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RESEARCH ARTICLE

THE ROLE OF SURGERY IN SMALL CELL LUNG CANCER.

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Abstract

OBJECTIVE: To study the role of surgery as a primary modality of treatment for patients with small cell lung cancer (SCLC). **PATIENTS AND METHODS:** The study was conducted in the departments of CVTS and Medical oncology SKIMS Soura from May-2008 to Sep-2010. The study was prospective /retrospective in design. All the patients (n=30) who underwent pulmonary resection for LD-SCLC from Jan-2000 to Sep-2010 were included in the study. **RESULTS:** The median age was 56 years (range, 35-80 years). Operations performed included lobectomy in 21, bilobectomy in 3, and pneumonectomy in 6. Postoperative therapy included chemotherapy alone in 8 patients, radiation therapy in 6, and combined chemotherapy and radiation therapy in 10, PCI was given to 7 patients. Postsurgical tumor stage was IA (n=6), IB (n=6), IIA (n=3), IIB (n=9), IIIA (n=6). Postoperative complications occurred in 20% of the patients (6/30), including 3 cases of supraventricular arrhythmia, 1 case of pneumonia, 1 case of prolonged air leakage and 1 case of wound site infection. Operative mortality was 3.3% (1/30). Patients were followed up for 1-70 months postoperatively, with a mean follow-up of 36.5 months. The 5-year survival rate according to the pathologic stage was 58.3% for patients with stage I, 25% for patients with stage II and 16.7% for patients with stage III. **CONCLUSION:** Pulmonary resection in patients with stage I or stage II SCLC is safe with low mortality and morbidity. Curative resection is associated with long-term survival in early stage SCLC and should be considered in selected patients.

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Introduction:-

Lung cancer is most common cancer in the world, and a leading cause of death from cancer in men & second most common in women. It accounts for nearly 13% of all new cancer diagnoses in both sexes combined. By any conventional measure, the enormity of this global problem is immense. In some countries incidence and mortality rates have peaked and are beginning to decline. In many developing nations the burden of disease is rising and will

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continue to rise because aggressive tobacco industry marketing is leading to a growing prevalence of cigarette smoking. This is also one of the major causes of cancer deaths in our valley. Lung cancer has been found to be the second commonest cancer according to a hospital-based data from Kashmir. The crude incidence rate, age standardized (world), and truncated age adjusted (40-69 years, world) incidence rates for lung cancer per 100 000 population are 4.01, 6.48 and 15.28 respectively (Males 6.55, 10.09 and 23.94 respectively and females 1.19, 2.14 and 4.65)¹.

Small cell lung cancer (SCLC) accounts for approximately 15% of new cases of lung cancer diagnosed annually and for up to 25% of lung cancer deaths each year². However, the overall incidence and mortality rates of SCLC in the United States have decreased during the past few decades^{2,3}. Possible causes for this trend include the decrease in smoking prevalence especially in white men and a change to low-tar filters³. Recent evidence suggests that women of all ages are more likely to present with SCLC than men, and that younger women are more likely to present with SCLC than older women. Women who begin smoking at an early age are more susceptible to SCLC^{4,6}.

Material and Methods:-

The study was conducted in the departments of CVTS and Medical oncology SKIMS Soura from May-2008 to Sep-2010. The study was prospective /retrospective in design. All the patients who underwent pulmonary resection for LD-SCLC from Jan-2000 to Sep-2010 were included in the study. In all patients diagnosis was established by histologic examination of resected specimen. Some patients did not have a confirmed diagnosis of SCLC before resection and were taken to surgery for peripheral solitary pulmonary nodules suspected of being cancerous. All the patients whose pre operative diagnosis was known underwent a complete staging procedure. This included, a detailed history and physical examination, the evaluation of the performance status according to Karnofsky, a complete blood count and biochemical profile, cardiac and pulmonary function tests, chest X-ray, bronchoscopy, computed tomography of chest, the upper abdomen and brain, abdominal ultrasonography, and bone scan. Patients were classified using the TNM staging system according to the criteria established by the American Joint Committee for Cancer Staging. Operative mortality was defined as death within 30 days of operation or during same hospitalisation. The time of surgery was used as the starting date. Survival was defined as the interval between date of surgery and date of death or last follow-up. Patients who died in the perioperative period were not considered in the survival analysis. Survival for all patients was recorded upto Sep-30, 2010.

