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TEXTO 1

Cancer 79:1329-37, 1997

Altered Retinoblastoma Protein Expression in Nonsmall Cell Lung Cancer

Its Synergistic Effects with Altered *ras* and p53 Protein Status on Prognosis

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ABSTRACT

BACKGROUND. Inactivation of the retinoblastoma (Rb) gene has been documented in various types of cancer, including lung cancer. Alterations of the p53 and *ras* genes are also common features in the molecular biology of lung carcinoma, and the authors of this article have reported previously on the prognostic significance of both of them. In the present study, the authors evaluated the prognostic significance of the loss of Rb protein expression alone, then performed a combined analysis of Rb protein and *ras* p21 status (Rb/*ras*) as well as an analysis of Rb and p53 protein status (Rb/p53) in patients with nonsmall cell lung cancer (NSCLC).

METHODS. Ninety-one patients with NSCLC underwent potentially curative resection between 1977 and 1988, 65 of whom received postoperative combination chemotherapy. Tumor specimens were analyzed for Rb protein expression by immunohistochemistry. Univariate and multivariate analyses were performed to assess the association between Rb protein expression and survival.

RESULTS. Nineteen (21%) of the 91 NSCLCs showed negative Rb protein expression. Positive or negative Rb protein expression (Rb+ or Rb-) as an individual factor was not statistically correlated with survival or prognosis in this cohort of NSCLC patients, although a tendency among Rb- patients to do worse was observed. The authors then combined the Rb protein status with previously studied results of *ras* p21 and p53 protein expression in the same tumor specimens, and compared the prognosis between the individuals with theoretically the best pattern of gene expression in their tumors and those with theoretically the worst pattern of expression, i.e., Rb+/*ras*- versus Rb-/*ras*+ and Rb+/p53- versus Rb-/p53+. In patients with adenocarcinoma, those with Rb-/*ras*+ tumors survived for a significantly shorter period after surgery (13% 5-year survival) than those with Rb+/*ras*- tumors (82% 5-year survival) ($P = 0.01$). Similarly, patients with Rb-/p53+ tumors survived for a significantly shorter period (20% 5-year survival) compared with those who had Rb+/p53- tumors (73% 5-year survival) ($P = 0.008$). Rb/*ras* status was a significant prognostic factor ($P = 0.02$ by univariate analysis, $P = 0.048$ by multivariate analysis), and Rb/p53 status tended to be significant as a prognostic factor ($P = 0.04$ by univariate analysis, $P = 0.08$ by multivariate analysis). In patients with squamous cell carcinoma, neither Rb/*ras* nor Rb/p53 status was a significant prognostic factor in this cohort.

CONCLUSIONS. These results suggest that combined immunohistochemical analyses of Rb and *ras* p21 proteins and of Rb and p53 proteins may indicate their potentially synergistic effects on survival and prognosis. These analyses may also be useful for stratifying patients with adenocarcinoma of the lung into different prognostic groups and identifying populations with different risks of recurrence. Larger prospective studies with Stage I NSCLC patients are necessary to confirm the current findings.

KEYWORDS
retinoblastoma protein, *ras* p21 protein, p53 protein, nonsmall cell lung cancer, prognosis.

Lung cancer is one of the leading causes of cancer-related death throughout the world. Despite major advances in cancer treatment in the past two decades, the prognosis of patients with lung cancer has improved only minimally.[1] A new understanding of the molecular pathogenesis and multistep carcinogenesis of lung cancer has emerged from research advances in the field of molecular biology.[2] Increased knowledge of the biologic role of genetic changes and other aberrations in tumorigenesis provokes an intriguing search for clinical applications of these alterations.[3-5] It may be possible to predict the responses of individual patients with lung cancer to treatment and to identity patients with a good or poor prognosis using molecular biologic alterations as clinical biomarkers.[6-8]

Inactivation of the retinoblastoma (Rb) gene has been documented in various types of cancers, including lung cancer.[9-14] It has also been associated with aggressive tumor behavior and poor clinical outcome in specific types of cancer, including sarcomas as well as bladder and lung cancers.[15-18] Loss of Rb protein expression was shown to occur frequently in primary nonsmall cell lung cancer (NSCLC) by both Western blot and immunohistochemical analyses.[13] Alterations of the p53 gene have been shown to be among the most common molecular biologic changes in lung cancer.[19-21] Several studies have yielded conflicting results regarding the prognostic relevance of alterations in the p53 gene itself or in p53 protein expression.[22-27] Abnormalities in the *ras* family of oncogenes, including point mutations and overexpression, are also common features in the molecular biology of lung cancer.[28,29]

In previous studies,[26,29] we performed immunohistochemical analysis of *ras* p21 and p53 protein expression in the 96 NSCLC tumor specimens of all stages, including Stages IIIb and IV. In these studies, we found that patients with *ras* p21 positive (*ras*+) or p53 positive (p53+) tumors had significantly shorter survival than those with *ras* p21 negative (*ras*-) or p53 negative (p53-) tumors, respectively, that both *ras* p21 and p53 protein status were significant and independent prognostic factors for patients with surgically treated NSCLC, and that combined analysis of *ras* p21 and p53 protein expression could stratify these NSCLC patients into more accurate prognostic groups. In the present study, we extended the number of tumor specimens that were taken from patients who had undergone potentially curative surgery and had been analyzed for *ras* p21 and p53 protein expression to 91, and we included Rb protein expression as an additional potential prognostic factor. We combined the current results of Rb protein expression with those of *ras* p21 and p53 protein expression in the same tumor specimens, and we analyzed the survival and prognosis of NSCLC patients based on Rb, *ras* p21, and p53 protein expression.

In the present study, loss of Rb protein expression was not a statistically significant prognostic variable as an individual factor in the cohort examined. However, our data suggested that the combined analysis of Rb and *ras* p21 or of Rb and p53 protein status could potentially identify adenocarcinoma patients with significantly better or worse prognoses, although this association was not found for patients with squamous cell carcinoma of the lung.

MATERIALS AND METHODS

Tumor Specimens and Survival Data

Tumor specimens from 91 patients with NSCLC who had undergone potentially curative resection at the Hokkaido University Medical Hospital between 1977 and 1988 were analyzed. The patients consisted of 61 men and 30 women (average age at diagnosis, 61.8 years). The histologic classification of the tumor specimens was based on World Health Organization criteria,[30] and the specimens included 44 adenocarcinomas, 41 squamous cell carcinomas, four large cell carcinomas, and 2 adenosquamous cell carcinomas. They represented 49 Stage I, 10 Stage II, and 32 Stage IIIa tumors. The postsurgical pathologic TNM stage (pTNM) was determined according to the guidelines of the American Joint Committee on Cancer.[31] Survival was analyzed for the 89 patients who met the following criteria: (1) survived for more than 3 months after surgery; (2) did not die of causes other than lung cancer within 5 years after surgery; and (3) were followed for more than 3 years after surgery (for patients who remained alive). Two of 91 patients who did not meet the above criteria (because they died within 3 months after surgery) were excluded from the survival analysis. Because all the patients enrolled in the current study were coded, they could not be individually identified. Sixty-five patients received combination chemotherapy as postsurgical treatment. These chemotherapy-treated patients had 34 of the 44 adenocarcinomas, 28 of the 41 squamous cell carcinomas, and 3 of the 6 adenosquamous and large cell carcinomas. Among these 65 were also 41 of the 59 Stage I and II patients and 24 of the 32 Stage III patients. Radiation therapy was not performed before or after surgery for any patients. We had previously reported on 63 of the 91 patients for the prognostic significance of *ras* p21 and p53 protein expression in NSCLC.[26,29]

Immunohistochemical Analysis

The methods for staining of Rb nuclear protein in paraffin embedded sections have been described previously.[13,17] Briefly, the highly specific affinity-purified polyclonal anti-Rb antibody, Rb-WL-1,[32,33] was used. It recognizes both the phosphorylated and unphosphorylated Rb protein and can be completely blocked in the presence of an excess of the immunizing Rb peptide.[32] Four investigators (H.D.A., I.K., H.-J.X., and W.F.B.) separately evaluated the Rb nuclear protein staining pattern. At the time of review, none of these investigators were aware of the clinical outcome of the patients, since all the slides had been coded and the clinical outcome was disclosed only after all four investigators were in agreement on the Rb protein status for a given specimen. In all cases, adequate nuclear staining

was obtained in the adjacent normal lung tissues, which represented an internal positive control for the Rb protein staining of each section. A tumor was considered to be Rb positive (Rb+) if the Rb protein staining was heterogeneous, with a portion of the tumor cells showing typical Rb nuclear protein staining. Tumors were scored as Rb negative (Rb-) only if all malignant cells showed no Rb nuclear protein staining and normal stromal cells were Rb+ as an internal control. Two tumors had large areas of malignant cells with no Rb nuclear protein staining that were surrounded by Rb+ stroma cells, whereas in other small tumor areas the Rb staining was heterogeneously positive. These two tumors were considered to have altered Rb protein expression and were included as Rb- tumors.

For the *ras* p21 and p53 protein staining of 63 of 91 tumor specimens, the slides and results that had been previously reported[26,29] were used for the current study. The remaining 28 tumor specimens were newly analyzed for p53 and *ras* p21 protein expression by immunohistochemical staining; paraffin embedded sections were used, as previously described.[26,29] Both *ras* p21 and p53 protein staining were scored as positive (+) and negative (-) for the current study, as in one of the previous studies.[26] Therefore, the positive staining of *ras* p21 protein in the current study included moderate and strong staining in our first *ras* p21 report.[29] Typical staining patterns for Rb, p53, and *ras* p21 proteins are shown in Figure 1.

Statistical Analysis

The correlation of various characteristics of patients and tumors with Rb protein expression was analyzed by the chi square test. Survival curves were estimated using the Kaplan-Meier method,[34] and differences in survival distributions were evaluated by the generalized Wilcoxon test.[35] For simultaneous adjustment of the effects of other variables on the association between Rb, Rb/*ras,* and Rb/p53 protein status and survival outcome, the Cox proportional hazards general linear model was used.[36] All *P* values reported are two-sided. These computations were performed with the SAS program package (SAS Institute, Cary, NC)[36] at the Hokkaido University Computer Center.

RESULTS

Immunohistochemical Detection of Rb Protein in NSCLC

Nineteen (21%) of the 91 NSCLCs analyzed showed negative Rb protein expression (Fig. 1). Rb protein status was analyzed in relation to various clinical and clinicopathologic characteristics (Table 1). No characteristics except gender ($P = 0.04$) correlated with Rb protein status. In patients with squamous cell carcinoma, no correlation was observed between Rb protein status and the various characteristics examined (data not shown). However, when patients with adenocarcinoma were analyzed, loss of Rb protein expression correlated with lymph node metastasis, or pN status ($P = 0.02$ for pN0 vs. pN1-2) (Table 1).

Prognostic Significance of Rb Protein Expression in NSCLC

The relationship between Rb protein expression and postsurgical survival was analyzed for 89 patients. When all of the NSCLC patients were evaluated together, patients with Rb+ and Rb- tumors did not show a significant difference in survival (5-year survival rates, 50% and 34%, respectively; $P = 1.0$) (Fig. 2A). When only patients with squamous cell carcinoma were analyzed, Rb protein status still did not show a significant effect on survival (5-year survival rates, 47% for Rb+ patients and 69% for Rb- patients, respectively; $P = 0.2$). Among adenocarcinoma patients, those with Rb- tumors survived shorter periods than those with Rb+ tumors, although this difference in survival did not reach statistical significance (5-year survival rates, 23% and 59%, respectively; $P = 0.07$) (Fig. 2B). Univariate analysis of various potential prognostic factors (Table 2) indicated that Rb protein expression was not a significant prognostic factor for NSCLC patients overall ($P = 0.8$) or for adenocarcinoma ($P = 0.07$) or squamous cell carcinoma patients ($P = 0.2$) individually.

Combined Analysis of Rb and *ras* p21 and of Rb and p53 Protein Expression in NSCLC

The significance of *ras* p21 and p53 protein status as potential prognostic markers was analyzed to confirm our previous studies of patients with all stages of NSCLC, which included, unlike our current cohort, Stages IIIb and IV.[26,29] Both *ras* p21 and p53 protein status were significant prognostic factors ($P < 0.01$ and $P = 0.04$, respectively, by univariate analysis) for the cohort overall (Table 2). Multivariate analysis was performed to adjust for differences and influences of the other prognostic factors, pStage and chemotherapy, on the results. Again, both *ras* p21 and p53 protein status were independent prognostic factors for these patients overall ($P < 0.01$ and $P = 0.045$, respectively; Models 1 and 2, Table 3), confirming results from previous studies.[26,29] When examined by histologic type for squamous cell carcinoma, *ras* p21 protein status was a significant prognostic factor by both univariate and multivariate analyses ($P < 0.01$), although p53 protein status was not a significant prognostic factor ($P = 0.2$ by univariate analysis). In contrast, when patients with adenocarcinoma were studied, neither *ras* p21 nor p53 protein status was a significant predictor for prognosis ($P = 0.1$ and $P = 0.2$, respectively, by univariate analysis) or for survival ($P = 0.1$ and $P = 0.09$, respectively, by the generalized Wilcoxon test) (Figs. 3A and 4A).

The results of Rb protein expression was then combined with *ras* p21 or p53 protein status, and the combinations were analyzed as prognostic markers in patients with theoretically the best or worst pattern of expression, i.e., Rb+/*ras*- versus Rb-/*ras*+ or Rb+/p53- versus Rb-/p53+, respectively. For the overall cohort, patients with Rb-/*ras*+ tumors had a significantly lower 5-year survival rate than those with Rb+/*ras*- tumors (21% and 75%, respectively, $P = 0.03$, data not shown). Patients with Rb-/p53+ tumors also showed a lower 5-year survival rate than those with Rb+/p53- tumors (28% and 63%, respectively), although this did not reach statistical significance ($P = 0.1$, data not shown). However, when only patients with adenocarcinoma were analyzed, individuals with Rb-/*ras*+ or Rb-/p53+ tumors had significantly lower 5-year survival rates than those with Rb+/*ras*- or Rb+/p53- tumors, respectively (13% and 82%, $P = 0.01$ for Rb/*ras,* Fig. 3B; 20% and 73%, $P = 0.008$ for Rb/p53, Fig. 4B). In contrast, there were no statistical differences in 5-year survival rates for patients with squamous cell carcinoma using the same comparisons (50% and 75%, $P = 0.5$ for Rb/*ras;* 38% and 56%, $P = 0.8$ for Rb/p53), although the same trends were observed.

Finally, univariate and multivariate analyses using the Cox proportional hazards general linear model were performed to assess the prognostic significance of Rb/*ras* (Rb+/*ras*- vs. Rb-/*ras*+) and Rb/p53 (Rb+/p53- vs. Rb-/p53+) status before and after adjusting for differences in other variables (Tables 2 and 3). For the overall cohort, Rb/*ras* status tended to be a significant prognostic factor ($P = 0.03$ by univariate analysis; $P = 0.07$ by multivariate analysis in Model 3, Table 3), although Rb/p53 status did not reach statistical significance as a prognostic factor by univariate analysis ($P = 0.1$). When patients with adenocarcinoma were analyzed, Rb/*ras* status was a significant prognostic factor ($P = 0.02$ by univariate analysis; $P = 0.048$ by multivariate analysis in Model 1, Table 3), and Rb/p53 status tended to be significant as a prognostic factor ($P = 0.04$ by univariate analysis; $P = 0.08$ by multivariate analysis in Model 2, Table 3). Wide confidence intervals for Rb/*ras* and Rb/p53 status for patients with adenocarcinoma were observed; these might be due to the smaller numbers of patients in each group. For patients with squamous cell carcinoma, neither Rb/*ras* nor Rb/p53 status was a significant prognostic factor ($P = 0.6$ and $P = 1.0$, respectively, by univariate analysis).

DISCUSSION

Contrary to the results of our previous study,[18] Rb protein status was not significant as an individual factor for survival and prognosis in the current NSCLC cohort, although this study included Stage IIIa patients, whereas the other[18] did not. Nevertheless, when both Rb and *ras* p21 protein expression in the same tumors were considered, patients whose tumors showed both Rb and *ras* p21 protein alterations had a markedly shorter survival than those having tumors without measurable changes in these two proteins; this was the case for the overall NSCLC cohort and particularly for patients with adenocarcinoma. Similarly, patients whose tumors exhibited both Rb and p53 protein alterations had shorter survival than those having tumors without such changes; this was the case for the overall NSCLC cohort, and again especially for those with adenocarcinoma.

Both *ras* p21 and p53 protein status were significant and independent prognostic factors for the overall NSCLC cohort, confirming the results of previous studies.[26,29] Postsurgical chemotherapy was also a significant prognostic factor in the univariate analysis and was an independent prognostic factor in one of three multivariate analyses. However, it was not a significant prognostic factor by univariate analysis either for patients with adenocarcinoma or for those with squamous cell carcinoma when the two groups were analyzed separately. These data suggest that postsurgical chemotherapy may have only limited importance for the prognosis of NSCLC patients. Both *ras* p21 and p53 protein status were independent as prognostic factors from postsurgical chemotherapy and pStage by multivariate analysis, indicating that the effects on prognosis of altered *ras* p21 and p53 proteins were not dependent on the chemotherapy administered or on the stage of the disease.

