keywords:

Metastasis, non-small cell, lung, Cancer, resection.

Introduction

Lung cancer is the leading cause of cancer-related deaths in the United States. Estimated new cases of lung cancer (non-small cell lung cancer "NSCLC" and small cell lung cancer "SCLC" combined) in the United States in 2016 are 224,390 and estimated deaths from lung cancer158,080(1). Among males in Egypt cancer of the lung occupied the third or fourth rank representing 5–7% of cancers(2).

The World Health Organization (WHO) divides lung cancer into two major classes based on its biological nature, treatment, and prognosis: the first is NSCLC and the second is SCLC. NSCLC accounts for around 85% of total lung cancers, and it includes 2 major types: 1) non-squamous carcinoma (as adenocarcinoma, large-cell carcinoma, and other cell types); and 2) squamous cell carcinoma. Adenocarcinoma is the most common subtype of lung cancer in the USA and is the most frequent cell type among nonsmokers. Certain prognostic factors are predictive of survival in patients with NSCLC (3).

Good prognostic factors include early-stage disease at diagnosis, good performance status (PS), no significant weight loss (not more than 5%), and female gender(4).Of lung and bronchial cancer cases, 57% were diagnosed after the cancer had already metastasized(5).

Brain metastasis is very common among patients with metastatic NSCLC. At time of its diagnosis, about 7%–10% of NSCLC patients present with brain metastases, and up to 20-40% of patients develop brain metastasis at some time during their course(6-8).The incidence of brain metastasis is increasing in the last years; however, this may just reflect advancement in diagnostic imaging(8).

Pretreatment work-up for NSCLC patients includes taking of clinical history, Eastern Cooperative Oncology Group Performance status (PS) determination, physical examination, stage of disease at presentation and the presence or absence of neurological symptoms that should be analyzed with exclusion of those of neurological manifestations. Blood tests, X-ray chest, chest and/or upper abdominal computed tomography (CT), bone scintigraphy or positron emission tomography (PET), and brain MRI are the most needed investigations(9).

Surgery, radiation therapy (RT), local ablative procedures, chemotherapy, and targeted systemic treatment are the approved modalities used to treat patients with NSCLC. They can be used alone or in combination, for radical or palliative treatment according to stage of the disease and patient's PS (10, 11).

Surgical resection of a single brain metastasis addressed as a well-defined role proved by prospective and retrospective studies, while the role of surgical resection is controversial in patients with multiple brain metastasis (10-14).

Patients and methods

It's a prospective study conducted during the period from July 2012 to January 2016 for 942 patients presented in Sohag University Clinical Oncology Department, Sohag Cancer Center and Clinical Oncology Clinic at Sohag Health Insurance. All patients had histopathological prove of NSCLC. Some of them had documented metastatic lesions (liver, suprarenal, bone and others) at presentation. All patients subjected to pretreatment work-up including taking a clinical history, Eastern Cooperative Oncology Group (ECOG) Performance status (PS) determination as showed in table 1(15), physical examination, the presence or absence of neurological symptoms, blood tests including (complete blood count, kidney function tests, liver function tests and blood glucose level), chest radiography, computed tomography (CT) of the thorax and upper abdomen, bone scintigraphy or positron emission tomography (PET), and brain MRI(9, 15).

Contrast-enhanced conventional magnetic resonance imaging (MRI) of the brain was done for all patients at first visit. All patients proved to have brain metastasis were examined by

multidisciplinary team including clinical oncologist, neurosurgeon, radiologist and pathologist with detailed neurological assessment. Patients selected for metastatectomy (excision of brain metastatic deposit or the prominant lesion from multiple) according to the following inclusion criteria especially with no any neurological deficits:

- ***Inclusion criteria:***

  * Patients with solitary brain metastasis or oligo-metastasis (few number of metastasis) to brain with prominent single lesion.
  * ≤70 years old, medically fit and accepting surgery.
  * ECOG performance status grade 0,1 or 2.
  * Potentially controlled extra-cranial disease.