Observations:-

The study group consisted of 30 patients (27 men and 3 women). The median age was 56 (range, 35-80 years). There were 27 males and 3 female, male to female ratio was 9:1. Twenty eight patients were active smokers or had a history of smoking at the time of diagnosis; the remaining two patients were non-smokers. All the patients included in our study were symptomatic. Cough was the most common presenting symptom (30%), followed by dyspnea (20%), chest pain (20%) and weight loss (10%). All patients were classified using the TNM staging system according to the criteria established by the American Joint Committee for Cancer Staging. Most of the patients had stage I disease ; 18 patients(60%), IA(n=9), IB(n=9), stage II; 6 patients(20%), IIA(n=3), IIB(n=3), stage III; 6 patients(20%), IIIA(n=6). Lobectomy was carried out in 21 patients (70%), patients. Bilobectomy in 3 patients (10%), and pneumonectomy in 6 patients (20%). The pathologic subtype was pure small cell lung carcinoma in 21(70%) of patients, small and large cell neuroendocrine carcinoma (LCNEC) in 3 (10%) of patients and small cell in combination with other tumor type in the remaining 6(20%) cases. Post surgical pathological staging was done using the TNM staging system according to the criteria established by the American Joint Committee for Cancer Staging. Most of the patients were in stage I (40%), stage II (40%), and in stage III (20%) patients. A total of 6 patients (20%) had complications, which included supraventricular arrhythmia in 3 patients, pneumonia, prolonged air leak and wound infection in 1 each. There was only one postoperative death that of a patient with a pulmonary embolism at post operative day 13, giving a 30-day surgical mortality of 3.3%. Postoperative therapy included chemotherapy in 8 patients, radiotherapy in 6, chemo-radiotherapy in 10, PCI in 7 patients and 6 patients received no adjuvant therapy including one patient who died in immediate post-op period. The follow up ranged from 6 weeks to 68 weeks, mean follow up was 36.52 months (SD 25.69). One year survival was better for female patients, it was 59.3% and 100% for males and females respectively (p= .165).Five year survival for females was better than that of males. For females it was 66.7% and 33.3% for males. Patients who underwent lobectomy had a 5 year survival of 42.9%, bilobectomy patients had a 5 year survival of 33.3% and in pneumonectomy patients 5 year survival was 16 7%. Patients who underwent lobectomy had a 5 year survival of 42.9%, bilobectomy patients had a 5 year survival of 33.3% and in pneumonectomy patients 5 year survival was 16 7%. Patients who received chemo-radiotherapy after surgery had a 5 year survival of 40%, patients receiving chemotherapy had a survival of 62.5%,

and in patients receiving no adjuvant therapy, none of the patient survived for more than 2 years. 5 year survival for post surgical stage I was 58.3%, stage II was 25.0% and for stage III 16.7%. A total of 6 patients had relapse, 3 patients had local relapse and 3 patients had a relapse at distant site.

Discussion:-

The most frequent localized relapse is at the site of the tumor. Even with the addition of thoracic radiation, relapse continues to occur at the primary site in up to one third of patients.⁷ This suggests that if survival is to improve, more aggressive local tumor control is necessary. This has led to renewed interest in the role of surgical resection of the primary tumor and regional lymph nodes.

In our study the incidence of lung cancer (SCLC) increased with increasing age. Majority of the patients (80%) were seen in the age group 46-75 years with maximum 40% patients in age group 56-65 years. The median age was 56 years (range, 35-80 years). These observations were in accordance with the literature available. Federico Rea et al⁸ reported the median age of 57 years (range, 30-75 years) in their series.