In the cohort of patients with adenocarcinoma, however, Rb, *ras* p21, and p53 protein status, when examined individually, were not significant predictors for survival or prognosis, indicating their limited value as prognostic markers. However, Rb studied simultaneously with *ras* p21 and Rb studied simultaneously with p53 protein status became potential predictors of shortened survival for patients with adenocarcinoma. Therefore, alterations of Rb and *ras* p21 or of Rb and p53 proteins may have synergistic effects on survival and prognosis for lung carcinoma patients, especially for those with adenocarcinoma. However, the multivariate analysis showed borderline significance for Rb/*ras* ($P = 0.048$) and Rb/p53 status ($P = 0.08$) as independent prognostic factors for adenocarcinoma patients. These observations might have resulted from the smaller numbers of patients in each group. Larger studies that include patients with more homogeneous stages of disease are required to confirm whether the combinations of Rb and *ras* p21 or of Rb and p53 protein status can predict clinical outcome. It is noteworthy that similar synergistic effects on prognosis were found when Rb and p53 protein alterations were analyzed together in two other cohorts of Stage I and II NSCLC.[18,37]

Combined analyses of biologically important factors in addition to Rb protein have also been reported to be useful as prognostic markers in NSCLC in several studies, including ours.[26,38,39] We reported previously that the combined analysis of *ras* p21 and p53 protein expression could divide NSCLC patients into more accurate prognostic groups in a cohort that was basically the same in composition as the current cohort, but smaller.[26] We also reported the importance of a combination of *ras* p21 protein status and nuclear DNA ploidy as a biologic marker for the survival of resected NSCLC patients.[38] Kern et al. also reported additive effects of c-*erb* B2 protein expression and K-*ras* mutations on the survival of patients with adenocarcinoma of the lung.[39] They found that patients with

adenocarcinoma of the lung that expressed c-*erb* B2 protein and harbored an activating K-*ras* point mutation had significantly shorter survival than patients whose tumor had none or only one of these two alterations.

The alterations of Rb protein expression were correlated with pN classification in the patients with adenocarcinoma. This finding is also consistent with our previous study,[13] which showed a significant difference in the occurrence of altered Rb protein expression between patients with Stage I/II disease and Stage III/IV disease, since pN classification is the most important determinant of the stage of NSCLC.[31] A recently cloned tumor suppressor gene, CDKN2/MTS1,[40,41] the gene product of which ($p16^{INK4}$) is known to function as a cell-cycle inhibitor through a Rb protein-dependent pathway,[42] was also shown to be frequently inactivated in NSCLC.[43,44] It is noteworthy that the inactivation of CDKN2/MTS1 was more frequently observed in Stage III/IV disease than in Stage I/II disease,[44] like the alterations of Rb protein. From these studies of Rb protein and CDKN2/MTS1 in NSCLC, including the current study, inactivation of the p16/Rb pathway may be involved in the clinical progression of NSCLC, especially in lymph node metastasis. Lymph node metastasis is accepted as the most important determinant of the stage of surgically treated NSCLC[31] and as a significant prognostic factor in such cases.[7] Taken together, the inactivation of the p16/Rb pathway may make the clinical outcome worse by having a role in lymph node metastasis and clinical progression. It would therefore be interesting to see the relationship between $p16^{INK4}$ inactivation and prognosis in NSCLC patients.

In conclusion, it may be possible to identify patients with lung cancer, especially adenocarcinoma, with better or worse prognosis by using alterations of Rb protein expression in combination with *ras* p21 or p53 protein changes as combined clinical markers. If the current findings are confirmed in larger prospective studies, including especially those with Stage I NSCLC, then combined immunohistochemical analysis of Rb and *ras* p21 proteins or of Rb and p53 proteins can be used to stratify patients with lung cancer into different prognostic groups and to identify populations with different risks of recurrence.

TEXTO 2

EL MUNDO/ 46 SALUD JUEVES 1 DE FEBRERO DE 1996

ONCOLOGIA

Prevenir el cáncer de cuello de útero

Experimentan un vacuna contra este tumor

EL MUNDO

Un tratamiento experimental podría llegar a salvar a miles de mujeres de tener que tratarse de un cáncer de cuello de útero. Investigadores de Baltimore acaban de usar en ratones una vacuna contra este tipo de tumor y la experiencia ha resultado exitosa.

El estudio, publicado en la revista Cancer Research, revela que los científicos utilizaron una proteína, llamada E7, que juega un papel fundamental en la progresión del cáncer de cuello de útero. Esta proteína se encuentra en la superficie del papiloma virus humano, que causa el 90% de este tipo de tumores.

Los autores del trabajo utilizaron la vacuna antes y después de haber inyectado células cancerosas en los ratones. El 80% de los roedores en los que se usó la vacuna de forma preventiva, tres meses después de inocular las células malignas se encontraron libres de tumores. Mientras que los expertos comprobaron que aquéllos que fueron tratados una semana después de recibir la inyección de células malignas se curó de los tumores pequeños que habían desarrollado. El siguiente paso será probar la efectividad de esta vacuna en humanos.

TEXTO 3

JUEVES 25 DE ENERO DE 1996 SALUD EL MUNDO/ 49

UROLOGIA

Fórmulas prostáticas

Sigue la polémica sobre la terapia del cáncer de la glándula

EL MUNDO

La polémica continúa. La publicación en el último número del JAMA de un trabajo de la Clínica Mayo (EEUU), en el que se aconseja qué es lo que hay que hacer con los cánceres de próstata, añade más leña al fuego de la discusión que hace años existe sobre la terapia del tumor maligno más frecuente en el hombre.

Especialistas de la prestigiosa Institución estadounidense, revisaron las últimas 337 prostatectomías radicales que habían realizado en otros tantos enfermos afectados de cáncer de la glándula para contrastar la edad de los pacientes, el tamaño del tumor, la malignidad del mismo y el índice de crecimiento anual que habían tenido. De los resultados de este examen, los autores del trabajo concluyen que ante un cáncer de próstata se puede utilizar una fórmula para saber cómo tratarlo.

Los parámetros que -según los expertos de Rochester- habría que tener siempre en cuenta antes de tomar decisiones prostáticas demasiado radicales serían: la edad del paciente (menor de 70 años), el volumen tumoral y las posibilidades de crecimiento del mismo.

De hecho, cuando los especialistas revisaron su casuística concluyeron que en el 49% de las operaciones realizadas, el resultado del tratamiento hubiera sido el mismo si los cirujanos no hubieran actuado. Los investigadores recomiendan prudencia basándose en la biología tan particular que tienen los tumores prostáticos. Aunque el 40% de los varones mayores de 50 años tiene cáncer de próstata, sólo el 8% de todos los tumores acabará produciendo un problema al paciente. Por eso es necesario encontrar métodos y fórmulas que concreten mucho más el qué hacer con los enfermos. Dado que la prostatectomía radical es una operación con bastantes problemas secundarios, hay que llevarla a cabo sólo cuando vaya a beneficiar claramente al enfermo.

TEXTO 4

CANCERLIT Topic Searches

CITATIONS AND ABSTRACTS FROM THE NCI'S CANCERLIT DATABASE

CHEMOTHERAPY FOR NONSMALL CELL LUNG CANCER - April 1998

Role of vindesine in induction chemotherapy in locally-advanced non-small-cell lung cancer.

Unique Identifier: 98158593

Author: Fischer JR; Drings P

Source: J Cancer Res Clin Oncol 1998;124(1):4-9

Address: Department of Medical Oncology, Thoraxklinik der LVA Baden, Heidelberg, Germany.

Abstract:

Locally advanced non-small-cell lung cancer (NSCLC) in most cases is not curable at the present time. Owing to the local extent of the tumor, the rate of complete resections is low and, therefore, survival in these patients is poor. For this reason, induction chemotherapy is being *investigated* in patients expected to have a poor prognosis after standard surgery and radiotherapy. The rationale for induction chemotherapy is to increase the rate of complete resections and achieve early elimination of micrometastases. Clinical *investigations* have reported an improvement of survival in stage III NSCLC after induction chemotherapy by using different combinations of cytotoxic drugs. Vindesine ranks among the most active single agents in this disease and has been part of a number of combination regimens in induction chemotherapy. The combination of mitomycin, vindesine or vinblastine and cisplatin has produced encouraging results in several *studies*, indicating a possible improvement of survival in stage III NSCLC, although its superiority to other combinations yet has to be demonstrated. (32 Refs)

JUEVES 4 DE ENERO DE 1996 SALUD EL MUNDO 45

ONCOLOGIA

El triunfo del taxol

El fármaco pasa a primera línea en el tratamiento del cáncer ovárico

JOSE LUIS DE LA SERNA

Ha dejado de ser un segundón. El taxol (paclitaxel en su nombre genérico), el avance quimioterápico frente al cáncer más importante de la última década, ha adquirido hoy la categoría de producto oncológico de primera línea. Con la publicación en el número de este jueves del New England Journal of Medicine de un trabajo en el que se demuestra la superioridad de una combinación de taxol y cisplatino sobre la quimioterapia estándar del cáncer de ovario, los oncólogos tendrán que pensar en él desde el principio cuando se enfrenten a un tumor maligno de la gónada.

En el trabajo, realizado con el patrocinio de los Institutos Nacionales de la Salud de EEUU, se comprobó el resultado de tratar inicialmente a 386 mujeres con cáncer del ovario con dos tipos de quimioterapia diferentes. La mitad de ellas -elegidas de forma aleatoria- recibió cisplatino y ciclofosfamida y la otra mitad cisplatino y taxol. Los resultados al cabo de cuatro años de seguimiento clínico fueron significativamente mejores -tanto en supervivencia como en número de recidivas- para el grupo que recibió inicialmente el taxol que para las féminas tratadas de forma estándar.

Toxicidad

Sin embargo, la toxicidad secundaria al tratamiento fue superior en las mujeres tratadas con taxol y cisplatino, que en aquellas que formaban parte del grupo control. No obstante, los investigadores aseguran que los efectos secundarios, aunque serios, no fueron excesivamente peligrosos. En el editorial que acompaña al artículo, escrito por el doctor Jan Neijt, de la Universidad de Utrech en Holanda, se pone énfasis en que el taxol debería ser considerado de entrada en el tratamiento de todos los cánceres de ovario.

Este tipo de tumor, sin ser excesivamente frecuente, es el más común de todos los cánceres ginecológicos. Tiene, por desgracia, una mortalidad elevada, aunque su tratamiento ha mejorado mucho en los últimos años. Con cirugía y quimioterapia, buena parte de las afectadas responden bien a la medicación. Sin embargo, el tumor suele recidivar con gran frecuencia por lo que su mortalidad a los 10 años de haberse presentado es todavía muy elevada, en torno al 80%. La posibilidad de aumentar la supervivencia de este tipo de cáncer usando taxol es sin duda una buena noticia con la que los oncólogos empiezan el año.

Por otra parte, el paclitaxel ha ampliado sus acciones y éstas no sólo estarán limitadas al tratamiento del tumor del ovario sino que serán beneficiosas también en el de mama y el de pulmón. En uno de ellos -el de mama- se utiliza como producto de segunda línea con buenos resultados y en el otro -el de pulmón- su uso es aún experimental pero todos los datos disponibles indican que prometedor.

TEXTO 6

Servicio producido por Sarenet Información mantenida por Pulso100. Patrocinado por Sanitas

¿QUE ES EL CANCER?

DESCRIPCION

El cáncer no es una sola enfermedad sino un grupo de más de 200 enfermedades distintas en las que se produce un crecimiento anormal de las células, hasta convertirse en masas de tejidos llamados tumores. Hay dos tipos de tumores: benignos o no cancerosos y malignos o cancerosos.

Los tumores benignos tienen seis características principales:

- Sólo crecen hasta un determinado tamaño.
- Normalmente no crecen muy rápido.
- No destruyen células normales.
- No se propagan al tejido que les rodea.
- Normalmente no producen efectos secundarios graves.
- Por lo general crecen de una manera ordenada.

Los tumores malignos se conocen por su capacidad para invadir y destruir tejidos y órganos, tanto los que están cerca como los que están lejos del tumor original. La muerte se produce cuando la propagación del cáncer daña los tejidos y los órganos vitales, de tal manera que no pueden funcionar.

Las células del cáncer atacan el tejido sano y nunca dejan de multiplicarse. El cáncer tiene un comportamiento distinto en cada persona, según su tipo. Puede darse a cualquier edad, pero es mas probable que afecte a personas de edad avanzada; por lo general a partir de los 55 años. El cáncer también puede presentarse en niños, y de hecho, es la segunda causa principal de muerte en niños de edades comprendidas entre 1 y 15 años.

El cáncer puede ser causado por causas externas al cuerpo, o por causas internas.

Los factores externos que pueden causar el cáncer incluyen el estar expuesto a determinados productos químicos como el benceno y el asbesto (amianto). Los pintores, los fabricantes de neumáticos, los destiladores y los fabricantes de zapatos, están expuestos a menudo al benceno. Los trabajadores de minas, aislamiento y astilleros están expuestos a menudo al asbesto. Otros factores ambientales que causan cáncer incluyen:

- Exposición a agentes contaminantes ambientales, como los gases del escape del automóvil.
- Exposición a las radiaciones del sol.
- Exposición a niveles altos de rayos X.
- Exposición a radiaciones Electromagnéticas
- Dieta con gran cantidad de grasas y poca fibra.
- Consumo de tabaco.
- Abuso de las bebidas alcohólicas o de determinadas drogas.

Los factores internos que pueden causar cáncer incluyen la obesidad, las infecciones causadas por virus, como la hepatitis B crónica y un historial familiar en el que exista el cáncer.

Las posibilidades de supervivencia al cáncer dependen del lugar del cuerpo en que se encuentre el cáncer y de las clases de tratamiento utilizadas. Hay cinco formas principales de tratar el cáncer:

- Cirugía
- Radioterapia
- Quimioterapia
- Terapia hormonal
- Terapia biológica.

Para el tratamiento del cáncer, el médico puede utilizar un solo método una combinación de varios.

VER TAMBIEN:

- Cáncer de Mama, Cirugía
- Cáncer de Testículos
- Tumores de Páncreas
- Cáncer colorectal
- Cáncer de cuello de uterino
- Cancer de mama
- Melanoma
- Cáncer de pulmón de células grandes
- Cáncer de pulmón de células pequeñas
- Cáncer laringe
- Dolor en el cáncer
- Linfoma de Hodgkin en adultos

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TEXTO 7

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Lung Carcinoma Patients with a Family History of Cancer and Lymphocyte Primary Chromosome 9 Aberrations

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ABSTRACT

BACKGROUND. Deletion of chromosome 9p has been reported in numerous tumor types. The authors demonstrated in an earlier study that spontaneous chromosome aberrations on chromosome 9 in peripheral blood lymphocytes (PBLs) were a significant risk predictor for lung carcinoma.

METHODS. The current study evaluated the relationship between self-reported family history of cancer and spontaneous chromosome aberrations in the PBLs of 97 previously untreated lung carcinoma patients. The authors' hypothesis was that individuals exhibiting specific chromosome aberrations might have inherited genetic instability and thus be more likely to report a family history of cancer. For each individual, a personal interview was conducted to construct a detailed family history, and 100 metaphases from PBLs were analyzed for spontaneous aberrations by G-banding.

RESULTS. The patients reported having 829 first-degree relatives, including 74 (8.9%) with cancer. A significantly elevated odds ratio (OR) of 2.7 was noted in smokers for having chromosome 9 aberrations and a first-degree relative with cancer. When the family history of cancer was dichotomized into lung carcinoma or other cancers, the OR associated with chromosomal aberrations was 8.5 for lung carcinoma but only 2.3 for other cancers. In addition to chromosome 9 aberrations, other spontaneous chromosome aberrations and family history of cancer were also evaluated, but no associations were found. There were no associations between age, gender, ethnicity, or smoking status and the chromosome 9 aberration profile.

CONCLUSIONS. The findings of this study suggest that chromosome 9 aberrations may be a marker of cancer susceptibility and may be associated with familial aggregation of cancer.

KEYWORDS
chromosome 9, lymphocytes, family history of cancer, lung carcinoma.

Carcinoma of the lung is an excellent model for studying genetic-environmental interactions. The incidence of lung carcinoma is dependent not only on the dose, duration, form, and type of tobacco smoked but also host susceptibility factors. In this molecular epidemiologic case-control study of lung carcinoma in two minority populations, the authors have integrated epidemiologic data with a panel of susceptibility markers. One of the study objectives was to examine primary chromosome changes in peripheral blood lymphocytes (PBLs) as a predictor of lung carcinoma risk.

Screening of PBLs for cytogenetic defects has proven useful in studying other cancers.[1-9] The nonrandom chromosome 13 anomalies in retinoblastoma and chromosome 11 anomalies in Wilms' tumor were first identified in the lymphocyte cultures of children with morphological birth defects and mental retardation.[1-4] Later, it became apparent that similar specific cytogenetic anomalies were present in the tumor cells of children with retinoblastoma and Wilms' tumor who were otherwise phenotypically normal. It is well established that abnormalities of chromosome 3p are a primary defect in human renal cell carcinoma,[6] and they have also been reported in the lymphocyte cultures of certain renal cell carcinoma patients.[7] Similar abnormalities have been observed in the lymphocyte cultures of patients with adenomatous polyps and colorectal carcinomas, which have specific chromosome 5 defects.[8] Studies of the lymphocyte cultures of patients with breast carcinoma (both familial and sporadic) and their asymptomatic relatives have revealed chromosome 1q rearrangement, a defect previously reported in a number of breast carcinoma cell lines and freshly harvested pleural effusions.[9]

Previously, the authors demonstrated by univariate analysis that the odds ratio (OR) was significantly higher for spontaneous chromosome 7, 9, 12, and 21 aberrations in the PBLs of lung carcinoma cases than of controls.[10] However, only aberrations in chromosomes 9 and 21 were associated with significantly higher risk in lung carcinoma cases than in controls after adjustment by age, gender, ethnicity, and pack-years smoked. Of 97 cases, 43 (44.3%) exhibited chromosome 9 aberrations, compared with 17 (23.0%) of 74 controls. The hot spots on chromosome 9 were located at 9p13-9q13. The multiple tumor suppressor MSTI (p16) and MST2 (p15) genes are located at 9p21,[11] and 9p deletion is frequent in lung carcinomas.[12-14]

Based on this information, it was hypothesized that spontaneous chromosome aberrations reflect genetic instability and that individuals with such aberrations would be more likely to report a family history of cancer than individuals without such aberrations. Therefore, in this study, the authors evaluated the relationship between self-reported family history of cancer and spontaneous chromosome aberrations in PBLs of lung carcinoma patients. Family history of cancer was defined as any cancer reported in the patient's first-degree relatives.

MATERIALS AND METHODS

Study Subjects

The patients included in this report are a subset from a molecular epidemiologic study of lung carcinoma in minority populations (African Americans and Mexican Americans). The 97 patients studied had newly diagnosed, histologically confirmed lung carcinoma, had not been previously treated with radiotherapy or chemotherapy, and reported themselves as being of African-American (n = 73) or Mexican-American (n = 24) ancestry. The patients were recruited from The University of Texas M. D. Anderson Cancer Center; from county, community, and Veterans Administration hospitals in the Houston metropolitan area; and from community hospitals in San Antonio, Texas. There were no age, histologic, or stage restrictions.

