Considerations about Tumor Size as a factor of Prognosis in NSCLC

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Abstract

A literature review of the initial attempt to correlate tumor size in NSCLC with the expectancy of survival is presented starting from the 60s. The larger size was connected with an increased risk of metastatic diffusion. In the 70s resulted evident the relationship between tumor size and lymph node involvement so affecting survival. In the context of the TNM Staging System (Mountain 1986) size appeared a well assessed factor of prognosis and is recognised to play a major role in Stage I where the subsets T1N0 and T2N0 showed a consistent difference in survival across the 3 cm cut-off. The peculiar relation between largest size and mediastinal lymph node metastases is discussed as well as the proposal to allocate T2 descriptor within the range 3-5 cm. Finally, series of clinical observations from Japanese experience about small sized T1N0 tumors are presented and discussed.
Key words: Lung cancer, tumor size, staging, T factor, survival.

Riassunto

Viene presentata una revisione della letteratura a partire dagli anni 60, quando venne inizialmente correlato il diametro dei tumori polmonari non a piccole cellule con la prognosi del paziente. Le maggiori dimensioni delle lesioni sono risultate connesse ad un aumentato rischio di diffusione sistemica della malattia tumorale. Negli anni 70, numerosi studi clinici hanno consentito di accertare la stretta correlazione tra dimensione e coinvolgimento metastatico linfonodale con le conseguenti implicazioni sul piano della sopravvivenza a distanza. Nel contesto del Sistema di Stadiazione TNM del carcinoma del polmone proposto da Mountain nel 1986, il diametro della lesione è apparso fin da subito un sicuro fattore prognostico. Tale influenza appare tantopiù spiccata nello Stadio I di malattia, all'interno del quale, peraltro, i sottogruppi T1N0 e T2N0 mostrano una significativa differenza nella sopravvivenza nel passaggio del limite dimensionale di 3 cm. Viene inoltre discussa la particolare relazione esistente tra dimensioni e coinvolgimento linfonodale che tende a decrescere con l'aumento estremo dei diametri tumorali, così come la recente proposta di limitare la definizione di T2 al range dimensionale compreso tra 3 e 5 cm. Infine sono presentati e discussi una serie di rilievi clinici tratti da recenti esperienze di gruppi di studio giapponesi in selezionati pazienti affetti da tumori T1N0 di dimensioni molto piccole.
Parole chiave: Carcinoma del polmone, dimensione del tumore, staging, sopravvivenza.

All of us are aware that the tumoral size has represented, from the beginning, one of the most quoted features to which all concerned people were referring when called to present the tumor. It is even easy to explain it, since the formal language of pathologists in the past, considered the size as a fundamental feature of any tumor mass.
On the other hand, tumor size represented the most important variable of the radiological image since it was first offered by the pioneer radiology to the attention of clinicians.
Presently, the variation of tumoral image in terms of measurable sizes, is used to objectively evaluate the effect upon the tumor mass of some combined treatment protocols[1, 2, 3].
Surgeons were involved with the initial attempt to correlate tumor size with the expectancy of survival, speculating upon the intuitive evidence that the bigger the size the shorter was the life span, even after an apparently complete resection of the tumor.
The most important scientific contributions on this matter belong by now to the past (back in the 60s-70s) when a large amount of papers considering the size as an autonomous factor of prognosis, were offered.
In Steele's study[4] of 887 resected solitary pulmonary nodules, the rate of 30-month survival in patients with primary carcinoma was approximately 61% for nodules measuring 2 cm, 55% for nodules measuring more than 2 up to 3 cm, and about 40% for those measuring 3.5 to 6 cm. However, if the cancer measured 5 to 7 cm, the rate of 5yr survival was 27%, while there were no survivors with nodules of over 7 cm. The prognosis for the larger-sized cancers, 5 to 7 cm and over, thus appeared to be very poor.
Wellons in 1968[5] supported the idea that a definite

relationship had to exist between tumor size and survival of lung cancer patients, with a poor prognosis in cancers of more than 5 cm in diameter.