- ***Exclusion criteria:***

  * Medically unfit and refusing surgery
  * >70 years old,
  * ECOG performance status grade 3 or 4.
  * Disseminated expected uncontrolled extra-cranial disease

- ***Protocol***

  Patients proved to have brain metastases received whole brain radiotherapy (WBRT) 30 Gray/10 fractions/2 weeks using 6 million volt photon beam therapy delivered by linear accelerator. All patients who received this course of radio therapy were treated in supine position with thermoplastic mask head fixation. All of them were planned for radiotherapy using conventional simulator. All patients with brain metastasis received corticosteroids and diuretics before and during whole brain radiotherapy course. After resection of brain lesion as upfront line of treatment this was followed by WBRT or conformal radiotherapy boost as an additive treatment after WBRT.

- ***Statistical Analysis:***

  Data were analyzed using Microsoft Excel 2016 software and IBM-SPSS version 24, quantitative data were expressed as mean±SD; while qualitative data were expressed as number and percentage. Pearson Chi Square statistic was used to compare percentages of qualitative data. P value less than <0.05 was considered significant

Results

A total of 942patients presented from July 2012 to January 2016 in Sohag University Clinical Oncology Department, Sohag Cancer Center and Clinical Oncology Clinic at Sohag Health Insurance. The characteristics of these patients are summarized in Table 2. All of them had histopathological prove of NSCLC, Seventy-six percent of patients were male and twenty-four were female. Seventy-eight percent of patients were in the age group of 40-60 years and median age is 50 years.

We found that 362 patients (38.4%) had brain metastasis at time of their presentation, brain metastasis occurred in 91.4% of those with metastasis in general. About 69% of patients with brain metastasis had multiple brain deposits and 31% had only single brain deposits. This is shown in table 3.

Histopathology of primary lung lesion of 850 patients (90.2%)were squamous cell carcinoma (SCC) and adenocarcinoma collectively. Out of them 462 patients had SCC and 388 had adenocarcinoma. Stage and tumor characteristics are listed in table 4.

Nearly 90.3% of patients with brain metastasis had either SCC or adenocarcinoma. No significant relation between histopathology and the presence or absence of the brain metastasis (p= 0.297). Obviously, there is a relation neither between pathology nor metastasis generally, or brain metastasis specifically which addressed in tables 5 and 6; respectively.

All those diagnosed to have brain metastasis received palliative whole brain irradiation and 20 patients received further local treatment directed to the metastatic brain deposits. Surgical resection of brain metastases was done for 8 patients and conformal radiotherapy for twelve

patients. Among the eight candidates for surgery, six patients were males. Five of them had single lesion necessitated operative intervention. MRI revealed multiple lesions in three patients and they were eligible for surgical intervention to resects the dominant lesion.65% of those with brain metastasis received systemic treatment (chemotherapy and or targeted therapy), 35% received best supportive care. The criteria of the patients who were surgically treated was shown in table 7.

All patients with brain metastasis completed brain-directed therapy WBR, which may be the result of discovering brain metastasis earlier.

- ***Case presentation:***

Four cases are presented in this manuscript.

Table 1 : ECOG performance status developed by the eastern cooperative oncology group(15)

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self care; totally confined to bed or chair
5	Dead

Table 2: Patient characteristics

		No(%)
Sex	Male n(%)	716(76.01%)
	Female n(%)	226(23.99%)
Age	Mean±SD	52.10±7.70
	Median (range)	50(35-76)
Performance status	I	71(7.54%)
	II	766(81.32%)
	III	105(11.15%)

Table 3: Metastasis

		N.(%)
Metastasis	No	546(57.96%)
	Yes	396(42.04%)
Number of organs affected by metastasis	Single organ metastasis	177(18.79%)
	Two organ metastasis	114(12.10%)
	Three organ metastasis	101(10.72%)
	Four organ metastasis	4(0.42%)
Organs affected by metastasis	Brain	362(38.43%)
	Bone	147(15.61%)
	Liver	158(16.77%)
	Contralateral lung	54(5.73%)
Brain metastasis	Brain metastases/total number of cases	362/942(38.43%)
	Brain metastases/total metastases	362/396(91.41%)
	Single brain metastasis/total brain metastases	113/362(31.22%)
	Multiple brain metastases/total brain metastases	249/362(68.78%)