Data Collection

The epidemiologic data were collected by personal interviews.[15] After informed consent was obtained, a structured interview approximately 45 minutes long was conducted in English or Spanish by trained interviewer-phlebotomists. Data were collected on sociodemographic characteristics, recent and past tobacco use, and other lifestyle habits using standardized questions. A detailed family history of the patient's first-degree relatives was collected and included the number of siblings and offspring and the dates of birth, death, and cancer diagnoses in first-degree relatives.

Lymphocyte Cultures and Chromosome Analysis

From each subject, 10 mL of peripheral blood was drawn into heparinized tubes. The lymphocyte culture and chromosome preparation techniques used were those of Hsu et al.[16] All G-banded slides were coded before analysis. One hundred metaphase spreads from each individual were examined with a Genetiscan (PSI, Houston, TX). For each subject, abnormal metaphases and three normal metaphases were karyotyped.

Statistical Analysis

Chromosome 9 aberration was defined as translocation, deletion, or inversion of chromosome 9 or the presence of a dicentric chromosome 9. A smoker was defined as someone who had smoked at least 100 cigarettes in his or her lifetime. To test for significant associations between family history of cancer and specific chromosomal aberrations, ORs with 95% confidence limits were computed as estimates of the relative risk. Logistic regression was conducted to estimate risks associated with chromosome 9 aberrations, which were adjusted for multiple factors using STATA statistical software.[17]

RESULTS

Host Characteristics

The study population was described previously.[10] There were 68 men and 29 women, 24 of whom were Mexican American and 73 African American. The mean age was 60.3 years. As reported previously,[10] overall, 43 of the patients (44.3%) exhibited spontaneous chromosome 9 aberrations, (compared with 23% of the controls). For 9 p aberrations specifically, the comparable percentages were 22% and 13%, respectively, in patients and controls.

The patients reported having 829 first-degree relatives, including 74 (8.9%) with cancer. Table 1 summarizes the proportion of relatives with any reported cancer by chromosome 9 aberration status. The proportions of parents, siblings, and all first-degree relatives with cancer in individuals with chromosome 9 aberrations were higher than in individuals without chromosome 9 aberrations (26.0% vs. 15.0%, 10.1% vs. 8.0%, and 10.6% vs. 7.6%, respectively). None of these differences were statistically significant.

The associations between age, gender, ethnicity, smoking status, and chromosome 9 aberration profile were also evaluated. There were no statistically significant associations between chromosome 9 aberration status and current or former smoking status, gender, ethnicity, age, pack-years smoked, or family size (Table 2). There were also no statistically significant differences in the first-degree relatives' mean age at cancer diagnosis or in the distribution of cancer sites (data not shown).

Table 3 shows the risk estimates among smokers for chromosome 9 aberrations by family history of any cancer, of lung carcinoma, and of other cancers. A significantly elevated OR of 2.7 was noted for chromosome 9 aberrations and any reported cancer in a first-degree relative. When the data were dichotomized into lung carcinoma or other cancers, the OR was 8.5 for having a family history of lung carcinoma, but only 2.1 for having a family history of other cancers.

In the control population selected for the previous study[10], 11 of those with chromosome 9 aberrations (64.7%) reported a positive family history, compared with 28 of the controls without such aberrations (49.1%). Although this pattern was consistent with that for the cases, these differences were not statistically significant. In addition to chromosome 9 aberrations, the relationship between other spontaneous chromosome aberrations and family history of cancer were also evaluated in both the cases and controls, but no associations were noted. There was no trend for increasing risk with increased frequency of aberrations. However, of four cases with six or more different chromosomal aberrations, three reported a history of cancer in a first-degree relative.

DISCUSSION

Lung carcinoma is the epitome of an environmentally induced disease. Approximately 90% of lung carcinomas are attributed to tobacco exposure. However, only a fraction of smokers develop neoplastic lesions and genetically determined modulation of environmental exposures is an attractive mechanism to explain the variation in host susceptibility. Epidemiologic studies of familial aggregation of lung carcinoma provide indirect evidence for the role of genetic predisposition to this disease. Tokuhata and Lilienfeld[18] and Ooi et al.[19] found increased risks for lung carcinoma for both smoking and nonsmoking relatives of lung carcinoma patients. Sellers et al.[20] also documented an increased familial risk for lung carcinoma after controlling for the effects of age, gender, occupation, and smoking. They subsequently performed segregation analysis and reported results compatible with Mendelian codominant inheritance of a rare major autosomal gene for lung carcinoma predisposition.[21] Twin studies have also confirmed that monozygotic twins discordant for smoking behavior have different risks for lung carcinoma.[22]

In vitro chromosomal analyses have been frequently used to study individual sensitivity to genotoxicity and cancer risk. Using a molecular epidemiologic approach, the authors and other investigators have found that lymphocyte analysis can be used to identify individuals at a higher risk of developing cancer.[15,23-28]

In their previous lung carcinoma study, the authors demonstrated that spontaneous chromosome 9 aberrations detected by G-banding in PBLs were a significant risk predictor for lung carcinoma with an OR of 3.6, after adjusting for age, gender, ethnicity, cigarette smoking, and occupational exposure. In this study, the authors found that these chromosome 9 aberrations were also significantly associated with family history of cancer. Furthermore, the current data showed that there was no significant association between chromosome 9 aberration and smoking status, pack-years smoked, gender or ethnicity.

A number of cytogenetic studies in lung carcinoma specimens have revealed consistent deletions involving chromosome 9p.[11,29,30] Center et al.[30] reported nonrandom abnormalities of 9p in most primary samples from patients with nonsmall cell lung carcinoma (NSCLC). Several recent molecular studies complemented these cytogenetic observations by showing loss of heterozygosity (LOH) in lung carcinoma tumors and cell lines.[12-14,31-35] Merlo et al.[32] have reported frequent LOH on chromosome 9p, especially at 9p,[21-22] and identified novel tumor suppressor gene loci on 9q in small cell lung carcinomaα and NSCLC.

A recent report suggested that the putative tumor suppressor gene MTS1 is very near the interferon gene cluster, at chromosome 9p21.[11] Xiao et al.[12] concluded that p15 and p16 are deleted or mutated in most primary NSCLCs and also provided evidence that at least one additional tumor suppressor gene on chromosome 9 is involved in NSCLC. Kishimoto et al.[14] tested for deletions and LOH of 9p loci in preneoplastic and neoplastic loci in the lungs of patients with NSCLC by polymerase chain reaction-based assays for polymorphism in dinucleotide repeats (microsatellite markers) in the interferon and D9S171 loci on 9p. They concluded that LOH at 9p loci occurs at the earliest stage in the pathogenesis of lung carcinoma and involves all regions of the respiratory tract.

To determine whether the same chromosomal changes were present in the normal and target, diseased tissue, Dave et al.[36] analyzed the concordance of chromosomal alterations in primary lung tumors and PBLs from 10 lung carcinoma patients. Using molecular cytogenetic techniques, they reported that each paired sample (PBL and lung tumor tissue) had at least three chromosomes and two chromosomal regions with the same structural rearrangements. Genomic instability at the chromosomal level in PBLs thus appears to reflect the genetic changes in tumors and it is possible that cytogenetic analysis of primary chromosome changes in PBLs could provide a clue to the primary role of those changes in tumorigenesis.

The current hypothesis-generating study is limited by the small sample size and thus the results require cautious interpretation. Furthermore, the authors relied on the probands' self-reported family history of cancer without validation by medical documentation. However, Bondy et al.[37] found that self-reported cancer information regarding first-degree relatives was 88% accurate when compared with medical documentation.

The complex pattern of karyotypic changes in tumor cells emphasizes the need for more investigations of normal tissue (PBLs) and premalignant bronchial lesions to identify the primary genetic changes important for the identification of high risk populations, early detection, and intervention in this aggressive neoplasm. Chromosome 9 aberrations may be a marker of lung carcinoma susceptibility and may be associated with familial aggregation of cancer. These chromosome aberrations could be used as biomarkers to identify high risk populations. The authors are currently using molecular cytogenetic techniques to confirm these findings in a larger study of lung carcinoma patients.

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TEXTO 8

Noticias Hoy

16/04/1997

El cáncer de pulmón se asocia a alteraciones del cromosoma 9

Jano Diario, Barcelona

Investigadores de la Universidad de Texas (Estados Unidos) han descubierto que ciertas alteraciones en el cromosoma 9 parecen ser marcadores del riesgo de cáncer pulmonar y de la agregación familiar de este tipo de tumor, que es precisamente el que parece ser en mayor medida inducido por factores ambientales.

Investigaciones previas del equipo que dirige el Dr. Xifeng Wu mostraban que las anomalías del cromosoma 9 en los linfocitos periféricos constituían un predictor de riesgo significativo de carcinoma pulmonar. En el nuevo estudio, publicado en el último número de "Cancer", trataron de determinar si esta asocación se debía a una inestabilidad genética heredada. Identificaron a 97 pacientes con cáncer de pulmón y alteraciones en el cromosoma 9, y a continuación evaluaron a sus familiares de primer grado.

Los resultados indican que estos familiares presentan una probabilidad 8,5 veces superior de desarrollar carcinoma pulmonar si tienen mutaciones del cromosoma 9 respecto a los que no las tienen. Aunque se trata de resultados preliminares, el Dr. Wu sugiere que el estudio de estas alteraciones cromosómicas podrían utilizarse como marcadores para identificar a poblaciones de alto riesgo.

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Treatment – Health Professionals

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PDQ Tratamiento Profesionales de la Salud

TEXTO 9: Treatment summaries for health professionals (QDT1)

---------- MALIGNANT MESOTHELIOMA ----------

********** GENERAL INFORMATION

Prognosis in this disease is difficult to assess consistently because there is great variability in the time before diagnosis and the rate of disease progression. Various surgical procedures may be possible in selected patients, providing long-term survival without cure. In large retrospective series of pleural mesothelioma patients, important prognostic factors were found to be stage, age, performance status, and histology [1,2]. For patients treated with aggressive surgical approaches, factors associated with improved long-term survival include epithelial histology, negative lymph nodes, and negative surgical margins [3,4]. For those patients treated with aggressive surgical approaches, nodal status is an important prognostic factor [3]. Median survival for malignant local pleural disease has been reported as 16 months, and extensive disease as 5 months. In some instances the tumor grows through the diaphragm making site of origin difficult to assess. Cautious interpretation of treatment results in this disease is imperative because of the selection differences among series. Effusions, both pleural and peritoneal, represent major symptomatic problems for at least two thirds of the patients. A history of asbestos exposure is reported in about 70%-80% of all cases of mesothelioma [1,5,6].

<References>

********** CELLULAR CLASSIFICATION

Histologically, these tumors are composed of fibrous or epithelial elements or both. The epithelial form occasionally causes confusion with peripheral anaplastic lung carcinomas or metastatic carcinomas. Attempts at diagnosis by cytology or needle biopsy of the pleura are often noncontributory. It can be especially difficult to differentiate mesothelioma from carcinoma on small tissue specimens. Thoracoscopy can be valuable in obtaining adequate tissue specimens for diagnostic purposes [1]. Examination of the gross tumor at surgery and use of special stains or electron microscopy can often help. The special stains reported to be most useful include periodic acid-Schiff diastase, hyaluronic acid, mucicarmine, CEA, and Leu M1 [2]. Histologic appearance appears to be of prognostic value, with most clinical studies showing that epithelial mesotheliomas have a better prognosis than fibrous or sarcomatous mesotheliomas [2-4].

<References>

********** STAGE INFORMATION

Patients with stage I disease have a significantly better prognosis than those with more advanced stages. However, because of the relative rarity of this disease, exact survival information based upon stage is limited [1]. A proposed staging system based upon thoracic surgery principles and clinical data is shown below [2]. It is a modification of the older system proposed by Butchart et al [3]. Other staging systems that have been employed, including a proposed new international TNM staging system, are summarized by the International Mesothelioma Interest Group [4].

Stage I: Disease confined within the capsule of the parietal pleura: ipsilateral pleura, lung, pericardium, and diaphragm.

Stage II: All of stage I with positive intrathoracic (N1 or N2) lymph nodes.

Stage III: Local extension of disease into the following: chest wall or mediastinum; heart or through the diaphragm, peritoneum; with or without extrathoracic or contralateral (N3) lymph node involvement.

Stage IV: Distant metastatic disease.

Localized malignant mesothelioma: See description of stage I above.

Advanced malignant mesothelioma: See descriptions of stages II, III, and IV above.

For the purposes of the discussion of treatment in this statement, the disease is categorized as either localized or advanced.

<References>

********** TREATMENT OPTION OVERVIEW

Standard treatment for all but localized mesothelioma is generally not curative. Although some patients will experience long-term survival with aggressive treatment approaches, it remains unclear if overall survival has been significantly altered by the different treatment modalities or by combinations of modalities. Extrapleural pneumonectomy in selected patients with early stage disease may improve recurrence-free survival, but its impact on overall survival is unknown [1]. Pleurectomy and decortication can provide palliative relief from symptomatic effusions, discomfort caused by tumor burden, and pain caused by invasive tumor. Operative mortality from pleurectomy/decortication is less than 2%,[2]. while mortality from extrapleural pneumonectomy has ranged from 6% to 30% [1,3]. The addition of radiation therapy and/or chemotherapy following surgical intervention has not demonstrated improved survival [2]. The use of radiation therapy in pleural mesothelioma has been shown to alleviate pain in the majority of patients treated. However, the duration of symptom control is short-lived [4,5]. Single agent and combination chemotherapy have been evaluated in single and combined modality studies. The most studied agent is doxorubicin, which has produced partial responses in approximately 15%-20% of patients studied [6]. Some combination chemotherapy regimens have been reported to have higher response rates in small phase II trials. However the toxicity reported is also higher and there is no evidence that combination regimens result in longer survival or longer control of symptoms [6,7].. Recurrent pleural effusions may be treated with pleural sclerosing procedures; however, failure rates are high secondary to the restrictive nature of the tumor.

The designations in PDQ that treatments are "standard" or "under clinical evaluation" are not to be used as a basis for reimbursement determinations.

<References>

********** LOCALIZED MALIGNANT MESOTHELIOMA (STAGE I)

Treatment options:[1].

Standard:

1 Solitary mesotheliomas: Surgical resection en bloc including contiguous structures to ensure wide disease-free margins. Sessile polypoid lesions should be treated with surgical resection to ensure maximal potential for cure [2].

2 Intracavitary mesothelioma:
A) Palliative surgery (pleurectomy and decortication) with or without postoperative radiation therapy

B) Extrapleural pneumonectomy
C) Palliative radiation therapy.

Under clinical evaluation:

1 Intracavitary chemotherapy following resection [3,4].

2 Multimodality therapy [4-6].

3 Other clinical trials.

<References>

********** ADVANCED MALIGNANT MESOTHELIOMA (STAGES II, III, AND IV)

Treatment options:

1 Symptomatic treatment to include drainage of effusions, chest tube pleurodesis, or thoracoscopic pleurodesis [1].

2 Palliative surgical resection in selected patients [2,3].

3 Palliative radiation therapy [4,5].

4 Single-agent chemotherapy. Partial responses have been reported with doxorubicin,epirubicin, mitomycin, cyclophosphamide, cisplatin, carboplatin, and ifosfamide [6-8].

5 Multimodality clinical trials [9-13].

6 Intracavitary therapy. Intrapleural or intraperitoneal administration of chemotherapeutic agents (e.g, cisplatin, mitomycin, and cytarabine) has been reported to produce transient reduction in the size of tumor masses and temporary control of effusions in small clinical studies [14-16]. Additional studies are needed to define the role of intracavitary therapy.

<References>

********** RECURRENT MALIGNANT MESOTHELIOMA

Treatment of recurrent mesothelioma usually utilizes procedures and/or agents not previously employed in the initial treatment attempt. No standard treatment approaches have been proven to improve survival or control symptoms for a prolonged period of time. These patients should be considered candidates for phase I and II clinical trials evaluating new biologicals, chemotherapeutic agents, or physical approaches [1-5]. Consult the PDQ protocol file for a current listing of active clinical trials.

<References>

TEXTO 10: Treatment summaries for health professionals (QDT2)

PDQ® Treatment Health Professionals

Important: *This information is intended for use by doctors and other health care professionals. If you are a cancer patient, your doctor can explain how it applies to you, or you can call the Cancer Information Service at* ***1-800-422-6237.***

Non-small cell lung cancer

Table of Contents

GENERAL INFORMATION

Non-small cell lung cancer (NSCLC) is a heterogeneous aggregate of at least three distinct histologies of lung cancer including epidermoid or squamous carcinoma, adenocarcinoma, and large cell carcinoma. These histologies are often classified together because, when localized, all have the potential for cure with surgical resection. Systemic chemotherapy can produce objective partial responses and palliation of symptoms for short durations. Local control can be achieved with radiation in a large number of patients with unresectable disease, but cure is seen only in a small minority of patients.

At diagnosis, patients with NSCLC can be divided into three groups that reflect the extent of disease and treatment approach. The first group of patients has tumors that are surgically resectable (generally stages I and II). This is the group with the best prognosis, depending on a variety of tumor and host factors. Patients with resectable disease who have medical contraindications to surgery can be considered for curative radiotherapy. The second group includes patients with either locally (T3-T4) or regionally (N2-N3) advanced lung cancer who have a diverse natural history. This group is treated with radiotherapy or with radiotherapy in combination with other therapy modalities. Selected patients with T3 or N2 disease can be treated effectively with surgical resection alone. The final group of patients have distant metastases (M1) found at the time of diagnosis. This group can be treated with radiotherapy or chemotherapy for palliation of symptoms from the primary tumor. Patients with good performance status, women, and patients with distant metastases confined to a single site appear to live longer than others.[1] Cisplatin-based chemotherapy has been associated with short-term palliation of symptoms and a small survival advantage. Currently no single chemotherapy regimen can be recommended for routine use.