Jackman in 1969[6] reported an overall 5yr survival of 51% in a group of 169 patients affected by lung cancer, exclusively presenting as solitary nodules up to a maximum diameter of 4 cm, and then completely resected. When the survival was specifically correlated to the size of nodules, it appeared largely changing, with rates of 68.2% 5yr for the smaller ones (< 2 cm), while for the nodules measuring 2.1 to 3.0 cm it was of 46,5% and, respectively, of 41% for the larger ones with a maximum diameter ranging from 3.1 to 4.0 cm.

In Yasar's study of 1975[7], survival appears to be closely related to the size of the tumor. In 18 patients with a tumor less than 2 cm, 61% were alive and well 5 years after surgery, while for the 62 patients with tumors less than 4.5 cm, the 5yr survival (43%) was significantly better than that of the 56 patients with larger lesions who showed a 23% 5yr survival only. No long-term survivors were registered among the group of 9 patients with tumors larger than 7 cm.

Soorae in 1977[8] upon a group of 295 operated patients, found that 95.5% of those affected by larger tumors with a mean diameter of 8.2 cm (range of 7-21), systematically died within 30 months from the operation. 2yr overall survival was of 60% in tumors < 3cm, while it was of only 4.5% in tumors of > 7 cm.

In addition, the author affirmed that the prognosis in large carcinomas could not be directly attributed to a preponderance of either an unfavourable cell type or lymph node metastasis or mediastinal extension. Vascular dissemination at the time of operation, instead, was believed to be a major factor for the poor prognosis in this group of carcinomas. Accordingly, he concludes that the early ligation of pulmonary vein, as a prophylactic manoeuvre against the tumor emboli release into the vascular bed, might improve the surgical results, by improving the overall survival.

Years after, Abbey Smith[9] resumed the same concept affirming that large tumors fare badly in the long term, while the reasons for such a poor prognosis still remain speculative: handling and squeezing at operation are to be considered possible unfavourable causes since they promote tumor emboli.

According to these data, one can objectively acknowledge that, at that time, surgeons in general agreed with the idea that the larger tumoral size was closely connected with an increased risk of (systemic) metastatic diffusion already while operating, and this was, ultimately, responsible to directly affect the prognosis.

Around the same period of time, crucial, indeed, for the steady progress of the knowledge in the field of lung cancer, another factor of prognosis was identified and then progressively taken to its actual clinical role. It is that of hilar and mediastinal lymph nodes metastasis by the primary tumor.

Based initially upon the anatomical background given by Rouvière[10] and Nohl[11], surgeons tried to extend the radicality of pulmonary resection there including the satellite lymph nodes, already aware of the negative prognostic role played by the regional lymphatic spread. It has clearly emerged from the contribution of many surgical sources since the masterful presentations of Cahan in 1951 and 1960 on the radical Pneumonectomy and radical Lobectomy[12, 13].

In this ground resulted soon evident the close relationship existing between tumor size and lymph nodes involvement, the latter representing, ultimately, the main cause in affecting survival.

Soorae in 1977 (8) was (the first who tried to correlate size and the hilar lymph nodes involvement, reporting a rate of 41% positive nodes in tumors of < 3 cm while it increased to 56% for tumors of > 5 to < 7 cm in maximum diameter. In spite of this, the Author didn't attribute a direct influence of the lymphatic spread upon survival.

In 1984, Ogata and Naruke[14] presenting their 20yr experience with the radical lymph node dissection, offered the first whole rationale picture of the lymph nodes involvement strictly related to the tumor size, starting from the smallest figure of 0-2 cm till the maximum diameter of 5.1 cm. N2 was present in 24.6% of the smallest tumors group (0-2 cm) while it increased to 27.9% among, those of 2.1-3 cm, and to 44.7% among those of 3.1-5 cm. Surprisingly this involvement resulted a bit less (43.8%) for these tumors of more than 5 cm in their maximum diameters.