Table4: Tumor characteristics

		N.(%)
Pathological type	Adenocarcinoma	462(49.04%)
	Bronchoalveolar carcinoma	20(2.12%)
	Carcinosarcoma	13(1.38%)
	Large cell carcinoma	59(6.26%)
	Squamous cell carcinoma	388(41.19%)
Grade	I	8(0.85%)
	II	694(73.67%)
	III	240(25.48%)
Tumor stage	1	7(0.74%)
	2	402(42.68%)
	3	423(44.90%)
	4	110(11.68%)
Nodal stage	0	83(8.81%)
	1	393(41.72%)
	2	333(35.35%)
	3	129(13.69%)
	4	4(0.42%)

Table 5:Relation between pathological type and metastasis

Pathological type	Metastasis	No metastasis	Chi square	P value
Adenocarcinoma	176(38.10%)	286(61.90%)	6.828	0.245
Bronchoalveolar carcinoma	8(40.00%)	12(60.00%)		(NS)
Carcinosarcoma	5(38.46%)	8(61.54%)		
Large cell carcinoma	25(42.37%)	34(57.63%)		
Squamous cell carcinoma	182(46.91%)	206(53.09%)		

Table 6:Relation between pathological type and brain metastasis

Pathological type	Metastasis	No metastasis	Chi square	P value
Adenocarcinoma	171(37.01%)	291(62.99%)	1.457	0.834
Bronchoalveolar carcinoma	7(35.00%)	13(65.00%)		(NS)
Carcinosarcoma	4(30.77%)	9(69.23%)		
Large cell carcinoma	24(40.68%)	35(59.32%)		
Squamous cell carcinoma	156(40.21%)	232(59.79%)		

Table 7: criteria of patients who were candidates for surgery

Case No	Age	Sex	No of Metastasis	PS	Location	Histopathology	GOS 30 day	GOS 6 month
1	60	M	Single	0	Parital	Adeno	MD	GR
2	58	M	Multiple	I	Fronto - Parital	Squ	SD	MD
3	62	F	Multiple	II	Pariato - occipital	Adeno	MD	GR
4	52	M	Single	I	Parital	Adeno	GR	GR
5	66	M	Multiple	II	Fronto - Temporal	Squ	GR	GR
6	48	F	Single	I	Parital	Adeno	MD	SD
7	67	M	Single	I	Temporal	Sque	MD	MD
8	59	M	Single	0	Parital	Adeno	GR	*

* GR =Good recovery
* MD = Moderate disability
* SD = Sever disability
* Adeno = Adenocarcinoma
* Squ = Squamous cell Carcinoma
* M = Male
* F = Female

Case 1:

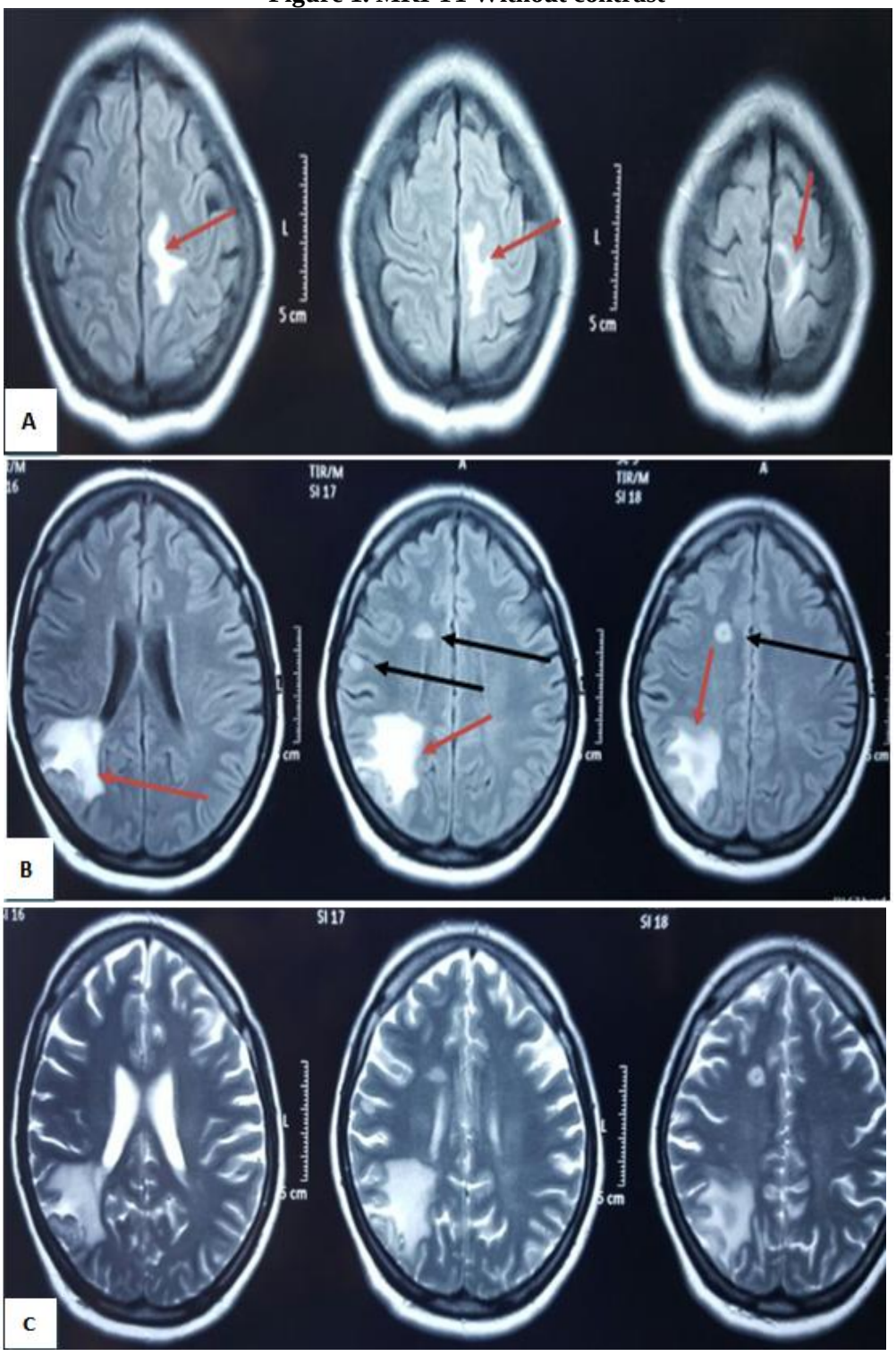
Clinical data: 46 years old female presented after wedge resection for left lung upper lobe mass lesion, histopathology was invasive adenocarcinoma grade III. MRI brain revealed:

Radiological data: (Figure 1), MRI brain axial T1 (A, B) pre irradiation, and chemotherapy and MRI brain axial T2 (C) post irradiation, and chemotherapy

- Left high parietal parasaggital extra axial lesion with related mild perilesional edema. .as shown in (A), red arrow
- Right sided parieto-occipital dural based abnormal lesions with related mild perilesional edema. as shown in (B), red arrow
- Other three small nodular lesions seen at right fronto-parietal white matte as shown in (B), black arrow.

Course: The patient received WBI 30Gy/10 sessions/2 weeks, then received 6 cycles chemotherapy (Gemcitabin and Cisplatin)