In our patients overwhelming majority (90%) were males as compared to only 10% females. The present study has revealed that mainly the males were affected with a male to female ratio of 9/1 which was higher than the previous studies in western countries, but was consistent with that of the developing countries, that either lack regulations or are far less strict in regulating nicotine and tar content of cigarettes and also in which the average tar yield is higher than western countries³. This observation was contrary to most of the western literature where the incidence of SCLC among females is also on the rise due to increase in smoking⁴⁻⁶. Similar observations were made by HasanTatlisozet al⁹ the study group consisted of 141 male and 14 female patients, with a male to female ratio of 10:1.

In our study histopathologic profile of patients revealed 70% of patients with histopathology of pure small cell carcinoma, 10% small cell carcinoma and large cell neuroendocrine carcinoma (LCNEC), small cell and other combinations in 20%. These findings were consistent with other studies. Lim E et al¹⁰ reported that pure small cell carcinoma was present in 73% of patients whilst combined small cell carcinoma was present in 27% patients.

All operations were elective. Most of patients underwent lobectomy (n=21, 70%), because that was the preferred operation if the lesion was completely resectable, the general medical condition of the patient was acceptable, and respiratory mechanics and gas exchange were satisfactory. In 3 patients (10%) a bilobectomy was performed and in 6 patients (20%) a pneumonectomy was necessary due to centrally located tumors or tumors crossing the interlobar fissure affecting more than one lobe. These observations were consistent with literature. Shepherd et al¹¹ reported 15 patients (19.4%) had a pneumonectomy, 46 had a lobectomy (60%), and 2 had wedge resections. Post surgical stage was IA (n=6), IB (n=6), IIA (n=3), IIB (n=9), IIIA (n=6).

In our study R0 resection was achieved in 28 patients (93.3%) and R1 resection was achieved 2 patients (6.7%). Similar observations were reported by A. Granetznyet al¹², with R0 resection in 90 patients (94.7%) and R1 resection in 5 patients (5.3%).

There was one postoperative death, that of a patient with a pulmonary embolus at 13 postoperative day, giving a 30-day surgical mortality of 3.3%. These findings were in accordance with other studies. Vidhan Chandra et al¹³ reported a operative mortality of 3% (2/77) in their study.

Postoperative complications occurred in 20% of the patients (6/30). There were 6 nonfatal complications, all involving the cardiorespiratory system, including 3 cases of supraventricular arrhythmia, 1 case of pneumonia, 1 case of prolonged air leakage and 1 case of wound site infection. These observations were consistent with other studies. A. Granetzny et al¹² reported a postoperative complication rate of 17% (16/95) which comprised of 6 cases of atrial fibrillation, 5 cases of atelectasis, 3 cases of pneumonia and 2 cases of wound infection.

Table 1:-showing postoperative complications

Complications	Frequency	Percent
Arrhythmia	3	10.0
Pneumonia	1	3.3

Prolonged air leak	1	3.3
Wound infection	1	3.3
None	24	80.0
Total	30	100.0

Adjuvant treatment was recorded as radiotherapy, chemotherapy, or both as appropriate. Although all patients were referred for consideration of adjuvant therapy 5 patients did not receive any additional postoperative treatment. Of the 5 patients who underwent surgery alone, 3 refused any adjuvant therapy and 2 died before completion of chemotherapy recommended by the medical oncologist. 8 patients received chemotherapy, 6 patients received radiotherapy, 10 patients received combined chemo-radiotherapy, and 7 patients received prophylactic cranial irradiation (PCI), including 2 patients with stage-I disease.

The results of our study show an overall 20.7% of relapse with only a 10.4% of relapse at the primary site alone, the remaining 10.3% of patients had a relapse at distant site alone. Federico Rea et al⁸ reported an overall relapse rate of 49%, with a 15.4% of relapse at primary site alone. The results are similar to other studies which included surgery in multimodality therapy for SCLC.