Meanwhile, these were also the times for the new TNM classification of lung cancer to mature and then to be offered to the attention of specialists. This new rationale, based upon the recognition of TNM factors (tumor – nodes – metastases)[15] with the following categorisation in Stages of disease, was expanded at an international level through the concerned activity of some national Committees properly established and actively co-operating[16, 17, 18, 19]. With the publication of the New Intl. Staging System for Lung Cancer by Clifton F. Mountain in 1986[20], it became the world cultural event well known to all of us.

In the context of TNM criteria, tumor size appears as a well assessed factor of prognosis as far as the smaller figures are concerned (Stage I), with a sharp 3 cm cut off separating T1 from T2 tumors and the best expectation of survival recognised to the subset T1N0M0 Stage I A, according to the last revision of 1997[21], since it includes only tumors smaller than 3 cm and without evidence of N and M involvement. Differently, in the next subset T2N0M0, the size begins to be less specifically defined as "more than 3 cm" and it follows to be lesser considered from the side of prognostic value, even for the bigger sizes. Other representative features of T2 status than the size, such as the position of tumor, the pleural infiltration and the obstructive effect upon the pulmonary airways, are

recognised, instead, as the only T2 components prognostically determinant.

Further on, T3 and T4 descriptors include tumors of "any size", so automatically limiting the role of their size compared to the other representative features of the advanced, locally invasive T status.

These latter features, together with N and M status, are, again, the prevailing factors who actually give the shape to the higher Stage III A-B and Stage IV.

That is in line with the postulate that the prognostic power of each T, N and M factor should exert a sort of mutual selective pressure, going up the scale of tumor progression. Consequently, the concise organisation of the disease in Stages which firstly appeared with the New Staging System in 1986[20], can sequentially single out only that factor(s) which actually prevails in directly affecting survival, within its own assigned Stage of tumor progression. Indeed, Stage grouping definitively ratifies this situation, considering, for instance, at the bottom of the statistical scale the subset T3N0M0 – Stage IIB, while, in the more higher Stages, are still included the subsets T1N2M0 – Stage IIIA, T1N3M0 – Stage IIIB, and any T status in Stage IV. As a matter of fact, bigger sizes, usually present, but not necessarily always, in higher Stages, remain constantly excluded from the recognition of exerting a direct influence upon the prognosis.

To sum up, tumor size is recognised to play a major role in shaping Stage I where the subsets T1N0 and T2N0 appear well differentiated by a consistent difference in survival across the 3 cm cut off. According to the recent review of Nesbitt and Mountain (1995)[22] patients with T1 tumors have an overall 5yr survival advantage of 15% to 20% on those affected by T2 tumors.

As to the larger sizes, only few considerations can be presently added, even though the matter clearly appears widely debatable.

The first issue can be represented by the peculiar relationship, which seems to exist between the largest tumoral bodies and the declining rate of mediastinal lymph nodes involvement.

This fact already beckoned through the Soorae data and again reported by Ogata and Naruke since 1986, appears to be definitively confirmed by the last statistical analysis recently offered by Watanabe[23], with a 33.6% N2 in tumor ranging from 51 to 70 mm, and a contrasting lower figure of 27.3% N2 in the larger ones, ranging from 71 to 100 mm in their maximum diameter. Moreover when analysed altogether, these three different studies show a surprising homogeneously falling trend of the N2 rates in connection with the higher figures of sizes, respectively of > 7 cm for Sooare, > 5 cm for Ogata and between 71 and 100 mm for Watanabe.

In this case, one cannot help thinking of the old conclusions of Soorae, supporting the major role of an enhanced autonomous spreading by the bulky tumors, which seem to prefer different routes to the more anatomical lymphatic ones!

Finally, of true interest appears the initial proposal of Watanabe to formally allocate the T2 descriptor within the range of 3-5 cm, so leaving back the vague definition of "> 3 cm" assigned by the Staging System[24]. Moreover, according to the same Author, an additional group of peripheral tumors bigger than 5 cm but still N0M0 and strictly featured by the size, could be considered as still T2 Stage II because of their 5yr survival rate of 46.3% is comparable to that of the formal Stage II (47.1%). This latter data has recently received further support by the ongoing database of GCCB-SEPAR (Co-operative Spanish Group), with a 3yr survival rate of 56% for tumors pT2 of > 5.4 cm[25].