Figure 1. MRI T1 Without contrast



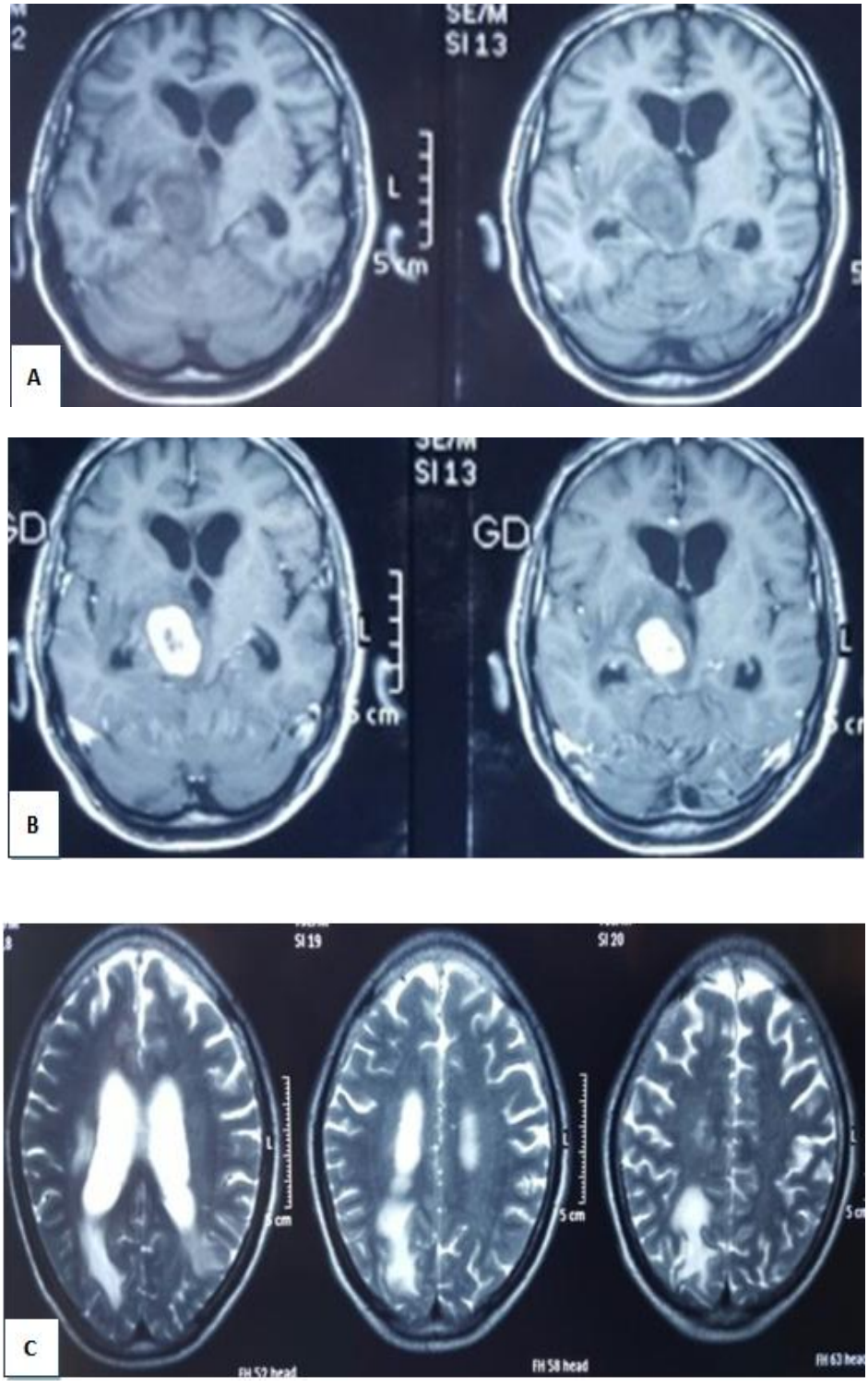
Case 2:

Clinical data: 65 years old male presented with right lung hilar mass lesion, histopathology was invasive adenocarcinoma grade II.

Radiological data: (Figure 2). MRI brain revealed single deep right sized thalamic lesion, with mild perilesional odema (A) and showing contrast enhancement at post gadolinium scans(B). The largest lesion was at the right thalamic region about 3×2cm surrounded by edema compressing 3rd ventricle. Nearlly complete improvement after radio, and chemotherapy (C)

Course: The patient received WBI 30Gy/10 sessions/2 weeks, then received 6 cycles chemotherapy (Vinorelbine and Cisplatin)