For operable patients, prognosis is adversely influenced by the presence of pulmonary symptoms, large tumor size (>3 centimeters), and presence of the erbB-2 oncoprotein.[1-6] Other factors that have been identified as adverse prognostic factors in some series of patients with resectable non-small cell lung cancer include mutation of the K-ras gene, vascular invasion, and increased numbers of blood vessels in the tumor specimen.[3,7,8]

Since treatment is not satisfactory for almost all patients with NSCLC, with the possible exception of a subset of pathologic stage I (T1, N0, M0) patients treated surgically, eligible patients should be considered for clinical trials.

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CELLULAR CLASSIFICATION

Prior to initiating treatment of any patient with lung cancer, a review of pathologic material by an experienced lung cancer pathologist is critical since some cases of small cell lung cancer (which responds well to chemotherapy) can be confused on microscopic examination with non-small cell carcinoma.[1] Nonsquamous cell cancers may be more likely to recur after surgical resection of early stage I tumors than other types of non-small cell lung cancers.[2] Bronchoalveolar carcinoma represents 10%-25% of adenocarcinomas and sometimes has a distinct presentation and biologic behavior.[3-5] Bronchoalveolar cancer may present as a more diffuse lesion than other types of cancer; 30%-40% of patients undergoing an attempt at surgical resection present with an infiltrate on their chest radiograph. Bronchoalveolar

cancer is more common in women and in patients who do not smoke cigarettes than other histologic types of lung cancer.

Histologic classification of non-small cell lung cancer:

- squamous cell (epidermoid) carcinoma
- spindle cell variant
- adenocarcinoma
- acinar
- papillary
- bronchoalveolar [4,5]
- solid tumor with mucin
- large cell carcinoma
- giant cell
- clear cell
- adenosquamous carcinoma
- undifferentiated carcinoma

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STAGE INFORMATION

Since determination of stage has important therapeutic and prognostic implications, careful initial diagnostic evaluation to define location and extent of primary and metastatic tumor involvement is critical for the appropriate care of patients.

Stage has a critical role in the selection of therapy. The stage of disease is based on a combination of clinical (physical examination, radiologic, and laboratory studies) and pathologic (biopsy of lymph nodes, bronchoscopy, mediastinoscopy, or anterior mediastinotomy.[1] The distinction between clinical stage and pathologic stage should be considered when evaluating reports of survival outcome. Surgical staging of the mediastinum is considered standard if accurate evaluation of the nodal status is needed to determine therapy. The Radiology Diagnostic Oncology Group reported that the sensitivity and specificity of computerized tomography (CT) scanning is only 52% and 69%, respectively.[2] Magnetic resonance imaging (MRI) does not appear to improve the accuracy of staging.[2] Early evaluation of the role of positron emission tomography (PET) suggests that the combination of CT and PET may have greater sensitivity and specificity than CT alone.[3] A report evaluating the staging of 1,400 patients undergoing tumor resection found that clinical staging by radiologic studies accurately assessed the T stage in 78% of patients and the N stage in only 47% of patients. Errors in clinical staging were equally divided between overstaging and understaging.[4]

The Revised International Staging System for Lung Cancer

The Revised International System for Staging Lung Cancer was adopted in 1997 by the American Joint Committee on Cancer and the Union Internationale Contre le Cancer.[5] These revisions were made to provide greater specificity for patient groups. Stage I is divided into two categories by the size of the tumor; IA, T1N0M0 and IB, T2N0M0. Stage II is divided into two categories by the size of the tumor and by the nodal status; IIA, T1N1M0 and IIB, T2N1M0. T3N0 has been moved from stage IIIA in the 1986

version of the staging system to stage IIB. The other change has been to clarify the classification of multiple tumor nodules. Satellite tumor nodules in the same lobe as the primary lesion that are not lymph nodes should be classified as T4 lesions. Intrapulmonary ipsilateral metastasis in a lobe other than the lobe containing the primary lesions should be classified as an M1 lesion (stage IV).
The American Joint Committee on Cancer (AJCC) has designated staging by TNM classification.[6]

TNM definitions
Primary tumor (T)

TX: Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy

T0: No evidence of primary tumor

Tis: Carcinoma in situ

T1: A tumor that is 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, and without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)*

T2: A tumor with any of the following features of size or extent:

More than 3 cm in greatest dimension
Involves the main bronchus, 2 cm or more distal to the carina
Invades the visceral pleura
Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T3: A tumor of any size that directly invades any of the following: chest

wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung

T4: A tumor of any size that invades any of the following: mediastinum,

heart, great vessels, trachea, esophagus, vertebral body, carina; or separate tumor nodules in the same lobe; or tumor with a malignant pleural effusion **

*Note: The uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1.
**Note: Most pleural effusions associated with lung cancer are due to tumor. However, there are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor. In these cases, fluid is non-bloody and is not an exudate. When these elements and clinical judgement dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be staged as T1, T2, or T3.

Regional lymph nodes (N)

NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumor

N2: Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
N3: Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant metastasis (M)

MX: Distant metastasis cannot be assessed
M0: No distant metastasis

M1: Distant metastasis present

Note: M1 includes separate tumor nodule(s) in a different lobe (ipsilateral or contralateral).

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Specify sites according to the following notations:

       BRA = brain              EYE = eye                HEP = hepatic
       LYM = lymph nodes        MAR = bone marrow        OSS = osseous
       OTH = other              OVR = ovary     PER = peritoneal
       PLE = pleura             PUL = pulmonary          SKI = skin
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AJCC stage groupings

Occult carcinoma

TX, N0, M0

Stage 0

Tis, N0, M0

Stage IA

T1, N0, M0

Stage IB

T2, N0, M0

Stage IIA

T1, N1, M0

Stage IIB

T2, N1, M0
T3, N0, M0

Stage IIIA

T1, N2, M0
T2, N2, M0
T3, N1, M0
T3, N2, M0

Stage IIIB

Any T, N3, M0
T4, Any N, M0

Stage IV

Any T, Any N, M1

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TREATMENT OPTION OVERVIEW

In non-small cell lung cancer (NSCLC), results of standard treatment are poor in all but the most localized cancers. All newly diagnosed patients with NSCLC are potential candidates for studies evaluating new forms of treatment. Surgery is the major potentially curative therapeutic option for this disease; radiotherapy can produce cure in a small minority and palliation in the majority of patients. In advanced-stage disease, chemotherapy offers modest improvements in median survival although overall survival is poor.[1,2] Where studied, chemotherapy has been reported to produce short-term improvement in disease-related symptoms. In one study, symptomatic relief with combination chemotherapy was significant but independent of objective response.[3,4] The impact of chemotherapy on quality of life requires more study.

Current areas under evaluation include combining local (surgery), regional (radiotherapy), and systemic (chemotherapy and immunotherapy) treatments and developing more effective systemic therapy. Several new agents, including paclitaxel (Taxol), docetaxel (Taxotere), topotecan, irinotecan, vinorelbine, and gemcitabine have been shown to be active in the treatment of advanced NSCLC. Chemoprevention of second primary cancers of the upper aerodigestive tract is also under active investigation in early-stage lung cancer.[5]

The designations in PDQ that treatments are "standard" or "under clinical evaluation" are not to be used as a basis for reimbursement determinations.

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OCCULT NON-SMALL CELL LUNG CANCER

TX, N0, M0

In occult lung cancer, a diagnostic evaluation often includes chest x-ray and selective bronchoscopy with close follow-up (e.g., computed tomography scan), when needed, to define the site and nature of the primary tumor; tumors discovered in this fashion are generally early stage and curable by surgery. After discovery of the primary tumor, treatment is determined by establishing the stage of the patient's tumor. Therapy is identical to that recommended for other non-small cell lung cancer patients with similar stage disease.

STAGE 0 NON-SMALL CELL LUNG CANCER

Tis, N0, M0

Stage 0 non-small cell lung cancer (NSCLC) is the same as carcinoma in situ of the lung. Because these tumors are by definition noninvasive and incapable of metastasizing, they should be curable with surgical resection; however, there is a high incidence of second primary cancers, many of which are unresectable. Endoscopic phototherapy with a hematoporphyrin derivative has been described as an alternative to surgical resection in carefully selected patients.[1-3] This investigational treatment seems to be most effective for very early central tumors that extend less than 1 centimeter within the bronchus.[2] Efficacy of this treatment modality in the management of early NSCLC remains to be proven.

Treatment options:

1. Surgical resection using the least extensive technique possible (segmentectomy or wedge resection) to preserve maximum normal pulmonary tissue since these patients are at high risk for second lung cancers.

2. Endoscopic photodynamic therapy.[2,3]

References:

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STAGE I NON-SMALL CELL LUNG CANCER

T1, N0, M0 or T2, N0, M0

Surgery is the treatment of choice for patients with stage I non-small cell lung cancer (NSCLC). Careful preoperative assessment of the patient's overall medical condition, especially the patient's pulmonary reserve, is critical in considering the benefits of surgery. The immediate postoperative mortality rate is age-related, but 3%-5% with lobectomy can be expected.[1] Patients with impaired pulmonary function may be considered for segmental or wedge resection of the primary tumor; the Lung Cancer Study Group has conducted a randomized study (LCSG-821) to compare lobectomy with limited resection for patients with stage I cancer of the lung. The results of this study show a reduction in local recurrence for patients

treated with lobectomy compared with those treated with limited excision but no significant difference in overall survival.[2] Similar results have been reported from a nonrandomized comparison of anatomic segmentectomy and lobectomy.[3] A survival advantage was noted with lobectomy for patients with tumors greater than 3 centimeters, but not for those with tumors smaller than 3 centimeters. However, the rate of local/regional recurrence was significantly less after lobectomy, regardless of primary tumor size. Another study of stage I patients showed that those treated with wedge or segment resections had a local recurrence rate of 50% (31 of 62) despite having undergone complete resections.[4] Exercise testing may aid in the selection of patients with impaired pulmonary function who can tolerate lung resection.[5] The availability of video-assisted thoracoscopic wedge resection permits limited resections in patients with poor pulmonary function who are not usually considered candidates for lobectomy.[6]

Inoperable patients with stage I disease and with sufficient pulmonary reserve may be considered for radiotherapy with curative intent. In one report of patients older than 70 years of age who had resectable lesions smaller than 4 centimeters but who were medically inoperable or who refused surgery, survival at 5 years following radiotherapy with curative intent was comparable to a historical control group of patients of similar age resected with curative intent.[7] In the two largest retrospective radiotherapy series, inoperable patients treated with definitive radiotherapy achieved 5-year survival rates of 10% and 27%. Both series found that patients with T1, N0 tumors had better outcomes, with 5-year survival rates of 60% and 32% in this subgroup.[8,9]

Primary radiotherapy should consist of approximately 6,000 cGy delivered with megavoltage equipment to the midplane of the known tumor volume using conventional fractionation. A boost to the cone-down field of the primary tumor is frequently used to further enhance local control. Careful treatment planning with precise definition of target volume and avoidance of critical normal structures to the extent possible is needed for optimal results and requires the use of a simulator.

Many patients treated surgically subsequently develop regional or distant metastases.[10] Therefore, patients should be considered for entry into clinical trials evaluating adjuvant treatment with chemotherapy or radiotherapy following surgery. Trials of adjuvant chemotherapy regimens have failed to demonstrate a consistent benefit. Smokers who undergo complete resection of stage I NSCLC are also at risk for second malignant tumors. In the Lung Cancer Study Group trial of 907 stage T1, N0 resected patients, the rate of nonpulmonary second cancers was 1.8% per year and 1.6% per year for new lung cancers.[11] Others have reported even higher risks of second tumors in long-term survivors, including rates of 10% for second lung cancers and 20% for all second cancers.[4] A randomized trial of vitamin A versus observation in resected stage I patients showed a trend toward decreased second primary cancers in the vitamin A arm with no difference in overall survival rates.[12] An ongoing intergroup clinical trial will evaluate the role of isotretinoin in the chemoprevention of second cancers in patients resected for stage I NSCLC.[13]

Treatment options:

1. Lobectomy or segmental, wedge, or sleeve resection as appropriate.

2. Radiotherapy with curative intent (for potentially resectable patients who have medical contraindications to surgery).

3. Clinical trials of adjuvant chemotherapy following resection.[14,15]

4. Adjuvant chemoprevention trials.[12,13]

5. Endoscopic photodynamic therapy (under clinical evaluation in highly selected T1, N0, M0 patients).[16]

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STAGE II NON-SMALL CELL LUNG CANCER

T1, N1, M0 or T2, N1, M0 or T3, N0, M0

Surgery is the treatment of choice for patients with stage II non-small cell lung cancer (NSCLC). Careful preoperative assessment of the patient's overall medical condition, especially the patient's pulmonary reserve, is critical in considering the benefits of surgery. The immediate postoperative mortality rate is age-related, but up to 5%-8% with pneumonectomy or 3%-5% with lobectomy can be expected.

Inoperable patients with stage II disease and with sufficient pulmonary reserve may be considered for radiotherapy with curative intent.[1] Among patients with excellent performance status, up to a 20% 3-year survival rate may be expected if a course of radiotherapy with curative intent can be completed. In the largest retrospective series reported to date, 152 patients with medically inoperable NSCLC treated with definitive radiotherapy achieved a 5-year overall survival rate of 10%; however, the 44 patients with T1 tumors achieved an actuarial disease-free survival rate of 60%. This retrospective study also suggested that improved disease-free survival was obtained with radiotherapy doses greater than 6,000 cGy.[2] Primary radiotherapy should consist of approximately 6,000 cGy delivered with megavoltage equipment to the midplane of the volume of known tumor using conventional fractionation. A boost to the cone-down field of the primary tumor is frequently used to further enhance local control. Careful treatment planning with precise definition of target volume and avoidance of critical normal structures to the extent possible is needed for optimal results and requires the use of a simulator.

Many patients treated surgically subsequently develop regional or distant metastases.[3] Therefore, patients should be considered for entry into clinical trials evaluating the use of adjuvant treatment with chemotherapy or radiotherapy following surgery.[4] One controlled trial has failed to demonstrate an overall survival benefit for patients with carefully staged squamous cell carcinoma receiving postoperative irradiation, although local recurrences were significantly reduced.[5] In two controlled trials in carefully staged, surgically resected patients, adjuvant combination chemotherapy with cisplatin, doxorubicin, and cyclophosphamide produced modestly increased disease-free survival and a trend toward improved overall survival, especially in the first year after surgery.[6,7] Based on these data, participation in clinical trials evaluating adjuvant chemotherapy after surgical resection should be encouraged.

Treatment options:

1. Lobectomy, pneumonectomy, or segmental, wedge, or sleeve resection as appropriate.

2. Radiotherapy with curative intent (for potentially operable patients who have medical contraindications to surgery).

3. Radiotherapy combined with curative surgery.[8]

4. Adjuvant chemotherapy combined with other modalities.[4,6-8]

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STAGE IIIA NON-SMALL CELL LUNG CANCER

Some citations in the text of this section are followed by a level of evidence. The PDQ editorial boards use a formal ranking system to help the reader judge the strength of evidence linked to the reported results of a therapeutic strategy. Refer to the PDQ levels of evidence summary for more information.

T1, N2, M0 or T2, N2, M0 or T3, N1, M0 or T3, N2, M0

Depending on clinical circumstances, the principal forms of treatment that are considered for patients with stage III non-small cell lung cancer (NSCLC) are radiotherapy, chemotherapy, surgery, and combinations of these modalities. Although the majority of these patients do not achieve a complete response to radiotherapy, there is a reproducible long-term survival benefit in 5%-10% of patients treated with standard fractionation to 6,000 cGy, and significant palliation often results. Patients with excellent performance status and those who require a thoracotomy to prove that surgically unresectable tumor is present are most likely to benefit from radiotherapy.[1] Because of the poor long-term results, these patients should be considered for clinical trials. Trials examining fractionation schedules, endobronchial laser therapy, brachytherapy, and combined modality approaches may lead to improvement in the control of this regional disease.[2] One prospective randomized clinical study showed that radiotherapy given as three daily fractions improved overall survival compared to radiotherapy given as one daily fraction.[3][Level of evidence: 1iiA]

The addition of chemotherapy to radiotherapy has been reported to improve survival in prospective clinical studies that have used modern cisplatin-based chemotherapy regimens.[4-7] A meta-analysis of patient data from 11 randomized clinical trials showed that cisplatin-based combinations plus radiotherapy resulted in 10% reduction in the risk of death compared with radiotherapy alone.[8] The optimal sequencing of modalities and schedule of drug administration remains to be determined and is under study in ongoing clinical trials.[9]

Patients with N2 disease apparent on chest radiograph and documented by biopsy or discovered by prethoracotomy exploration have a 5-year survival rate of only about 2%. The use of preoperative (neoadjuvant) chemotherapy has been shown to be effective in these clinical situations in two small randomized studies of a total of 120 patients with stage IIIa NSCLC.[10,11] The 58 patients randomized to three cycles of cisplatin-based chemotherapy followed by surgery had a median survival more than three times as long as patients treated with surgery but no chemotherapy in both these studies. Two additional single-arm studies have evaluated either two to four cycles of combination chemotherapy or combination chemotherapy plus chest irradiation for 211 patients with histologically confirmed N2 stage IIIa NSCLC.[12] Sixty-five percent to 75% of patients were able to have a resection of their cancer, and 27%-28% were alive at 3 years. These results are encouraging, and combined-modality therapy with neoadjuvant chemotherapy with surgery and/or chest radiotherapy should be considered for patients with good performance status who have stage IIIa NSCLC.

Although most retrospective studies suggest that postoperative radiotherapy can improve local control for node-positive patients whose tumors were resected, it remains controversial whether it can improve survival.[13,14] One controlled trial in patients with completely resected stage II or III squamous cell lung cancer failed to demonstrate a survival benefit for patients who received postoperative irradiation,

although local recurrences were significantly reduced.[15] In two controlled trials with carefully staged surgically resected patients, adjuvant combination chemotherapy with cisplatin, doxorubicin, and cyclophosphamide produced modestly increased disease-free survival and a trend toward improved survival, especially in the first year after surgery.[16-18] Based on these data, participation in clinical trials evaluating adjuvant chemotherapy after surgical resection should be encouraged.