Watanabe's proposal represents, in our opinion, a worthy attempt to reduce, at least, the whole amount of bigger tumors which are still scantily recognised, due to the lack of consideration of their size by the rationale for Staging.

In conclusion, we are forced to realise that, at the present time, less importance is still attributed to the size than to the other features of T status, mainly when it is going up the Stage.

On the other end of the size scale, a series of interesting clinical observation with a group of carefully assessed small-sized T1N0 tumors, have been more recently added mainly through the valued support given by the Japanese research.

This cultural insight has also helped to clarify a problem to which the western surgical world has only lately been able to come closer, by softening the discrepancies existing among the methods of intraoperatively staging tumors.

In other words, the approach to the mediastinal lymphadenectomy was different, being basically conceived as lymph nodes sampling by the West, while systematically pursued as a radical mediastinal dissection by the Japanese.

As a consequence, the correct identification of N factor as well as the following staging assignment operated by the former, has often been critical. The high rate of migration from clinical to pathological Stage, as recently reported by Mountain[21], with a 25% rate between c and pT1N0M0, 54% between c and pT2NOMO and 61% between c and pT1N1M0, seems to greatly support this conclusion.

Moreover it is not by chance if the diagnostic recognition is more lacking in Stages I and IIA where the traditional belief of the less aggressiveness of smaller tumors in general and the reduced risk of lymph nodes involvement in particular, has let the majority of western surgeons prefer the lighter but less accurate lymph nodes sampling procedure.

Applying the aggressive mediastinal approach in a series of 337 small peripheral tumors of 3 cm or less in diameter, Asamura and Naruke have reported, in 1996[26], a rate of 8% N1 and 11.5% N2 in tumors of < 2.0 cm. with a whole 19.5% lymph nodes involvement, while there was a rate of 11% N1 and 21.5% N2 in tumors ranging from 2 to 3 cm with a whole lymph nodes involvement of 32.5%. The 5yr survival of completely resected N2 cases

in such category of small tumors, was of 44.5% with a recurrence rate of 27.7% (67.8% distant). Watanabe (1996)[27], found a 15% rate of N2 in tumors of 11-20 mm, a 24% rate in tumor of 21-30 mm, while it was of more than 30% in tumors > 30 mm. The 5yr-survival rate in operated patients with latent N2 (preoperatively N0-1) was of 33%.

In a comparable series of small cancers (3 cm or less in diameter) including one Tis, Tateishi et A1 (1995)[28], reported a rate of 10% N1 and 19% N2. According to T status the 5yr survival was of 100% in the single Tis, while 86% in T1 and 64% in T2 tumors. Finally it was of 30% in N2 resected patients.

The mention of Tis tumor, leads us to introduce the last advanced surgical application in the area of Stage I early tumors, namely the resection of smaller sized, "Roentgenografically occult" tumors, earlier detected by mass screening examination.

Again, in this specific field the Japanese research, besides the heavy involvement of carrying out a series of reliable screening plans, also assured a detailed pathologic evaluation in all the minute and differently shaped tumors, together with the accurate search for any lymphatic spread.

In a group of 27 patients with an early hilar lung cancer, 19 of whom symptomatic and 9 occult detected by mass screening examination of sputum cytology, Watanabe in 1991[29], found 9 Tis and 19 invasive carcinomas but still confined within the bronchial wall. In such a highly selected group of resected patients, 5 and 10yr survival was respectively of 100% and 91,7%.

In this category of minute tumors, indeed, *the concept of size is a bit varied* since, firstly, a cut off of 2 or even 1 cm is considered there; secondly, the length of longitudinal extension of tumor along the bronchial wall becomes the measure of the size, and, finally, the evidence that a carcinoma confined to the epithelium cannot metastasise, appears to be demonstrated.

Usuda et A1 (1993)[30] report a group of 127 resected occult carcinomas, with 55 sized < 10 mm where no lymphatic spread could be identified, and 46 sized > 10 to < 20 mm where 4 nodal metastases were found (9%). In the remaining 26 cases within the range of > 20 to < 55 mm, only 4 showed a nodal spread (15%).