Figure 2. MRI T1 without contrast



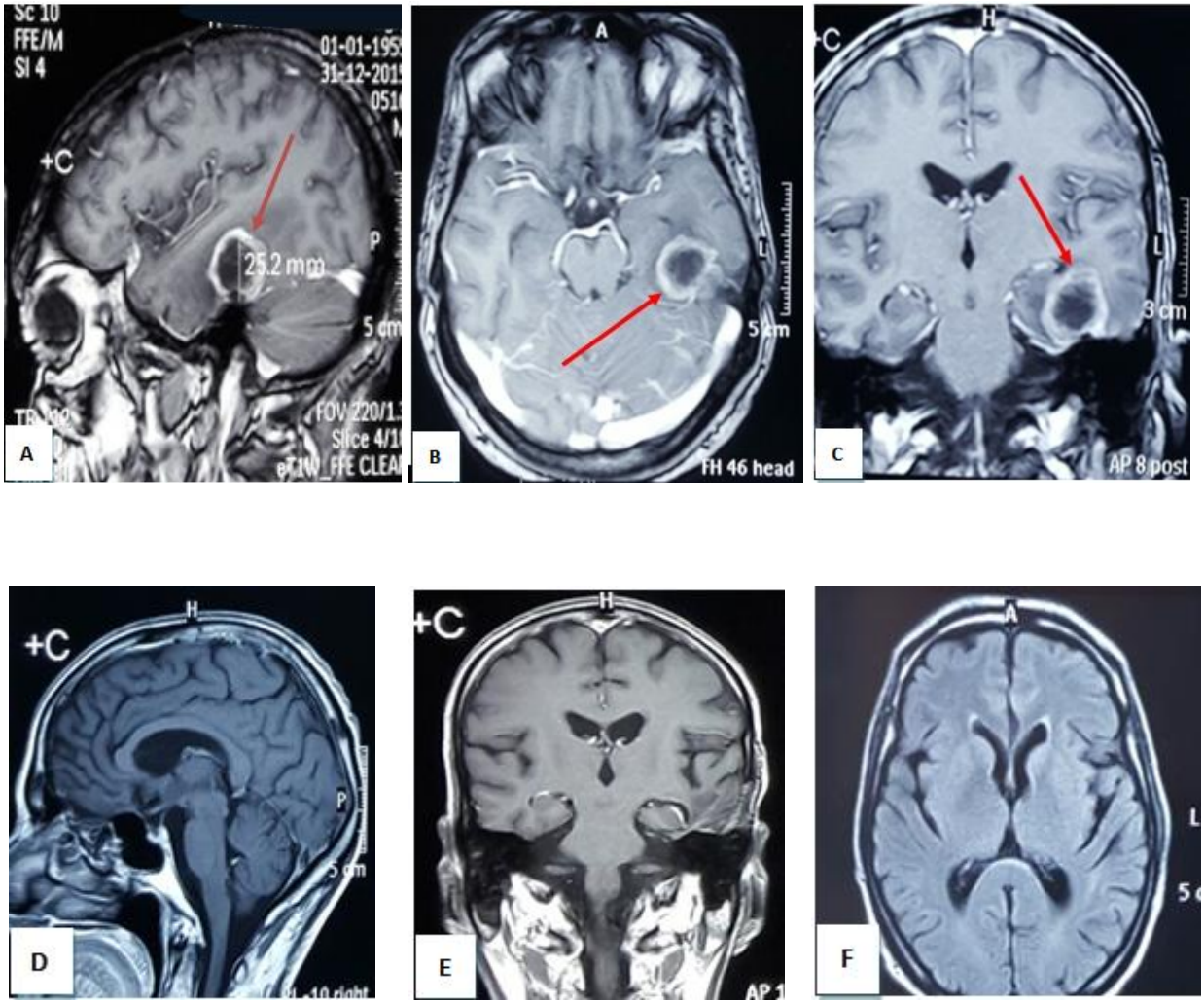
Case 3:

Clinical data: 60 years old male, heavy cigarette smoker, presented by cough and chest pain.

Radiological data (Figure 3):. CXR and CT chest revealed RT lung mass. MRI brain with and without contrast (A,B, C),showing left single temporal well defined SOL(red arrows) , with marked perilesional edema and MRI brain. Follow up 45 days postoperative(D, E, F)