No consistent benefit from any form of immunotherapy has been demonstrated thus far in the treatment of NSCLC.

Treatment options:

1. Surgery alone in highly selected cases.[19-21]
2. Chemotherapy combined with other modalities.[4-6,12,16-18]
3. Surgery and postoperative radiotherapy.[13,15,22]
4. Radiotherapy alone.[1,2]

Superior sulcus tumor (T3, N0 or N1, M0)

Another category that merits a special approach is that of superior sulcus tumors, a locally invasive problem usually with a reduced tendency for distant metastases. Consequently, local therapy has curative potential, especially for T3, N0 disease. Radiotherapy alone, radiotherapy preceded or followed by surgery, or surgery alone (in highly selected cases) may be curative in some patients, with a 5-year survival rate of 20% or more in some studies.[23] Patients with more invasive tumors of this area, or true Pancoast tumors, have a worse prognosis and generally do not benefit from primary surgical management. Follow-up surgery may be used to verify complete response in the radiotherapy field and to resect necrotic tissue.

Treatment options:

1. Radiotherapy and surgery.
2. Radiotherapy alone.
3. Surgery alone (selected cases).
4. Chemotherapy combined with other modalities.
5. Brachytherapy.[24]
6. Clinical trials of combined modality therapy.[22]

Chest wall tumor (T3, N0 or N1, M0)

Selected patients with bulky primary tumors that directly invade the chest wall can obtain long-term survival with surgical management provided that their tumor is completely resected.

Treatment options:

1. Surgery.[21,25]

2. Surgery and radiotherapy.

3. Radiotherapy alone.

4. Chemotherapy combined with other modalities.

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STAGE IIIB NON-SMALL CELL LUNG CANCER

Patients with stage IIIb non-small cell lung cancer (NSCLC) do not benefit from surgery alone and are best managed by initial chemotherapy, chemotherapy plus radiotherapy, or radiotherapy alone, depending

on sites of tumor involvement and performance status. Most patients with excellent performance status should be considered for combined modality therapy. However, patients with malignant pleural effusion are rarely candidates for radiotherapy, and should generally be treated similarly to stage IV patients (see separate section of this summary on treatment of stage IV disease). Many randomized studies of unresectable patients with stage III NSCLC show that treatment with neoadjuvant or concurrent cisplatin-based chemotherapy and chest irradiation is associated with improved survival compared to treatment with radiotherapy alone.[1-5] A meta-analysis of patient data from 11 randomized clinical trials showed that cisplatin-based combinations plus radiotherapy resulted in 10% reduction in the risk of death compared with radiotherapy alone.[6]

Patients with stage IIIb disease with poor performance status are candidates for chest irradiation to palliate pulmonary symptoms (e.g., cough, shortness of breath, or local chest pain). No consistent benefit from any form of immunotherapy has been demonstrated thus far.

T4 or N3, M0

An occasional patient with supraclavicular node involvement who is otherwise a good candidate for irradiation with curative intent will survive 3 years. Although the majority of these patients do not achieve a complete response to radiotherapy, significant palliation often results. Patients with excellent performance status and those who are found to have advanced-stage disease at the time of resection are most likely to benefit from radiotherapy.[7] Adjuvant systemic chemotherapy with radiotherapy has been tested in randomized trials for patients with inoperable or unresectable locoregional NSCLC.[1-3,8] Some patients have shown a modest survival advantage with adjuvant chemotherapy. The addition of chemotherapy to radiotherapy has been reported to improve long-term survival in some,[1,3,4] but not all,[9] prospective clinical studies. A meta-analysis of patient data from 54 randomized clinical trials showed an absolute survival benefit of 4% at 2 years with the addition of cisplatin-based chemotherapy to radiotherapy.[10] One study showed improvement in local control and survival when cisplatin was given daily with concurrent radiotherapy but not when it was given weekly.[4] It is not yet clear whether the schedule of drug administration is responsible for the variation in results; the optimal sequencing of modalities remains to be determined and is under study in ongoing clinical trials.[11]
Because of the poor overall results, these patients should be considered for clinical trials; trials examining fractionation schedules, radiosensitizers, radiolabeled antibodies, and combined modality approaches may lead to improvement in the control of regional disease.
Patients with NSCLC can present with superior vena cava syndrome. Refer to the PDQ supportive care summary on superior vena cava syndrome for more information. Regardless of stage, this problem should generally be managed with radiotherapy with or without chemotherapy.
Treatment options:

1. Radiotherapy alone.

2. Chemotherapy combined with radiotherapy.[1-3,8]

3. Chemotherapy and concurrent radiotherapy followed by resection.[12,13]

4. Chemotherapy alone.

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STAGE IV NON-SMALL CELL LUNG CANCER

Any T, any N, M1

Cisplatin-containing and carboplatin-containing combination chemotherapy regimens produce objective response rates (including a few complete responses) that are higher than those achieved with single-agent chemotherapy. Although toxic effects may vary, outcome is similar with most cisplatin-containing regimens; a randomized trial comparing five cisplatin-containing regimens showed no significant difference in response, duration of response, or survival.[1] Patients with good performance status and a limited number of sites of distant metastases have superior response and survival when given chemotherapy when compared to other patients.[2] A prospective randomized comparison of vinorelbine

plus cisplatin versus vindesine plus cisplatin versus single agent vinorelbine has reported improved response rate (30%) and median survival (40 weeks) with the vinorelbine plus cisplatin regimen.[3] Two small phase II studies reported that paclitaxel (Taxol) has single-agent activity in stage IV patients, with response rates in the range of 21%- 24%.[4,5] Reports of paclitaxel combinations have shown relatively high response rates, significant 1 year survival, and palliation of lung cancer symptoms.[6] With the paclitaxel plus carboplatin regimen, response rates have been in the range of 27%-53% with 1-year survival rates of 32%-54%.[6,7] The combination of cisplatin and paclitaxel was shown to have a higher response rate and higher 1 year survival rate than the combination of cisplatin and etoposide.[8] Additional clinical studies should better define the role of these newer combination chemotherapy regimens in the treatment of advanced non- small cell lung cancer.[8] Meta-analyses have shown that chemotherapy produces modest benefits in short-term survival compared to supportive care alone in patients with inoperable stages IIIb and IV disease.[9-11]

Although these results support further evaluation of chemotherapeutic approaches for both metastatic and locally advanced non-small cell lung cancer (NSCLC), efficacy of current programs is such that no specific regimen can be regarded as standard therapy. Appropriate patients should be encouraged to participate in clinical trials. Outside of a clinical trial setting, chemotherapy should be given only to patients with good performance status and evaluable tumor lesions who desire such treatment after being fully informed of its anticipated risks and limited benefits.
Radiotherapy may be effective in palliating symptomatic local involvement with NSCLC such as tracheal, esophageal, or bronchial compression, bone or brain metastases, pain, vocal cord paralysis, hemoptysis, or superior vena cava syndrome. In some cases, endobronchial laser therapy and/or brachytherapy has been used to alleviate proximal obstructing lesions.[12] Such therapeutic intervention may be critical in the prolongation of an acceptable lifestyle in an otherwise functional patient. In the rare patient with synchronous presentation of a resectable primary tumor in the lung and a single brain metastasis, surgical resection of the solitary brain lesion is indicated with resection of the primary tumor and appropriate postoperative chemotherapy and/or irradiation of the primary tumor site and with postoperative whole-brain irradiation delivered in daily fractions of 180-200 cGy to avoid long-term toxic effects to normal brain tissue.[13,14]
In asymptomatic patients kept under close observation, treatment may often be appropriately deferred until symptoms or signs of progressive tumor develop.

Treatment options:

1. External-beam radiotherapy, primarily for palliative relief of local symptomatic tumor growth.

2. Chemotherapy. The following regimens produce similar survival outcomes: cisplatin plus vinblastine.[1] cisplatin plus vinblastine plus mitomycin.[15] cisplatin plus vinorelbine.[3] cisplatin plus vindesine.[3] cisplatin plus paclitaxel.[8] carboplatin plus paclitaxel.[6,7]

3. Clinical trials evaluating the role of new chemotherapy regimens. Refer to the clinical trials section of PDQ for a list of clinical trials. The clinical trials in PDQ are also available on CancerNet (http://cancernet.nci.nih.gov/).

4. Endobronchial laser therapy and/or brachytherapy for obstructing lesions.[12]

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RECURRENT NON-SMALL CELL LUNG CANCER

Many patients with recurrent non-small cell lung cancer (NSCLC) are eligible for clinical trials. Radiotherapy may provide excellent palliation of symptoms from a localized tumor mass.
Patients who present with a solitary cerebral metastasis after resection of a primary NSCLC lesion and who have no evidence of extracranial tumor can achieve prolonged disease-free survival with surgical excision of the brain metastasis and postoperative whole-brain irradiation.[1,2] Unresectable brain metastases in this setting may be treated radiosurgically.[3] Because of the small potential for long-term survival, radiotherapy should be delivered by conventional methods in daily doses of 180-200 cGy, while higher daily doses over a shorter period of time (hypofractionated schemes) should be avoided because of

the high risk of toxic effects observed with such treatments.[4] Most patients not suitable for surgical resection should receive conventional whole-brain radiotherapy. Selected patients with good performance status and small metastases can be considered for stereotactic radiosurgery.[5]
Approximately one half of patients treated with resection and postoperative radiotherapy will develop recurrence in the brain; some of these patients will be suitable for additional treatment.[6] In those selected patients with good performance status and without progressive metastases outside of the brain, treatment options include reoperation or stereotactic radiosurgery.[3,6] For most patients, conventional radiotherapy can be considered; however, the palliative benefit of this treatment is limited.[7]
A solitary pulmonary metastasis from an initially resected bronchogenic carcinoma is unusual. The lung is frequently the site of second primary malignancies in patients with primary lung cancers. Determining whether the new lesion is a new primary cancer or a metastasis may be difficult. Studies have indicated that in the majority of patients the new lesion is a second primary tumor, and following resection some patients may achieve long-term survival. Thus, if the first primary tumor has been controlled, the second primary tumor should be resected if possible.[8,9]
The use of chemotherapy has produced objective responses and small improvement in survival for patients with metastatic disease.[10] In studies that have examined symptomatic response, improvement in subjective symptoms has been reported to occur more frequently than objective response.[11,12]
Informed patients with good performance status and symptomatic recurrence can be offered treatment with a cisplatin-based chemotherapy regimen for palliation of symptoms.

Treatment options:

1. Palliative radiotherapy.

2. Chemotherapy alone.

3. Surgical resection of isolated cerebral metastasis (highly selected patients).[6]

4. Laser therapy or interstitial radiotherapy for endobronchial lesions.[13]

5. Stereotactic radiosurgery (highly selected patients).[3,5,14]

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TEXTO 11: Treatment summaries for health professionals (QDT3)

---------- SMALL CELL LUNG CANCER ----------

********** GENERAL INFORMATION

Without treatment, small cell carcinoma of the lung has the most aggressive clinical course of any type of pulmonary tumor, with median survival from diagnosis of only 2-4 months. Compared with other cell types of lung cancer, small cell carcinoma has a greater tendency to be widely disseminated by the time of diagnosis, but is much more responsive to chemotherapy and irradiation.

Because of its propensity for distant metastases, localized forms of treatment, such as surgical resection or radiotherapy, rarely produce long-term survival [1]. With incorporation of current chemotherapy regimens into the treatment program, however, survival is unequivocally prolonged, with at least a 4- to 5-fold improvement in median survival compared with patients who are given no therapy. Furthermore, about 10% of the total population of patients remain free of disease over two years from the start of therapy, the time period during which most relapses occur. However, even these patients are at risk of dying from lung cancer (both small and non-small cell types) [2]. The overall survival at 5 years is 5%-10% [2-4].

At the time of diagnosis, approximately 40% of patients with small cell carcinoma will have tumor confined to the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes. These patients are designated as having limited stage disease, and most 2-year disease-free survivors come from this group. In limited stage disease, median survival of 16-24 months with current forms of treatment can reasonably be expected [5-8]. A small proportion of patients with limited stage disease may benefit from surgery with or without adjuvant chemotherapy; these patients have an even better prognosis. Patients with tumor that has spread beyond the supraclavicular areas are said to have extensive stage disease and have a worse prognosis than patients with limited stage. Median survival of 6-12 months is reported with currently available therapy, but long-term disease-free survival is rare.

The pretreatment prognostic factors which consistently predict for prolonged survival include good performance status, female gender, and limited stage disease [3,9,10]. Patients with involvement of the central nervous system or liver at the time of diagnosis have a significantly worse outcome [3,9-11]. In general, patients who are confined to bed tolerate aggressive forms of treatment poorly, have increased morbidity, and rarely attain 2-year disease-free survival. However, patients with poor performance status can often derive significant palliative benefit and prolongation of survival from treatment.

Regardless of stage, the current prognosis for patients with small cell lung cancer is unsatisfactory even though considerable improvements in diagnosis and therapy have been made over the past 10-15 years. Therefore, all patients with this type of cancer may appropriately be considered for inclusion in clinical trials at the time of diagnosis.

<References>

********** CELLULAR CLASSIFICATION

Review of pathologic material by an experienced lung cancer pathologist is important prior to initiating treatment of any patient with small cell lung cancer. The intermediate subtype of small cell carcinoma and the more readily recognized lymphocyte-like or "oat cell" subtype are equally responsive to treatment.

The current classification of subtypes of small cell lung cancer are:[1]

- small cell carcinoma;
- mixed small cell/large cell carcinoma;

combined small cell carcinoma (small cell lung cancer combined with neoplastic squamous and/or glandular components).

There is increasing evidence that light microscopy has some limitations as a means of classifying bronchogenic carcinomas, particularly small cell carcinomas. Electron microscopy, which can detect neuroendocrine granules, may help to differentiate between small cell and non-small cell cancers [2].
Neuroendocrine carcinomas of the lung represent a spectrum of disease. At one extreme is small cell lung cancer, which has a poor prognosis. At the other extreme are bronchial carcinoids, with an excellent prognosis after surgical excision [3]. Between these extremes is an unusual entity called well-differentiated neuroendocrine carcinoma of the lung [4]. It has been referred to as malignant carcinoid, metastasizing bronchial adenoma, pleomorphic carcinoid, nonbenign carcinoid tumor, and atypical carcinoid. Like small cell lung cancer, it occurs primarily in cigarette smokers, but it metastasizes less frequently. The 5-year survival rate is greater than 50% in some series, and surgical cure appears possible in most stage I patients. Careful diagnosis is important, however, since the differential pathologic diagnosis from small cell lung cancer may be difficult.

<References>

********** STAGE INFORMATION

Staging procedures do not currently have a major impact on treatment of small cell lung cancer since patients should initially receive combination chemotherapy regardless of the extent of tumor dissemination. However, determining the stage of cancer by nonsurgical means allows a better assessment of prognosis and identifies sites of tumor that can be evaluated for response. In clinical situations where the choice of treatment is affected by stage, particularly when chest irradiation or surgical excision is added to chemotherapy alone for limited stage patients, results of the staging process have therapeutic implications. Staging procedures commonly used to document distant metastases include bone marrow examination, computed tomographic or magnetic resonance imaging scans of the brain, computerized tomographic scans of the chest and the abdomen, and radionuclide bone scans.

Because occult or overt metastatic disease is present at diagnosis in most patients, survival is usually not affected by small differences in the amount of locoregional tumor involvement. Therefore, the detailed TNM staging system developed for lung cancer by the American Joint Committee on Cancer (AJCC) is not commonly employed in patients with small cell carcinoma. A simple 2-stage system developed by the Veterans Administration Lung Cancer Study Group is most commonly used.

The international staging system, which is outlined in detail in the PDQ summary for non-small cell lung cancer, may also be used, particularly for the small minority of patients who may be candidates for surgical resection.

----- Limited stage
Limited stage small cell lung cancer means tumor confined to the hemithorax of origin, the mediastinum, and the supraclavicular nodes, which can be encompassed within a "tolerable" radiotherapy port. There is no universally accepted definition of this term, and patients with pleural effusion, massive pulmonary tumor, and contralateral supraclavicular nodes have been both included within and excluded from limited stage by various groups.

----- Extensive stage
Extensive stage small cell lung cancer means tumor that is too widespread to be included within the definition of limited stage disease [1,2].

<References>

********** TREATMENT OPTION OVERVIEW

In small cell lung cancer, the majority of patients die of their tumor despite state-of-the-art treatment. Most of the improvements in survival in small cell lung cancer are attributable to clinical trials which have attempted to improve on the best available, accepted therapy. Patient entry into such studies is highly desirable.

Methods under clinical evaluation in small cell lung cancer include adding chest radiation to chemotherapy regimens, varying drug doses in current regimens, alternating different combinations of chemotherapy, using different schedules of chemotherapeutic agents, and using new drug regimens composed of standard and new agents.

Prospective randomized trials have not demonstrated a consistent survival advantage for patients treated with higher doses of chemotherapy [1-3]. Even chemotherapy of the intensity used in autologous bone marrow transplant regimens has not clearly been shown to improve survival in patients with small cell lung cancer [4,5].

The designations in PDQ that treatments are "standard" or "under clinical evaluation" are not to be used as a basis for reimbursement determinations.

<References>

********** LIMITED STAGE SMALL CELL LUNG CANCER

In patients with small cell lung cancer, combination chemotherapy produces results that are clearly superior to single-agent treatment, and moderately intensive doses of drugs are superior to doses that produce only minimal or mild hematologic toxicity. Current programs yield overall objective response rates of 65%-90% and complete response rates of 45%-75%. Because of the frequent presence of occult metastatic disease, chemotherapy is the cornerstone of treatment of limited stage small cell lung cancer. Combinations containing two or more drugs are needed for maximal effect.

Mature results of prospective randomized trials suggest that combined modality therapy produces a modest but significant improvement in survival compared with chemotherapy alone. Two meta-analyses showed an improvement in 3-year survival rates of about 5% for those receiving chemotherapy and radiotherapy compared to those receiving chemotherapy alone [1,2]. Most of the benefit occurred in patients less than 65 years of age. Combined modality treatment is associated with increased morbidity and, in some trials, increased treatment-related mortality from pulmonary and hematologic toxic effects; proper administration requires close collaboration between medical and radiation oncologists [3]. In general, those studies showing a positive effect for combined modality therapy employed thoracic irradiation early in the course of treatment, concurrently with chemotherapy [3-6].