Saito et Al (1992)(31) reported, in a group of 94 patients affected by occult carcinoma, a rate of 17% extrabronchial invasion with 16 patients affected. In 5 of these 16 (31%), only one lymph nodal involvement was detected. The overall cause-specific 5yr survival rate was 93.5%, while no recurrences were registered among the completely resected 72 patients, who showed an intrabronchial limited disease and no lymphatic spread.

On the other hand, Koike (1999)[32] has demonstrated a real improvement not only of the overall survival with the improvement of the mass screening programmes, but also an increase of the rate of early detected Stage I cases as well as of their specific 5yr survival rate. In this last group, the survival was of 79.2% and 70.4%, according to the size categories of 10 to 20 mm, and, respectively, of 21 to 30 mm as a maximum diameter[33].

In conclusion, the smaller size ranging from 10 to 20 mm, with a consequent high probability for the tumor to remain limited within the borders of bronchial wall layers, would appear to play a true role as positive factor of prognosis even regarding to the risk of nodal spread.

As a consequence, any consistent clinical yield collected in the ground of these smaller sized category of earlier detected tumors, could represent a basic answer, indeed, to the long standing expectancy for a definite cure of lung cancer.

References

1) Herschorn S., Hanley J., Wolkove N., Cohen C., Frank H., Palayew M., Kreisman H.: *Measurability of Non-Small Cell Lung Cancer on Chest Radiographs.* J Clin Oncol, 1986, 4:1184-1190.

2) Sandler H.M., Curran W.J. Jr., Turrisi A.T.: *The Influence of tumor Size and Pretreatment Staging on Outcome Following Radiation Therapy alone for Stage I Non-Small Cell Lung Cancer.* Int J Radiation Oncology Biol Phys, 1990, 19:9-13.

3) Dosoretz E., Galmarini D., Rubenstein H., Katin M.J., Blitzer P.H., Salenius S.A., Dosani R.A., Rashid M., Mestas G., Hannan S.E., Chadha T.T., Bhat S.B., Siegel A.D., Chandrahasa T., Metke M.P.: *Local Control in Medically Inoperable Lung Cancer: an Analysis of its Importance in Outcome and Factors Determining the Probability of Tumor Eradication.* Int J Radiation Oncology Biol Phys, 1993, 27:507:516.

4) Steele J.D.: *The Solitary Pulmonary Nodule.* Springfield, III, 1964, Charles C Thomas, Publisher.

5) Wellons H.A., Johnson G. Jr., Benson W.R., Pate D., Wilcox B.R., Peter R.M.: *Prognostic Factors in Malignant Tumors of the Lung.* Ann Thor Surg, 1968, 5:228-235.

6) Jackman R.J., Good C.A., Clagett O.T., Woolner L.B.: *Survival Rates in Peripheral Bronchogenic Carcinomas up to Four Centimetres in Diameter Presenting as Solitary Pulmonary Nodules.* J Thorac Cardiovasc Surg, 1969, Vol. 57, 1:1-8.

7) Yashar J., Yashar J.J.: *Factors Affecting Long-Term Survival of Patients with Bronchogenic Carcinoma.* Am J Surg, 1975, 129:386-393.

8) Soorae A.S., Abbey Smith R.: *Tumour Size as a Prognostic Factor After resection of Lung Carcinoma.* Thorax, 1977, 32:19-25.

9) Abbey Smith R.: *Evaluation of the Long-Term Results of Surgery for Bronchial Carcinoma.* J Thorac Cardiovasc Surg, 1981, 82(3):325-333.

10) Rouvière H.: *Anatomie des lymphatiques de l'homme.* Paris: Masson et Cie 1932; pp. 489.

11) Nohl H.C.: *An investigation into the lymphatic and Vascular Spread of Carcinoma of the Bronchus.* Thorax, 1956, 11:72.85.