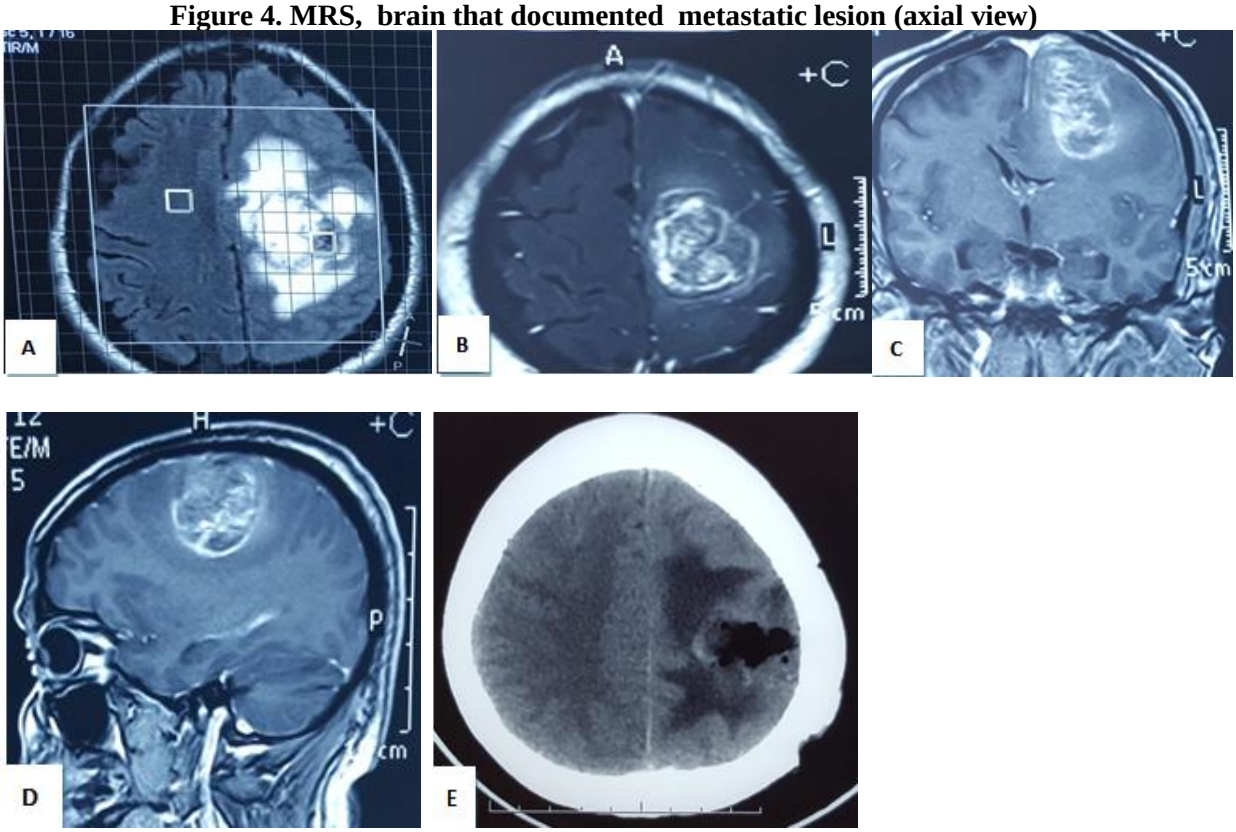
Course: single SOL resected, undifferentiated carcinoma, followed by WBI 3000 cgy /10TTT/2ws, received 3 cycles chemotherapy (Taxoter / cisplatin), stationary disease, 3 cycles vepside / cisplatin, can't tolerate further CHT.

Figure 3. MRI brain T1 with contrast at presentation (sagittal view)



Case 4:
Clinical data: 52 years old male, diagnosed to have right sided NSCLC(squamous cell carcinoma).
Radiological data: (Figure 4). MRI, MRS brain with and without contrast (A, B, C, D) showing left single deep parietal well defined SOL, with marked perilesional edema. Follow up CT brain postoperative, (E)
Course: single SOL resected, squamous cell carcinoma, and lost in follow up.

Figure 4. MRS, brain that documented metastatic lesion (axial view)



Discussion

This study was conducted to detect the percentage of brain metastases from NSCLC in patients with this disease at their presentation without evident symptoms point to brain disease. Previous studies showed that about 7%–10% of NSCLC patients present with brain metastases at the time of diagnosis, and up to 40% of them develop brain metastases at some time during their disease course(6, 8, 16). The incidence of brain metastasis in lung cancer patients at initial presentation has been described between 12-19% in various studies so far. Kim et al reported of 18.9% brain metastasis in patients with NSCLC (16).In other two studies the incidence of brain metastasis in patients with NSCLC was 14% and 28.9%(17).

While in our study 38.4% of patients had brain metastasis at presentation. We explained this difference by doing MRI brain as an upfront tool to investigate and stage the disease. From the histopathological view, most of metastatic patients had either adenocarcinoma or squamous cell carcinoma, that is mostly due to these two pathologies were the predominant pathology, which approved also in our study. Brain metastases from NSCLC were felt to represent a poor outlook in general (7, 18).

A wise tendency toward more local surgical management in eligible patients with brain metastasis has been recommended by our team to maximize survival and neurologic function, which delineated by many other authors (19).

Approximately 25% of NSCLC patients with single or oligo-metastatic brain metastases will be suitable for surgical resection of their metastatic brain lesion or lesions (20).