Studies strongly suggest that minimal tumor doses in the range of 4,000 to 4,500 cGy or more (standard fractionation) are necessary to effectively control tumors in the thorax.

The combination of etoposide and cisplatin chemotherapy with concurrent chest radiotherapy has now been used in multiple single institutional studies and in cooperative group studies. These studies have consistently achieved median survivals of 18-24 months and 40%-50% 2-year survival with less than 3% treatment-related mortality [3-9]. Once daily and twice daily chest radiation schedules have been used in regimens with etoposide and cisplatin, and a randomized study has not shown a significant survival advantage for patients treated with twice daily chest radiotherapy compared to once daily [9]. The current standard treatment of patients with limited stage small cell lung cancer should be a combination containing etoposide and cisplatin plus chest radiotherapy administered during the first or second cycle of chemotherapy administration.

The relative effectiveness of 2-5 drug regimens and different schedules of chest radiotherapy appear to be similar. A representative selection of regimens incorporating chemotherapy plus chest radiotherapy are listed below. The use of alternating chemotherapy regimens has not proven more effective than the consistent administration of a single regimen [3,6,8-12]. The optimal duration of chemotherapy for patients with limited stage small cell lung cancer is not clearly defined but there is no improvement in survival after the duration of drug administration exceeds 3-6 months [3,8,9,13]. There is no evidence from randomized trials that maintenance chemotherapy prolongs survival for patients with limited stage small cell lung cancer [10,14].

Patients presenting with superior vena cava syndrome are treated with combination chemotherapy with or without radiation therapy [15,16]. A small minority of limited stage patients with adequate pulmonary function and with tumor pathologically confined to the lung of origin, or the lung and ipsilateral hilar lymph nodes, may possibly benefit from surgical resection with or without adjuvant chemotherapy [17-20].

Patients with small cell lung cancer treated with chemotherapy with or without chest irradiation who have achieved a complete remission can be considered for administration of prophylactic cranial irradiation (PCI). Patients whose cancer can be controlled outside the brain have a 60% actuarial risk of developing central nervous system metastases within 2-3 years after starting treatment [21,22]. The majority of these patients relapse only in their brain and nearly all of those who relapse in their central nervous system die of their cranial metastases [3,8,22]. The risk of developing central nervous system metastases can be reduced by more than 50% by the administration of PCI in doses of 2400 cGy [22]. Retrospective studies have shown that long-term survivors of small cell lung cancer (>2 years from the start of treatment) have a high incidence of central nervous system impairment [23-25]. However, prospective studies have shown that patients treated with PCI do not have detectably different neuropsychological function than patients not treated [22]. In addition, the majority of patients with small cell lung cancer have neuropsychological abnormalities present before the start of cranial irradiation and have no detectable decline in their neurological status up to 2 years after the start of their cranial irradiation [26]. Patients treated for small cell lung cancer continue to have declining neuropsychologic function after 2 years from the start of treatment [23-25]. Therefore, additional neuropsychologic testing of patients beyond 2 years from the start of treatment will be needed before concluding that PCI does not contribute to the decline in intellectual function.

Treatment options:

Standard:

1 Combination chemotherapy with one of the following regimens and chest irradiation (with or without PCI given to patients with complete responses): The following regimens produce similar survival outcomes: EC: etoposide + cisplatin + 4000-4500 cGy chest radiotherapy [3,7-9]. ECV: etoposide + cisplatin + vincristine + 4500 cGy chest radiotherapy [5].

2 Combination chemotherapy (with or without PCI in patients with complete responses), especially in patients with impaired pulmonary function or poor performance status.

3 Surgical resection followed by chemotherapy or chemotherapy plus chest radiotherapy (with or without PCI in patients with complete responses) for patients in highly selected cases [17-20].

Under clinical evaluation:

Areas of active clinical evaluation in limited stage small cell lung cancer include new drug regimens, variation of drug doses in current regimens, surgical resection of the primary tumor, new radiotherapy schedules and techniques (e.g, 3-dimensional treatment planning), and timing of thoracic radiation [27-29].

<References>

********** EXTENSIVE STAGE SMALL CELL LUNG CANCER

As in limited stage small cell carcinoma, chemotherapy should be given as multiple agents in doses associated with at least moderate toxicity in order to produce the best results in extensive stage disease. Doses and schedules used in current programs yield overall response rates of 70%-85% and complete response rates of 20%-30% in extensive stage disease. Since overt disseminated disease is present, combination chemotherapy is the cornerstone of treatment of this stage of small cell lung cancer. Combinations containing two or more drugs are needed for maximal benefit.

The relative effectiveness of many two- to four-drug combination programs appears similar, and there are a large number of potential combinations. Therefore, a representative selection of regimens that have been found to be effective by at least two independent groups has been provided. Some physicians have administered two of these or other regimens in alternating sequences, but there is no proof that this strategy yields substantial survival improvement [1-3]. Optimal duration of chemotherapy is not clearly defined, but there is no obvious improvement in survival when the duration of drug administration exceeds 6 months [4,5]. There is no clear evidence from reported data that maintenance chemotherapy will improve survival duration [6-9].

Combination chemotherapy plus chest irradiation does not appear to improve survival compared with chemotherapy alone in extensive stage small cell lung cancer. However, radiotherapy plays an extremely important role in palliation of symptoms of the primary tumor and of metastatic disease, particularly brain, epidural, and bone metastases.

Chest irradiation is sometimes given for superior vena cava syndrome, but chemotherapy alone (with irradiation reserved for nonresponding patients) is appropriate initial treatment. Brain metastases are appropriately treated with whole-brain radiotherapy. However, intracranial metastases from small cell carcinoma may respond to chemotherapy as readily as metastases in other organs [9,10].

Patients with small cell lung cancer treated with chemotherapy with or without chest irradiation who have achieved a complete remission can be considered for administration of prophylactic cranial irradiation (PCI). Patients whose cancer can be controlled outside the brain have a 60% actuarial risk of developing central nervous system metastases within 2-3 years after starting treatment [11,12]. The majority of these patients relapse only in their brain and nearly all of those who relapse in their central nervous system die of their cranial metastases [12-14]. The risk of developing central nervous system metastases can be reduced by more than 50% by the administration of PCI in doses of 2400 cGy [12]. Retrospective studies have shown that long-term survivors of small cell lung cancer (>2 years from the start of treatment) have a high incidence of central nervous system impairment [15-17]. However, prospective studies have shown that patients treated with PCI do not have detectably different neuropsychological function than patients not treated [12]. In addition, the majority of patients with small cell lung cancer have neuropsychological abnormalities present before the start of cranial irradiation and have no detectable decline in their neurological status up to 2 years after the start of their cranial irradiation [18]. Patients treated for small cell lung cancer continue to have declining neuropsychologic function after 2 years from the start of treatment [15-17]. Therefore, additional neuropsychologic testing of patients beyond 2 years from the start of treatment will be needed before concluding that PCI does not contribute to the decline in intellectual function.

Many more patients with extensive stage small cell carcinoma have greatly impaired performance status at the time of diagnosis when compared to patients with limited stage disease. Such patients have a poor prognosis and tolerate aggressive chemotherapy or combined modality therapy poorly. Single-agent intravenous, oral, and low-dose biweekly regimens have been developed for these patients,[19-23]. However, prospective randomized studies have shown that patients with a poor prognosis who are treated with conventional regimens live longer than those treated with the single-agent or low-dose regimens [22-24].

Treatment options:

Standard:

1 Combination chemotherapy with one of the following regimens with or without PCI given to patients with complete responses: The following regimens produce similar survival outcomes: CAV: cyclophosphamide + doxorubicin + vincristine [25,26]. CAE: cyclophosphamide + doxorubicin + etoposide [27]. EP or EC: etoposide + cisplatin or carboplatin [28,29]. ICE: ifosfamide + carboplatin + etoposide [30].

Other regimens appear to produce similar survival outcomes but have been studied less extensively or are in less common use, including:

cyclophosphamide + methotrexate + lomustine [31].
cyclophosphamide + methotrexate + lomustine + vincristine [32].
cyclophosphamide + doxorubicin + etoposide + vincristine [33].
CEV: cyclophosphamide + etoposide + vincristine [34].
single-agent etoposide or teniposide [19,20].

2 Radiotherapy to sites of metastatic disease unlikely to be immediately palliated by chemotherapy, especially brain, epidural, and bone metastases.

3 Identification of effective new agents is difficult in patients who have previously been treated with standard chemotherapy because response rates to agents, even of known efficacy, are known to be lower than in previously untreated patients. This situation led to the suggestion that patients with extensive disease who are medically stable be treated with new agents under evaluation, with provisions for early change to standard combination therapy if there is no response [35]. Such a strategy has been shown to be feasible, with survival comparable to survival with initial standard therapy, as long as the patients with extensive disease are carefully chosen [36-38]. A variety of other strategies have been proposed, depending on the activity of the new agent in other tumors, in preclinical small cell lung cancer models, or the activity of drug analogs [39]. Active single agents undergoing further evaluation include teniposide, paclitaxel, and topotecan [19,40,41].

Under clinical evaluation:

Areas of active clinical evaluation in extensive stage small cell lung cancer include evaluation of new drug regimens, variation of drug doses, alternative drug schedules, and bone marrow transplants [42,43].

<References>

********** RECURRENT SMALL CELL LUNG CANCER

The prognosis for small cell lung carcinoma that has progressed despite chemotherapy is exceedingly poor regardless of stage. Expected median survival is 2-3 months. These patients should be considered for palliative therapy or clinical trials. Patients who are primarily resistant to chemotherapy and those who have received multiple chemotherapy regimens rarely respond to additional treatment. However, patients who have initially responded and relapsed more than 6 months following initial treatment are more likely to respond to additional chemotherapy [1-8].

Some patients with intrinsic endobronchial obstructing lesions or extrinsic compression due to tumor have achieved successful palliation with endobronchial laser therapy (for endobronchial lesions only) and/or brachytherapy [9]. Expandable metal stents can be safely inserted under local anesthesia via the bronchoscope, resulting in improved symptoms and pulmonary function in patients with malignant airways obstruction [10]. Patients with progressive intrathoracic tumor after failing initial chemotherapy can achieve significant tumor responses, palliation of symptoms, and short-term local control with external-beam

radiotherapy. However, only the rare patient will experience long-term survival following "salvage" radiotherapy [11].

Patients with central nervous system recurrences can often obtain palliation of symptoms with radiotherapy and/or additional chemotherapy. The majority of patients treated with radiotherapy obtain objective responses and improvement following radiotherapy [12]. A retrospective review showed that 43% of patients treated with additional chemotherapy at the time of CNS relapse respond to second-line chemotherapy [13].

Treatment options:

1 Palliative radiotherapy [11].

2 Salvage chemotherapy can provide some palliative benefit for patients previously sensitive to standard chemotherapy [2-5,8].

3 Local palliation with endobronchial laser therapy, endobronchial stents, and/or brachytherapy [9,10].

4 Clinical trials of phase I or phase II drugs. Refer to the PDQ protocol directory for active clinical trials for patients with recurrent small cell lung cancer.

<References>

TEXTO 12: Treatment summaries for patients (QPT1)

---------- MALIGNANT MESOTHELIOMA ----------

********** OVERVIEW OF PDQ

----- What is PDQ?

PDQ is a computer system that gives up-to-date information on cancer and its prevention, detection, treatment, and supportive care. It is a service of the National Cancer Institute (NCI) for people with cancer and their families and for doctors, nurses, and other health care professionals.

To ensure that it remains current, the information in PDQ is reviewed and updated each month by experts in the fields of cancer treatment, prevention, screening, and supportive care. PDQ also provides information about research on new treatments (clinical trials), doctors who treat cancer, and hospitals with cancer programs. The treatment information in this summary is based on information in the PDQ summary for health professionals on this cancer.

----- How to use PDQ

PDQ can be used to learn more about current treatment of different kinds of cancer. You may find it helpful to discuss this information with your doctor, who knows you and has the facts about your disease. PDQ can also provide the names of additional health care professionals who specialize in treating patients with cancer.

Before you start treatment, you also may want to think about taking part in a clinical trial. PDQ can be used to learn more about these trials. A clinical trial is a research study that attempts to improve current treatments or finds information on new treatments for patients with cancer. Clinical trials are based on past studies and information discovered in the laboratory. Each trial answers certain scientific questions in order to find new and better ways to help patients with cancer. Information is collected about new treatments, their risks, and how well they do or do not work. When clinical trials show that a new treatment is better than the treatment currently used as "standard" treatment, the new treatment may become the standard treatment. Listings of current clinical trials are available on PDQ. Many cancer doctors who take part in clinical trials are listed in PDQ.

To learn more about cancer and how it is treated, or to learn more about clinical trials for your kind of cancer, call the National Cancer Institute's Cancer Information Service. The number is 1-800-4-CANCER (1-800-422-6237); TTY at 1-800-332-8615. The call is free and a trained information specialist will be available to answer cancer-related questions.

PDQ is updated whenever there is new information. Check with the Cancer Information Service to be sure that you have the most up-to-date information----------.

********** DESCRIPTION

----- What is malignant mesothelioma?

Malignant mesothelioma, a rare form of cancer, is a disease in which cancer (malignant) cells are found in the sac lining the chest (the pleura) or abdomen (the peritoneum). Most people with malignant mesothelioma have worked on jobs where they breathed asbestos.

A doctor should be seen if a person has shortness of breath, pain in the chest, or pain or swelling in the abdomen. If there are symptoms, the doctor may order an x-ray of the chest or abdomen.

The doctor may look inside the chest cavity with a special instrument called a thoracoscope. A cut will be made through the chest wall and the thoracoscope will be put into the chest between two ribs. This test, called thoracoscopy, is usually done in the hospital. Before the test, the patient will be given a local anesthetic (a drug that causes a loss of feeling for a short period of time). Some pressure may be felt, but usually there is no pain.

The doctor may also look inside the abdomen (peritoneoscopy) with a special tool called a peritoneoscope. The peritoneoscope is put into an opening made in the abdomen. This test is also usually done in the hospital. Before the test is done, a local anesthetic will be given.

If tissue that is not normal is found, the doctor will need to cut out a small piece and have it looked at under a microscope to see if there are any cancer cells. This is called a biopsy. Biopsies are usually done during the thoracoscopy or peritoneoscopy.

The chance of recovery (prognosis) depends on the size of the cancer, where the cancer is, how far the cancer has spread, how the cancer cells look under the microscope, how the cancer responds to treatment, and the patient's age.

********** STAGE EXPLANATION

----- Stages of malignant mesothelioma

Once malignant mesothelioma is found, more tests will be done to find out if cancer cells have spread to other parts of the body. This is called staging. A doctor needs to know the stage of the cancer to plan treatment. The following stages are used for malignant mesothelioma.

----- Localized malignant mesothelioma
Stage I: The cancer is found in the lining of the chest cavity near the lung and heart or in the diaphragm or the lung.

----- Advanced malignant mesothelioma

Stage II: The cancer has spread beyond the lining of the chest to lymph nodes in the chest.

Stage III: Cancer has spread into the chest wall, center of the chest, heart, through the diaphragm, or abdominal lining, and in some cases into nearby lymph nodes.

Stage IV: Cancer has spread to distant organs or tissues.

----- Recurrent malignant mesothelioma
Recurrent disease means that the cancer has come back (recurred) after it has been treated. It may come back in the lining of the chest or abdomen or in another part of the body.

********** TREATMENT OPTION OVERVIEW

----- How malignant mesothelioma is treated

There are treatments for all patients with malignant mesothelioma. Three kinds of treatment are used:

surgery (taking out the cancer) /
radiation therapy (using high-dose x-rays or other high-energy rays to kill cancer cells) /
chemotherapy (using drugs to fight the cancer).

Surgery is a common treatment of malignant mesothelioma. The doctor may remove part of the lining of the chest or abdomen and some of the tissue around it. Depending on how far the cancer has spread, a lung also may be removed in an operation called a pneumonectomy. Sometimes part of the diaphragm, the muscle below the lungs that helps with breathing, is also removed.
Radiation therapy uses high-energy x-rays to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external radiation therapy) or from putting materials that produce radiation (radioisotopes) through thin plastic tubes in the area where the cancer cells are found (internal radiation therapy).

If fluid has collected in the chest or abdomen, the doctor may drain the fluid out of the body by putting a needle into the chest or abdomen and using gentle suction to remove the fluid. If fluid is removed from the chest, this is called thoracentesis. If fluid is removed from the abdomen, this is called paracentesis. The doctor may also put drugs through a tube into the chest to prevent more fluid from accumulating.

Chemotherapy uses drugs to kill cancer cells. Chemotherapy may be taken by pill, or it may be put into the body by a needle in the vein or muscle. Chemotherapy is called a systemic treatment because the drug enters the bloodstream, travels through the body, and can kill cancer cells throughout the body. In mesothelioma, chemotherapy may be put directly into the chest (intrapleural chemotherapy).

Intraoperative photodynamic therapy is a new type of treatment that uses special drugs and light to kill cancer cells during surgery. A drug that makes cancer cells more sensitive to light is injected into a vein several days before surgery. During surgery to remove as much of the cancer as possible, a special light is used to shine on the pleura. This treatment is being studied for early stages of mesothelioma in the chest.

----- Treatment by stage

Treatment depends on where the cancer is, how far it has spread, and the patient's age and general health.

Standard treatment may be considered because of its effectiveness in patients in past studies, or participation in a clinical trial may be considered. Not all patients are cured with standard therapy and some standard treatments may have more side effects than are desired. For these reasons, clinical trials are designed to find better ways to treat cancer patients and are based on the most up-to-date information. Clinical trials are ongoing in many parts of the country for many patients with malignant mesothelioma. To learn more about clinical trials, call the Cancer Information Service at 1-800-4-CANCER (1-800-422-6237); TTY at 1-800-332-8615.

********** LOCALIZED MALIGNANT MESOTHELIOMA (STAGE I)

If the cancer is only in one place in the chest or abdomen, treatment will probably be surgery to remove part of the pleura and some of the tissue around it.