There was only one postoperative death, with a 30-day surgical mortality of 3.3%. The mean follow-up period of the entire study population was 36.5 months. For the 30 patients, the overall 1-, and 5-year survival rate was 63.3% and 36.7% respectively, with an estimate median survival time of 24 months. Patients were followed up for 1-70 months postoperatively, with a mean follow-up of 36.5 months.

The 5-year survival rate according to the pre-operative clinical stage was 44.4% for patients with stage I, 33.3% for patients with stage II, and 16.7% for patients with stage III (p=0.252). The 5-year survival rate according to the pathologic stage was 58.3% for patients with stage I, 25% for patients with stage II and 16.7% for patients with stage III.

Regarding the impact of TNM staging on predicting the outcome in SCLC, we did not find any correlation between clinical stage and long term survival, we have to remark that 20% of patients clinically classified as stage I were understaged. On the other hand, when we consider pathologic stage, better results are obtained in stage I SCLC (T1-2 N0) who underwent complete surgical resection (58.3%, 5-year survival) compared with stage II (25% survival) and stage III (16.7%, 5-year survival); but this did not achieve any statistical significance due to small sample size (p= 0.125). Similar observations were made by Federico Rea et al⁸, who reported a 5-year survival of 52.2% in patients with stage I disease, 30% in patients with stage II, and 15.3% in patients with stage III disease.

Table 2:-Five year survival with respect to pathologic stage

Stage	AT 5 YEARS			P value
	ALIVE	DEAD	Total	
I	7	5	12	0.125
	58.3%	41.7%	100.0%	
II	3	9	12	
	25.0%	75.0%	100.0%	
III	1	5	6	
	16.7%	83.3%	100.0%	
Total	11	9	30	
	36.7%	63.3%	100.0%	

Another subgroup with good long-term survival was a group of 8 patients who received postoperative adjuvant chemotherapy, with overall 1-, and 5-year survivals of 82% and 62.2% respectively. Considering the subgroup of 5 patients who received no adjuvant therapy (surgery only), all died within two years of surgery. These results achieved statistical significance (p=0.001).

Table 3:-Five year survival with respect to Adjuvant therapy

Adjuvant Therapy	AT 5 YEARS			P value
	ALIVE	DEAD	Total	

Chemo-radiotherapy	4	6	10	0.001
	40.0%	60.0%	100.0%	
Chemotherapy	5	3	8	
	62.5%	37.5%	100.0%	
Radiotherapy	0	6	6	
	.0%	100.0%	100.0%	
NONE	0	6	6	
	.0%	100.0%	100.0%	
Total	11	19	0	
	36.7%	63.3%	100.0%	

Survival was also dependent on sex. Compared with male patients (n=27), female patients (n=3) had a survival advantage. The 1-, and 5-year survivals for male and female patients were 59.3% and 33.3%, versus 100%, and 66.7% respectively (p=0.256). Similar observations were made by Brock et al¹⁴. The 1-, 3-, and 5-year survivals for male and female patients were 73%, 35%, and 28%, versus 86%, 63%, and 60%, respectively.

Conclusion:-

As long as a complete surgical resection can be performed, surgery must be considered as the first step of the multi-modality treatment in these patients. Pulmonary resection in patients with stage I or stage II SCLC is safe with low mortality and morbidity. It is justified to offer primary surgery followed by chemoradiotherapy in stage T1, N0 and possibly in stage T2, N0. Prophylactic cranial irradiation should be part of the treatment program only for those patients obtaining a complete remission. Curative resection is associated with long-term survival in early stage SCLC and should be considered in selected patients.

Compliance with ethical standards:-

1. The authors declare that there is no conflict of interest.
2. A written informed consent was taken from every patient included in study.
3. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
4. The authors declare that they received no grant for the study.