12) Cahan W.G., Watson W.L., Pool J.L.: *Radical Pneumonectomy.* J Thorac Surg, 1951, 22:449-473.

13) Cahan W.G.: *Radical Lobectomy.* J Thor Cardiovasc Surg, 1960, 39(5):555-572.

14) Ogata T., Naruke T.: *Twenty year's Experience with Lymphnode Dissection in Patients with Lung Cancer. The Mode of Lymphnode Metastases and the effect of Dissection of Nodes on the Prognosis.* In *Cancer of the Lung and Pleura.* G. Motta Ed., Masson Italia Ed., Milano 1986; pp. 35-46.

15) Denoix P.F.: *Enquète permanent dans le centres anticancereux*. Bull Inst Natl Hyg, 1946, 1:70-75.

16) Harmer M.H. (ed): *TNM Classification of Malignant Tumors.* Geneve UICC, 1974.

17) Clinical Staging System for Carcinoma of the Lung. American Joint Committee for Cancer *Staging and End Results Reporting.* Chicago, IL, 1973.

18) Ishikawa S.: *Staging System on TNM Classification for Lung Cancer.* Jpn J Clin Oncol, 1973, 6:19-30.

19) Naruke T., Goya T., Tsuchiya R., Suemasu K.: *Prognosis and Survival in Resected Lung Carcinoma Based on New International Staging System.* J Thor Cardiovasc Surg, 1988, 96:440-7.

20) Mountain C.F.: *A new International Staging System for Lung Cancer.* Chest, 1986, 89:2255-335.

21) Mountain C.F.: *Revision in the International System for Staging Lung Cancer.* Chest, 1997, 111:1710-17.

22) Nesbitt J.C., Putnam J.B., Walsh G.L., Roth J.A., Mountain C.F.: *Survival in Early-Stage Non-Small Cell Lung Cancer.* Ann Thorac Surg 1995, 60:466-72.

23) Watanabe Y.: *Personal Communication*, 1999.

24) Watanabe Y., Shimizu J. et al.: *Proposal Regarding Some Deficiencies in the New International Staging System for Non-small Cell Lung Cancer.* Jpn J Clin Oncol, 1991, 21(3):160-168.

25) GCCB-SEPAR: *Personal Communication.* 1998.

26) Asamura H., Nakayama H., Kondo H., Tsuchiya R., Shimosato Y., Naruke T.: *Lymph Node Involvement, Recurrence and Prognosis in Resected Small Peripheral, Non-Small-Cell Lung Carcinomas: Are these Carcinomas Candidated for Video-Assisted Lobectomy?* J Thorac Cardiovasc Surg, 1996; 111:1125-34.

27) Watanabe Y.: *Results of Surgery for N2 Non-Small Cell Lung Cancer.* Ann Thorac Cardiovasc Surg, 1996, 2:85-86.

28) Tateishi M., Fukuyama Y., Hamatake M., Kondono S., Mitsudomi T., Ishida T., Susimachi K.: *Characteristics of Non-Small Cell Lung Cancer 3 cm or Less in Diameter.* J Surg Oncol, 1995, 59:251-54.

29) Watanabe Y., Shimizu J. et. al.: *Early Hilar Lung Cancer: Its Clinical Aspect.* J Surg Oncol, 1991, 48:75-80.

30) Usuda K., Saito Y. et al.: *Resected Roentgenographically Occult Bronchogenic Squamous Cell Carcinoma. Tumor Size, Survival and Recurrence.* J Thor Cardiovasc Surg, 1993, 106:1098-103.

31) Saito Y., Nakamoto N. et al.: *Results of Surgical Treatment for Roentgenographically Occult Bronchogenic Squamous Cell Carcinoma.* J Thor Cardiovasc Surg, 1992, 104:401-7.

32) Koike T., Teroshima M. et al.: *The influence of Lung Cancer Mass Screening on Surgical Results.* Lung Cancer, 1999, (in press).

33) Koike T., Terashima M. et al.: *Clinical Analysis of Small-Sized Peripheral Lung Cancer.* J Thor Cardiovasc Surg, 1998, 115:1015-1020.