If the cancer is found in a larger part of the pleura, treatment may be one of the following:

1 Surgery to remove the pleura and the tissue near it to relieve symptoms, with or without radiation therapy after surgery.

2 Surgery to remove sections of the pleura, the lung, part of the diaphragm, and part of the lining around the heart.

3 External beam radiation therapy to relieve symptoms.

4 A clinical trial of surgery followed by chemotherapy given inside the chest.

5 A clinical trial of surgery, radiation therapy, and/or chemotherapy.

********** ADVANCED MALIGNANT MESOTHELIOMA (STAGES II, III, AND IV)

Treatment may be one of the following:

1 Draining of fluid in the chest or abdomen (thoracentesis or paracentesis) to reduce discomfort. Drugs also may be put into the chest or abdomen to prevent further collection of fluid.

2 Surgery to relieve symptoms.

3 Radiation therapy to relieve symptoms.

4 Chemotherapy.

5 A clinical trial of surgery, radiation therapy, and chemotherapy.

6 Chemotherapy given in the chest or abdomen.

********** RECURRENT MALIGNANT MESOTHELIOMA

Treatment depends on many factors, including where the cancer came back and what treatment the patient received before. Clinical trials are testing new treatments.

<TO LEARN MORE>

TEXTO 13: Treatment summaries for patients (QPT2)

---------- NON-SMALL CELL LUNG CANCER ----------

********** DESCRIPTION
----- What is non-small cell lung cancer?

Lung cancers can be divided into two types: small cell lung cancer and non-small cell lung cancer. The cancer cells of each type grow and spread in different ways, and they are treated differently. Non-small cell lung cancer is usually associated with prior smoking, passive smoking, or radon exposure. (A separate patient information summary on small cell lung cancer is also available in PDQ).

The main kinds of non-small cell lung cancer are named for the type of cells found in the cancer: squamous cell carcinoma (also called epidermoid carcinoma), adenocarcinoma, large cell carcinoma, adenosquamous carcinoma, and undifferentiated carcinoma.

Non-small cell lung cancer is a common disease. It is usually treated by surgery (taking out the cancer in an operation) or radiation therapy (using high-dose x-rays to kill cancer cells). However, chemotherapy may be used in some patients.

The prognosis (chance of recovery) and choice of treatment depend on the stage of the cancer (whether it is just in the lung or has spread to other places), tumor size, the type of lung cancer, whether there are symptoms, and the patient's general health.

********** STAGE EXPLANATION
----- Stages of non-small cell lung cancer

Once lung cancer has been found (diagnosis), more tests will be done to find out if the cancer has spread from the lung to other parts of the body (staging). A doctor needs to know the stage to plan treatment. The following stages are used for non-small cell lung cancer:

----- Occult stage
Cancer cells are found in sputum, but no tumor can be found in the lung.

----- Stage 0
Cancer is only found in a local area and only in a few layers of cells. It has not grown through the top lining of the lung. Another term for this type of lung cancer is carcinoma in situ.

----- Stage I
The cancer is only in the lung, and normal tissue is around it.

----- Stage II
Cancer has spread to nearby lymph nodes.

----- Stage III
Cancer has spread to the chest wall or diaphragm near the lung; or the cancer has spread to the lymph nodes in the area that separates the two lungs (mediastinum); or to the lymph nodes on the other side of the chest or in the neck. Stage III is further divided into stage IIIA (usually can be operated on) and stage IIIB (usually cannot be operated on).

----- Stage IV
Cancer has spread to other parts of the body.

----- Recurrent
Cancer has come back (recurred) after previous treatment.

********** TREATMENT OPTION OVERVIEW

----- How non-small cell lung cancer is treated

Chemotherapy uses drugs to kill cancer cells. Chemotherapy may be taken by pill, or it may be put into the body by a needle in the vein or muscle. Chemotherapy is called a systemic treatment because the drug enters the bloodstream, travels through the body, and can kill cancer cells outside the lungs.

Chemoprevention uses drugs to prevent a second cancer from occurring.

Radiation therapy uses high-energy x-rays to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external radiation therapy) or from putting materials that produce radiation (radioisotopes) through thin plastic tubes in the area where the cancer cells are found (internal radiation therapy).

One new type of radiation therapy is called radiosurgery. In radiosurgery, radiation is directly focused on the tumor, and involves as little normal tissue as possible. Radiosurgery is usually used as treatment of tumors that involve the brain.

Cryosurgery freezes the tumor and kills it. Photodynamic therapy uses a certain type of light and a special chemical to kill cancer cells. Laser therapy uses a narrow beam of light to kill cancer cells. Cryosurgery and photodynamic therapy are usually used in clinical trials.

Surgery, radiation therapy, and chemotherapy are used to treat non-small cell lung cancer. However, these treatments often do not cure the disease.

If lung cancer is found, a patient may want to think about taking part in one of the many clinical trials being done to improve treatment. Clinical trials are ongoing in most parts of the country for all stages of non-small cell lung cancer. Treatment choices can be discussed with a doctor.

Patients with non-small cell lung cancer can be divided into three groups, depending on the stage of the cancer and the treatment that is planned. The first group (stages 0, I, and II) includes patients whose cancers can be taken out by surgery. The operation that takes out only a small part of the lung is called a wedge resection. When a whole section (lobe) of the lung is taken out, the operation is called a lobectomy. When one whole lung is taken out, it is called a pneumonectomy.

Radiation therapy may be used to treat patients in this group who cannot have surgery because they have other medical problems. Like surgery, radiation therapy is called local treatment because it works only on the cells in the area being treated.

The second group of patients has lung cancer that has spread to nearby tissue or to lymph nodes. These patients can be treated with radiation therapy alone or with surgery and radiation, chemotherapy and radiation, or chemotherapy alone.

The third group of patients has lung cancer that has spread to other parts of the body. Radiation therapy may be used to shrink the cancer and to relieve pain. Chemotherapy may be used to treat some patients in this group.

********** OCCULT NON-SMALL CELL LUNG CANCER

Tests are done to find the main tumor (cancer). Lung cancer that is found at this early stage can be cured by surgery.

********** STAGE 0 NON-SMALL CELL LUNG CANCER

Treatment may be one of the following:

1 Surgery to cure these very early cancers. However, these patients may get a second lung cancer that may not be able to be taken out by surgery.

2 Photodynamic therapy used internally.

********** STAGE I NON-SMALL CELL LUNG CANCER

Treatment may be one of the following:

1 Surgery.

2 Radiation therapy (for patients who cannot be operated on).

3 Clinical trials of chemotherapy following surgery.

4 Clinical trials of chemoprevention following other therapy.

5 Clinical trials of photodynamic therapy used internally.

********** STAGE II NON-SMALL CELL LUNG CANCER

Treatment may be one of the following:

1 Surgery to take out the tumor and lymph nodes.

2 Radiation therapy (for patients who cannot be operated on).

3 Surgery and/or radiation therapy with or without chemotherapy.

********** STAGE III NON-SMALL CELL LUNG CANCER

----- Stage IIIA non-small cell lung cancer

Treatment may be one of the following:

1 Surgery alone.

2 Chemotherapy with other treatments.

3 Surgery and radiation therapy.

4 Radiation therapy alone.

5 Laser therapy and/or internal radiation therapy.

----- Stage IIIB non-small cell lung cancer

Treatment may be one of the following:

1 Radiation therapy alone.

2 Chemotherapy plus radiation therapy.

3 Chemotherapy plus radiation therapy followed by surgery.

4 Chemotherapy alone.

5 Cryotherapy plus radiation therapy.

********** STAGE IV NON-SMALL CELL LUNG CANCER

Treatment may be one of the following:

1 Radiation therapy.

2 Chemotherapy.

3 Chemotherapy and radiation therapy.

4 Laser therapy and/or internal radiation therapy.

********** RECURRENT NON-SMALL CELL LUNG CANCER

Treatment may be one of the following:

1 Radiation therapy to control symptoms.

2 Chemotherapy.

3 Chemotherapy with radiotherapy.

4 For some patients who have a very small amount of tumor that has spread to the brain, surgery may be used to remove the tumor.

5 Laser therapy or internal radiation therapy.

6 Radiosurgery (for certain patients who cannot be operated on).

<TO LEARN MORE>

TEXTO 14: Treatment summaries for patients (QPT3)

---------- SMALL CELL LUNG CANCER ----------

********** DESCRIPTION

----- What is small cell lung cancer?

Small cell lung cancer is a disease in which cancer (malignant) cells are found in the tissues of the lungs. The lungs are a pair of cone-shaped organs that take up much of the room inside the chest. The lungs bring oxygen into the body and take out carbon dioxide, which is a waste product of the body's cells. Tubes called bronchi make up the inside of the lungs.

There are two kinds of lung cancer based on how the cells look under a microscope: small cell and non-small cell. If a patient has non-small cell lung cancer, see the PDQ patient information summary on non-small cell lung cancer.

Small cell lung cancer is usually found in people who smoke or who used to smoke cigarettes. A doctor should be seen if there are any of the following symptoms: a cough or chest pain that doesn't go away, a wheezing sound when breathing, shortness of breath, coughing up blood, hoarseness, or swelling in the face and neck.

If there are symptoms, a doctor may want to look into the bronchi through a special instrument, called a bronchoscope, that slides down the throat and into the bronchi. This test, called bronchoscopy, is usually done in the hospital. Before the test, the patient will be given a local anesthetic (a drug that causes a loss of feeling for a short period of time) in the back of the throat. Some pressure may be felt, usually with no pain. The doctor can take cells from the walls of the bronchi tubes or cut small pieces of tissue to look at under the microscope to see if there are any cancer cells. This is called a biopsy.

The doctor may also use a needle to remove tissue from a place in the lung that may be hard to reach with the bronchoscope. A cut will be made in the skin and the needle will be put in between the ribs. This is called a needle aspiration biopsy. The doctor will look at the tissue under the microscope to see if there are any cancer cells. Before the test, a local anesthetic will be given to keep the patient from feeling pain.

The chance of recovery (prognosis) and choice of treatment depend on the stage of the cancer (whether it is just in the lung or has spread to other places), and the patient's gender and general state of health.

********** STAGE EXPLANATION

----- Stages of small cell lung cancer

Once small cell lung cancer has been found, more tests will be done to find out if cancer cells have spread from one or both lungs to other parts of the body (staging). A doctor needs to know the stage of the disease to plan treatment. The following stages are used for small cell lung cancer:

----- Limited stage
Cancer is found only in one lung and in nearby lymph nodes. (Lymph nodes are small, bean-shaped structures that are found throughout the body. They produce and store infection-fighting cells.)

----- Extensive stage

Cancer has spread outside of the lung where it began to other tissues in the chest or to other parts of the body.

----- Recurrent stage
Recurrent disease means that the cancer has come back (recurred) after it has been treated. It may come back in the lungs or in another part of the body.

********** TREATMENT OPTION OVERVIEW
----- How small cell lung cancer is treated

There are treatments for all patients with small cell lung cancer. Three kinds of treatment are used:

surgery (taking out the cancer) /

radiation therapy (using high-dose x-rays or other high-energy rays to kill cancer cells) /

chemotherapy (using drugs to kill cancer cells).

Additionally, clinical trials are testing the effect of new therapies on the treatment of small cell lung cancer. Surgery may be used if the cancer is found only in one lung and in nearby lymph nodes. Because this type of lung cancer is usually not found in only one lung, surgery alone is not often used. Occasionally, surgery may be used to help determine exactly which type of lung cancer the patient has. If a patient does have surgery, the doctor may take out the cancer in one of the following operations:

Wedge resection removes only a small part of the lung.

Lobectomy removes an entire section (lobe) of the lung.

Pneumonectomy removes the entire lung.

During surgery, the doctor will also take out lymph nodes to see if they contain cancer.
Radiation therapy uses x-rays or other high-energy rays to kill cancer cells and shrink tumors. Radiation therapy for small cell lung cancer usually comes from a machine outside the body (external beam radiation therapy). It may be used to kill cancer cells in the lungs or in other parts of the body where the cancer has spread. Radiation therapy may also be used to prevent the cancer from growing in the brain. This is called prophylactic cranial irradiation (PCI). Because PCI may affect brain function, the doctor will help the patient decide whether to have this kind of radiation therapy. Radiation therapy can be used alone or in addition to surgery and/or chemotherapy.

Chemotherapy is the most common treatment of all stages of small cell lung cancer. Chemotherapy may be taken by pill, or it may be put into the body by a needle in the vein or muscle. Chemotherapy is called a systemic treatment because the drug enters the bloodstream, travels through the body, and can kill cancer cells outside the lungs, including cancer cells that have spread to the brain.

----- Treatment by stage

Treatment of small cell lung cancer depends on the stage of the disease, and the patient's age and overall condition.

Standard treatment may be considered because of its effectiveness in patients in past studies, or participation in a clinical trial may be considered. Most patients are not cured with standard therapy and some standard treatments may have more side effects than are desired. For these reasons, clinical trials

are designed to find better ways to treat cancer patients and are based on the most up-to-date information. Clinical trials are ongoing in most parts of the country for most stages of small cell lung cancer. To learn more about clinical trials, call the Cancer Information Service at 1-800-4-CANCER (1-800-422-6237); TTY at 1-800-332-8615.

********** LIMITED STAGE SMALL CELL LUNG CANCER

Treatment may be one of the following:

1 Chemotherapy and radiation therapy to the chest with or without radiation therapy to the brain to prevent spread of the cancer (prophylactic cranial irradiation).

2 Chemotherapy with or without prophylactic cranial irradiation.

3 Surgery followed by chemotherapy with or without prophylactic cranial irradiation.

Clinical trials are testing new drugs and new ways of giving all of the above treatments.

********** EXTENSIVE STAGE SMALL CELL LUNG CANCER

----- Treatment may be one of the following:

1 Chemotherapy with or without radiation therapy to the brain to prevent spread of the cancer (prophylactic cranial irradiation).

2 Radiation therapy to places in the body where the cancer has spread, such as the brain, bone, or spine to relieve symptoms.

Clinical trials are testing new drugs and new ways of giving all of the above treatments.

********** RECURRENT SMALL CELL LUNG CANCER

----- Treatment may be one of the following:

1 Radiation therapy to reduce discomfort.

2 Chemotherapy to reduce discomfort.

3 Laser therapy, radiation therapy, and/or surgical implantation of devices to keep the airways open to relieve discomfort.

4 A clinical trial testing new drugs.

<TO LEARN MORE>

TEXTO 15: Versión bitexto (inglés-español) de QDT1

164 Sentences and headings
<!--L1, S 1-->---------- MALIGNANT MESOTHELIOMA ----------
<!--L2, S 1-->Mesotelioma maligno
<!--L1, S 2-->********** GENERAL INFORMATION
<!--L2, S 2-->********** INFORMACION GENERAL
<!--L1, S 3-->Prognosis in this disease is difficult to assess consistently because there is great variability in the time before diagnosis and the rate of disease progression.
<!--L2, S 3-->El pronóstico de esta enfermedad es difícil de evaluar de manera consistente debido a la alta variabilidad de tiempo que existe antes del diagnóstico y la tasa de progresión de la enfermedad.
<!--L1, S 4-->Various surgical procedures may be possible in selected patients, providing long-term survival without cure.
<!--L2, S 4-->Es posible efectuar varios procedimientos quirúrgicos en pacientes seleccionados, proporcionando supervivencia sin curación a largo plazo.
<!--L1, S 5-->In large retrospective series of pleural mesothelioma patients, important prognostic factors were found to be stage, age, performance status, and histology [1,2].
<!--L2, S 5-->En series retrospectivas extensas de pacientes con mesotelioma pleural, se encontró que los factores de diagnóstico importantes fueron etapa, edad, nivel de funcionamiento e histología [1,2].
<!--L1, S 6-->For patients treated with aggressive surgical approaches, factors associated with improved long-term survival include epithelial histology, negative lymph nodes, and negative surgical margins [3,4].
<!--L2, S 6-->Para pacientes tratados con estrategias quirúrgicas agresivas, los factores relacionados con una supervivencia mejor a largo plazo incluyen histología epitelial, ganglios linfáticos negativos y márgenes quirúrgicos negativos [3,4].
<!--L1, S 7-->For those patients treated with aggressive surgical approaches, nodal status is an important prognostic factor [3].
<!--L2, S 7-->Para aquellos pacientes tratados con enfoques quirúrgicos agresivos, el estado ganglionar es un factor pronóstico importante [3].
<!--L1, S 8-->Median survival for malignant local pleural disease has been reported as 16 months, and extensive disease as 5 months.
<!--L2, S 8-->Se ha reportado que la supervivencia promedio de enfermedad pleural maligna local es de alrededor 16 meses, y en el caso de enfermedad extensa, de 5 meses.
<!--L1, S 9-->In some instances the tumor grows through the diaphragm making site of origin difficult to assess.
<!--L2, S 9-->En algunos casos el tumor crece a través del diafragma haciendo así difícil de detectar el sitio de origen.
<!--L1, S 10-->Cautious interpretation of treatment results in this disease is imperative because of the selection differences among series.
<!--L2, S 10-->La interpretación cautelosa de los resultados del tratamiento en esta enfermedad es indispensable debido a las diferencias de selección entre las series.
<!--L1, S 11-->Effusions, both pleural and peritoneal, represent major symptomatic problems for at least two thirds of the patients.
<!--L2, S 11-->Los derrames, tanto pleurales como peritoneales, representan problemas sintomáticos importantes en al menos dos tercios de los pacientes.
<!--L1, S 12-->A history of asbestos exposure is reported in about 70%-80% of all cases of mesothelioma [1,5,6].
<!--L2, S 12-->Se reporta una historia de exposición a asbestos en cerca del 70%-80% de todos los casos de mesotelioma [1,5,6].
<!--L1, S 13--><References>
<!--L2, S 13--><Bibliografía>