Bibliography:-

1. Parvaiz A. Koul, Satish Kumar Koul, Mohammed Mushtaq Sheikh, Reyaz A. Tasleem and Azra Shah; Lung Cancer in the Kashmir valley : Lung India, vol 27, issue 3, jul-sep 2010
2. Navada S, Lai P, Schwartz AG, Kalemkerian GP. Temporal trends in small cell lung cancer: analysis of the national Surveillance, Epidemiology, and End-Results (SEER) database [abstract 7082]. *J ClinOncol.* 2006;24(18S)(suppl):384S.
3. Govindan R, Page N, Morgensztern D, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. *J ClinOncol.* 2006;24(28):4539-4544.
4. Thompson S, Pearson MG. Changing patterns of lung cancer histology with age and gender. *Thorax.* 1998;53(suppl 4):A10.
5. Kmietowicz Z. Women at double risk of small cell lung cancer. *BMJ.* 1998;317(12):1614.
6. Cartman ML, Muers MF. Rising incidence of SCLC in young women [letter]. *Thorax* 1999;54(7):656.
7. Perez CA, Einhorn L, Oldham RK, et al. Randomized trial of radiotherapy to the thorax in limited small-cell carcinoma of the lung treated with multiagent chemotherapy and elective brain irradiation: a preliminary report. *J ClinOncol.* 1984; 2:1200-1208.
8. Federico Rea, Donatella Callegaroa, Adolfo Favarettob, Monica Loya, Adriano Paccagnellab, Umberto Fantonic, Giuliana Festic, Francesco Sartoria ; Long term results of surgery and chemotherapy in small cell lung cancer: *European Journal of Cardio-thoracic Surgery* 14 (1998) 398–402.
9. Hasan Tatlısöz, MD; M. Levent Erkan, MD; Serhat Fındık, MD; Bedri Kandemir, MD: Clinical Features and Outcomes of Small-Cell Lung Cancer Cases from Northern Turkey; *Turkish Respiratory Journal*, 2000; 2:25-29.

10. Eric Lim, FRCS (C-Th), Elizabeth Belcher, FRCS, Yoon Khoong Yap, MRCS, Andrew G. Nicholson, FRCPATH, and Peter Goldstraw, FRCS ; The Role of Surgery in the Treatment of Limited Disease Small Cell Lung Cancer Time to Reevaluate : *J Thorac Oncol.* 2008; 3: 1267–1271
11. F A Shepherd, W K Evans, R Feld, V Young, G A Patterson, R Ginsberg and E Johansen : Adjuvant chemotherapy following surgical resection for small-cell carcinoma of the lung ; *Journal of clinical oncology*, Vol 6, 832-838 (1988).
12. Andreas Granetzny , Ahmad Boseila , , Wolfgang Wagner , Georg Krukemeyer , Ulf Vogt c, Erich Hecker , Olaf M. Koch , FolkerKlinke ; Surgery in the tri-modality treatment of small cell lung cancer.Stage-dependent survival : *European Journal of Cardio-thoracic Surgery* 30 (2006) 212—216
13. VIDHAN CHANDRA, MD; MARK S. ALLEN, MD; FRANCIS C. NICHOLS III, MD; CLAUDE DESCHAMPS, MD; STEPHEN D. CASSIVI, MD; AND PETER C. PAIROLERO, MD : The Role of Pulmonary Resection in Small Cell Lung Cancer ; *Mayo Clin Proc.* 2006; 81(5):619-624
14. Malcolm V. Brock, MD Craig M. Hooker, MPH James E. Syphard, BS William Westra, MD Li Xu, MS Anthony J. Alberg, PhD David Mason, MD Stephen B. Baylin, MD James G. Herman, MD Rex C. Yung, MD Julie Brahmer, MD Charles M. Rudin, MD, PhD David S. Ettinger, MD Stephen C. Yang, MD ; Surgical resection of limited disease small cell lung cancer in the new era of platinum Chemotherapy: Its time has come: *The Journal of Thoracic and Cardiovascular Surgery* , Volume 129 , jan-2005.