Our study was conducted to detect brain metastasis in a symptomatic patient with NSCLC earlier, so aggressive local and systemic treatment can be highlighted for those to improve overall survival and progression-free survival.

A number of retrospective series showed promising survival of (11,6–14)months in selected patients who underwent complete resection of solitary or oligo-metastatic brain metastasis from NSCLC; with a good results and controlled extracranial conditions(21-23).

McPherson et al have analyzed the results of 358 patients with single brain metastases from different primary tumors, as regards tumor control and patients' survival. All patients were treated with either microsurgical resection alone (60% of cases) or with adjuvant WBRT (40% of cases) revealed hopeful, and encouraging results in those early discovered cases(24).In our study the number of patients exposed to resection of the single brain metastasis is lower than that of McPherson et al(24).Insight the high incidence of brain metastasis shown in non-small cell lung cancer patients in our study, and inspite of many randomized trials evaluating prophylactic cranial irradiation (PCI) in patients with locally advanced NSCLC have been published.[25-27] which showed that PCI decreases or delays the incidence of CNS manifestation , or failure in these patients [27-28, 30]. As regards the indication of PCI to the patients with locally advanced NSCLC has not become a standard of care despite evidence of its effectiveness in decreasing CNS failure rates. We feel that is partially due to the lack of a survival advantage associated with the therapy and concern about neurotoxicity. So in our study we didn't approved the application of PCI for patients with non-metastatic disease stages, or evidence.

In our study detection of brain metastasis in patients who didn't suffered from symptoms which means that those patients had relatively good PS than those presented with symptoms, this early detection help us to maximize local and systemic treatment due to good PS.

Conclusion:

We recommend routine MRI brain study for patients with NSCLC at their presentation as a neuro imaging to detect brain metastasis earlier, so aggressive local and systemic treatment can be given for those to improve overall survival and progression-free survival.

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الملخص العربى

معدل حدوث ثانويات صامتة بالمخ في مرضى سرطانات الرئة من غير نوع سرطانات الخلايا الصغيرة

خلفية:

الدماغ هي واحدة من الأماكن الأكثر شيوعا في حدوث ورم خبيث في المرضى الذين يعانون من سرطان الرئة. ومن المعروف أن تكون هذه الأورام منتشرة في حالات سرطان الخلايا الصغيرة في الرئة بصورة أكبر من من سرطانات الرئة ذات الخلايا غير الصغيرة

هدف الدراسة:

تقدير حدوث ورم خبيث ثانوي صامت في المخ في المرضى الذين يعانون من سرطانات الرئة ذات الخلايا غير الصغيرة.

المرضى والطرق:

أجريت دراسة مستقبلية خلال الفترة من يوليو 2012 إلى يناير 2016 على 942 مريضا في جامعة سوهاج قسم الأورام ومعهد أورام سوهاج والتأمين الصحي بسوهاج، يعانون من أورام سرطانية من غير الخلايا الصغيرة. وأجري لكل منهم التصوير بالرنين المغناطيسي للدماغ.

النتيجة:

كانت ستة وسبعون في المئة من المرضى من الذكور وأربع وعشرين بالمائة من الإناث. وكانت ثمانية وسبعون في المئة من المرضى في الفئة العمرية من 40-60 عاما. وكان 362 مريضا (38.4٪) لديهم ورم خبيث في الدماغ في وقت عرضها. تلقى جميع هؤلاء المرضى علاج إشعاعي للمخ وتلقى 20 مريضا مزيد من المعالجة المحلية الموجهة إلى الثانويات بالدماغ. وقد تم الاستئصال الجراحي للورم الخبيث في المخ لعدد 8 من المرضى وعلاج إشعاعي إضافي لعدد 12 مريض.

الخلاصة:

أورام الرئة من غير ذات الخلايا الصغيرة هي واحدة من الأسباب الشائعة لحدوث أورام خبيثة في الدماغ. ولهذا فإن التصوير بالرنين المغناطيسي للدماغ يجب أن تستخدم بشكل روتيني لتقييم المرضى الذين يعانون من أورام سرطانية رئوية من غير أورام الخلايا الصغيرة حتى في حال عدم وجود أعراض أو علامات ورم خبيث في الدماغ مما يساعد على بدء العلاج في وقت مبكر.