<!--L1, S 14-->********** CELLULAR CLASSIFICATION

<!--L2, S 14-->********** CLASIFICACION CELULAR
<!--L1, S 15-->Histologically, these tumors are composed of fibrous or epithelial elements or both.
<!--L2, S 15-->Histológicamente estos tumores están compuestos por elementos fibrosos o epiteliales o ambos.
<!--L1, S 16-->The epithelial form occasionally causes confusion with peripheral anaplastic lung carcinomas or metastatic carcinomas.
<!--L2, S 16-->La forma epitelial ocasionalmente causa confusión con carcinomas anaplásicos periféricos de pulmón o carcinomas metastáticos.
<!--L1, S 17-->Attempts at diagnosis by cytology or needle biopsy of the pleura are often noncontributory.
<!--L2, S 17-->Los intentos diagnósticos por citología o biopsia con aguja de la pleura a menudo ayudan.
<!--L1, S 18-->It can be especially difficult to differentiate mesothelioma from carcinoma on small tissue specimens.
<!--L2, S 18-->Puede ser especialmente difícil diferenciar el mesotelioma de un carcinoma en muestras pequeñas de tejido.
<!--L1, S 19-->Thoracoscopy can be valuable in obtaining adequate tissue specimens for diagnostic purposes [1].
<!--L2, S 19-->La toracoscopia puede ser valiosa para la obtención de especímenes adecuados de tejido con fines de diagnóstico [1].
<!--L1, S 20-->Examination of the gross tumor at surgery and use of special stains or electron microscopy can often help.
<!--L2, S 20-->El examen del tumor macroscópico durante la cirugía y el uso de colorantes especiales o microscopia electrónica pueden a menudo ayudar.
<!--L1, S 21-->The special stains reported to be most useful include periodic acid-Schiff diastase, hyaluronic acid, mucicarmine, CEA, and Leu M1 [2].
<!--L2, S 21-->Se ha reportado que los siguientes colorantes especiales son los más útiles: diastasa con ácido peryódico de Schiff, ácido hialurónico, mucicarmín, CEA y Leu M1 [2].
<!--L1, S 22-->Histologic appearance appears to be of prognostic value, with most clinical studies showing that epithelial mesotheliomas have a better prognosis than fibrous or sarcomatous mesotheliomas [2-4].
<!--L2, S 22-->La apariencia histológica parece tener valor pronóstico, al mostrar la mayoría de los estudios clínicos que los mesoteliomas epiteliales tienen un mejor pronóstico que los mesoteliomas fibrosos o sarcomatosos [2-4].
<!--L1, S 23--><References>
<!--L2, S 23--><Bibliografía>
<!--L1, S 24-->********** STAGE INFORMATION
<!--L2, S 24-->********** INFORMACION DE LAS ETAPAS
<!--L1, S 25-->Patients with stage I disease have a significantly better prognosis than those with more advanced stages.
<!--L2, S 25-->Los pacientes con enfermedad en etapa I tienen un pronóstico significativamente mejor que aquéllos con etapas más avanzadas.
<!--L1, S 26-->However, because of the relative rarity of this disease, exact survival information based upon stage is limited [1].
<!--L2, S 26-->Sin embargo, debido a que esta enfermedad es poco común, la información exacta de supervivencia basada en etapas es limitada [1].
<!--L1, S 27-->A proposed staging system based upon thoracic surgery principles and clinical data is shown below [2].
<!--L2, S 27-->Un sistema de clasificación propuesto basado en principios quirúrgicos torácicos y datos clínicos se brinda a continuación [2].
<!--L1, S 28-->It is a modification of the older system proposed by Butchart et al [3].
<!--L2, S 28-->Es una modificación del sistema más antiguo propuesto por Butchart [3].
<!--L1, S 29-->Other staging systems that have been employed, including a proposed new international TNM staging system, are summarized by the International Mesothelioma Interest Group [4].
<!--L2, S 29-->Otros sistemas de clasificación que se han empleado, incluyendo un nuevo sistema internacional de clasificación de TNM propuesto, han sido resumidos por el International Mesothelioma Interest Group [4].

<!--L1, S 30-->Stage I: Disease confined within the capsule of the parietal pleura: ipsilateral pleura, lung, pericardium, and diaphragm.
<!--L2, S 30-->Etapa I: Enfermedad confinada dentro de la cápsula de la pleura parietal: pleura ipsilateral, pulmón, pericardio y diafragma.
<!--L1, S 31-->Stage II: All of stage I with positive intrathoracic (N1 or N2) lymph nodes.
<!--L2, S 31-->Etapa II: Todo lo de la etapa I con ganglios linfáticos intratorácicos positivos (N1 o N2)
<!--L1, S 32-->Stage III: Local extension of disease into the following: chest wall or mediastinum; heart or through the diaphragm, peritoneum; with or without extrathoracic or contralateral (N3) lymph node involvement.
<!--L2, S 32-->Etapa III: Extensión local de la enfermedad a: pared torácica o mediastino; corazón o a través del diafragma, peritoneo; con o sin complicación extratorácica o contralateral (N3) de los ganglios linfáticos.
<!--L1, S 33-->Stage IV: Distant metastatic disease.
<!--L2, S 33-->Etapa IV: Enfermedad metastática distante
<!--L1, S 34-->---------- Localized malignant mesothelioma: See description of stage I above.
<!--L2, S 34-->---------- Mesotelioma maligno localizado: Ver descripción de etapa I arriba.
<!--L1, S 35-->---------- Advanced malignant mesothelioma: See descriptions of stages II, III, and IV above.
<!--L2, S 35-->---------- Mesotelioma maligno avanzado: Ver descripción de etapas II, III y IV arriba.
<!--L1, S 36-->For the purposes of the discussion of treatment in this statement, the disease is categorized as either localized or advanced.
<!--L2, S 36-->Para fines de discusión del tratamiento en este documento, la enfermedad se categoriza ya sea como localizada o avanzada.
<!--L1, S 37--><References>
<!--L2, S 37--><Bibliografía>
<!--L1, S 38-->********** TREATMENT OPTION OVERVIEW
<!--L2, S 38-->********** ASPECTOS DE LAS OPCIONES DE TRATAMIENTO
<!--L1, S 39-->Standard treatment for all but localized mesothelioma is generally not curative.
<!--L2, S 39-->El tratamiento estándar para todos los casos de mesotelioma con excepción del mesotelioma localizado es generalmente no curativo.
<!--L1, S 40-->Although some patients will experience long-term survival with aggressive treatment approaches, it remains unclear if overall survival has been significantly altered by the different treatment modalities or by combinations of modalities.
<!--L2, S 40-->Aunque algunos pacientes experimentarán supervivencia a largo plazo con estrategias agresivas de tratamiento, aún no está claro si la supervivencia en general ha sido alterada significativamente por las diferentes modalidades de tratamiento o por las combinaciones de modalidades.
<!--L1, S 41-->Extrapleural pneumonectomy in selected patients with early stage disease may improve recurrence-free survival, but its impact on overall survival is unknown [1].
<!--L2, S 41-->Una neumonectomía extrapleural en pacientes seleccionados con enfermedad en etapa inicial puede obtener una supervivencia libre de recidiva, pero su impacto en la supervivencia general es desconocido [1].
<!--L1, S 42-->Pleurectomy and decortication can provide palliative relief from symptomatic effusions, discomfort caused by tumor burden, and pain caused by invasive tumor.
<!--L2, S 42-->Pleurectomía y decorticación pueden brindar alivio paliativo contra efusiones sintomáticas, malestar causado por el agobio tumoral y dolor causado por invasión tumoral.
<!--L1, S 43-->Operative mortality from pleurectomy/decortication is less than 2%,[2]. while mortality from extrapleural pneumonectomy has ranged from 6% to 30% [1,3].
<!--L2, S 43-->La mortalidad quirúrgica por pleurectomía/decorticación es menos del 2%,[2] mientras que la mortalidad por neumonectomía extrapleural ha oscilado entre 6% y 30% [1,3].
<!--L1, S 44-->The addition of radiation therapy and/or chemotherapy following surgical intervention has not demonstrated improved survival [2].

<!--L2, S 44-->La adición de radioterapia y/o quimioterapia después de intervención quirúrgica no ha demostrado mejoras en la supervivencia [2].
<!--L1, S 45-->The use of radiation therapy in pleural mesothelioma has been shown to alleviate pain in the majority of patients treated.
<!--L2, S 45-->El uso de radioterapia en mesotelioma pleural ha demostrado alivio en el dolor en la mayoría de los pacientes tratados.
<!--L1, S 46-->However, the duration of symptom control is short-lived [4,5].
<!--L2, S 46-->Sin embargo, la duración del control de los síntomas es corta [4,5].
<!--L1, S 47-->Single agent and combination chemotherapy have been evaluated in single and combined modality studies.
<!--L2, S 47-->La quimioterapia de agente único y la quimioterapia de combinación han sido evaluadas en estudios de modalidad simple y combinada.
<!--L1, S 48-->The most studied agent is doxorubicin, which has produced partial responses in approximately 15%-20% of patients studied [6].
<!--L2, S 48-->El agente más estudiado es doxorrubicina, el cual ha producido respuestas parciales en aproximadamente el 15%-20% de los pacientes estudiados [6].
<!--L1, S 49-->Some combination chemotherapy regimens have been reported to have higher response rates in small phase II trials.
<!--L2, S 49-->Algunos regímenes de quimioterapia de combinación han reportado tener tasas de respuestas más altas en ensayos de fase II no muy extensos.
<!--L1, S 50-->However the toxicity reported is also higher and there is no evidence that combination regimens result in longer survival or longer control of symptoms [6,7].
<!--L2, S 50-->Sin embargo, la toxicidad reportada también es más alta y no hay evidencia de que los regímenes de combinación resulten en una supervivencia más larga o en control de síntomas más extenso [6,7].
<!--L1, S 51-->Recurrent pleural effusions may be treated with pleural sclerosing procedures; however, failure rates are high secondary to the restrictive nature of the tumor.
<!--L2, S 51-->Las efusiones pleurales recidivantes pueden tratarse con procedimientos esclerosantes pleurales; sin embargo, las tasas de fracaso son altas debido a la naturaleza restrictiva del tumor.
<!--L1, S 52-->The designations in PDQ that treatments are "standard" or "under clinical evaluation" are not to be used as a basis for reimbursement determinations.
<!--L2, S 52-->Las designaciones en PDQ que indican que un tratamiento es "estándar" o que está "en evaluación clínica" no deben emplearse como base para la determinación de reembolsos.
<!--L1, S 53--><References>
<!--L2, S 53--><Bibliografía>
<!--L1, S 54-->********** LOCALIZED MALIGNANT MESOTHELIOMA (STAGE I)
<!--L2, S 54-->********** MESOTELIOMA MALIGNO LOCALIZADO (ETAPA I)
<!--L1, S 55-->Treatment options:[1].
<!--L2, S 55-->Opciones de tratamiento:[1].
<!--L1, S 56-->Standard:
<!--L2, S 56-->Estándar:
<!--L1, S 57-->1 Solitary mesotheliomas: Surgical resection en bloc including contiguous structures to ensure wide disease-free margins.
<!--L2, S 57-->1 Mesoteliomas solitarios: Resección quirúrgica en bloque incluyendo estructuras contiguas para asegurar márgenes libres de enfermedad amplios.
<!--L1, S 58-->Sessile polypoid lesions should be treated with surgical resection to ensure maximal potential for cure [2].
<!--L2, S 58-->Las lesiones polipoides sésiles deben tratarse con resección quirúrgica para asegurar el potencial curativo máximo [2].
<!--L1, S 59-->2 Intracavitary mesothelioma: A) Palliative surgery (pleurectomy and decortication) with or without postoperative radiation therapy B) Extrapleural pneumonectomy C) Palliative radiation therapy.
<!--L2, S 59-->2 Mesotelioma intracavitario: A) Cirugía paliativa (pleurectomía y decorticación) con o sin radioterapia postoperatoria B) Neumonectomía extrapleural C) Radioterapia paliativa.
<!--L1, S 60-->Under clinical evaluation:
<!--L2, S 60-->En evaluación clínica:

<!--L1, S 61-->1 Intracavitary chemotherapy following resection [3,4].
<!--L2, S 61-->1 Quimioterapia intracavitaria después de resección [3,4].
<!--L1, S 62-->2 Multimodality therapy [4-6].
<!--L2, S 62-->2 Terapia de modalidades múltiples [4-6].
<!--L1, S 63-->3 Other clinical trials.
<!--L2, S 63-->3 Otras pruebas clínicas.
<!--L1, S 64--><References>
<!--L2, S 64--><Bibliografía>
<!--L1, S 65-->********** ADVANCED MALIGNANT MESOTHELIOMA (STAGES II, III, AND IV)
<!--L2, S 65-->********** MESOTELIOMA MALIGNO AVANZADO (ETAPAS II, III Y IV)
<!--L1, S 66-->Treatment options:
<!--L2, S 66-->Opciones de tratamiento:
<!--L1, S 67-->1 Symptomatic treatment to include drainage of effusions, chest tube pleurodesis, or thoracoscopic pleurodesis [1].
<!--L2, S 67-->1 Tratamiento sintomático que incluya drenaje de derrames, pleurodesis del tubo torácico o pleurodesis toracoscópica [1].
<!--L1, S 68-->2 Palliative surgical resection in selected patients [2,3].
<!--L2, S 68-->2 Resecciones quirúrgicas paliativas en pacientes seleccionados [2,3].
<!--L1, S 69-->3 Palliative radiation therapy [4,5].
<!--L2, S 69-->3 Radioterapia paliativa [4,5].
<!--L1, S 70-->4 Single-agent chemotherapy.
<!--L2, S 70-->4 Quimioterapia con un solo agente.
<!--L1, S 71-->Partial responses have been reported with doxorubicin,epirubicin, mitomycin, cyclophosphamide, cisplatin, carboplatin, and ifosfamide [6-8].
<!--L2, S 71-->Se ha informado de respuestas parciales con doxorrubicina, epirubicina, mitomicina, ciclofosfamida, cisplatino, carboplatino e ifosfamida [6-8].
<!--L1, S 72-->5 Multimodality clinical trials [9-13].
<!--L2, S 72-->5 Pruebas clínicas de modalidades múltiples [9-13].
<!--L1, S 73-->6 Intracavitary therapy.
<!--L2, S 73-->6 Terapia intracavitaria.
<!--L1, S 74-->Intrapleural or intraperitoneal administration of chemotherapeutic agents (e.g, cisplatin, mitomycin, and cytarabine) has been reported to produce transient reduction in the size of tumor masses and temporary control of effusions in small clinical studies [14-16].
<!--L2, S 74-->Se ha informado que la administración intrapleural o intraperitoneal de agentes quimioterapéuticos (p. ej., cisplatino, mitomicina y citarabina) produce reducción transitoria en el tamaño de las masas tumorales y control temporal de derrames en estudios clínicos pequeños [14-16].
<!--L1, S 75-->Additional studies are needed to define the role of intracavitary therapy.
<!--L2, S 75-->Se requieren estudios adicionales para definir la función de terapia intracavitaria.
<!--L1, S 76--><References>
<!--L2, S 76--><Bibliografía>
<!--L1, S 77-->********** RECURRENT MALIGNANT MESOTHELIOMA
<!--L2, S 77-->********** MESOTELIOMA MALIGNO RECURRENTE
<!--L1, S 78-->Treatment of recurrent mesothelioma usually utilizes procedures and/or agents not previously employed in the initial treatment attempt.
<!--L2, S 78-->El tratamiento de mesotelioma recidivante generalmente utiliza procedimientos y/o agentes que no han sido previamente empleados en el tratamiento tentativo inicial.
<!--L1, S 79-->No standard treatment approaches have been proven to improve survival or control symptoms for a prolonged period of time.
<!--L2, S 79-->Ningún enfoque de tratamiento ha demostrado mejorar la supervivencia o el control de síntomas por un período de tiempo prolongado.
<!--L1, S 80-->These patients should be considered candidates for phase I and II clinical trials evaluating new biologicals, chemotherapeutic agents, or physical approaches [1-5].
<!--L2, S 80-->Estos pacientes deben considerarse como candidatos para pruebas clínicas de fase I y II donde se evalúen productos biológicos nuevos, agentes quimioterapéuticos o enfoques físicos [1-5].
<!--L1, S 81-->Consult the PDQ protocol file for a current listing of active clinical trials.

<!--L2, S 81-->Consulte el PDQ para obtener una lista actual de pruebas clínicas activas.
<!--L1, S 82--><References>
<!--L2, S 82--><Bibliografía>

TEXTO 16: Noticia para profesionales de la salud publicada en *Diario Médico*

17/03/98: El tratamiento neoadyuvante incrementa la supervivencia en el cáncer de pulmón

http://www.diariomedico.com/oncologia/noticias.html

El tratamiento neoadyuvante incrementa la supervivencia en el cáncer de pulmón

El Grupo Español de Cáncer de Pulmón, que engloba a 37 centros, tiene previsto estudiar los efectos de la terapia neoadyuvante (preoperatoria) con los nuevos fármacos quimioterápicos en la mejora de la supervivencia de los pacientes afectados por tumores pulmonares en estadios iniciales, según ha anunciado Rafael Rosell, presidente de la asociación y jefe del Servicio de Oncología Médica del Hospital Universitario Germans Trias, de Badalona, en Barcelona, que coordinará esta investigación.
"Creemos que puede ser mucho más efectivo que el tratamiento postquirúrgico", ha indicado Rosell, co-director científico, junto con Paul A. Bunn, de la División de Oncología Médica del Centro de Ciencias de la Salud de la Universidad de Colorado, en Denver, Estados Unidos, del Foro interactivo pan-europeo sobre nuevas perspectivas en el manejo del cáncer de pulmón celebrado en Sitges, Barcelona, y organizado por el laboratorio Bristol-Myers Squibb, que financiará parte del estudio que se propone realizar el grupo español de expertos.
En concreto se quiere reunir una muestra de 600 pacientes en dos años y seguirlos durante tres, con el objetivo de llegar a demostrar una reducción de la mortalidad del 20 por ciento a lo largo de ese período.
Rosell, junto con un equipo interdisciplinar de su propio centro y de los hospitales La Fe y General de Valencia, publicó en 1994 en la revista The New England Journal of Medicine que la quimioterapia preoperatoria con fármacos clásicos incrementaba la supervivencia media de los pacientes con cáncer de pulmón localmente avanzado, y el pasado mes de enero, a través de la revista Annals of Oncology, dieron a conocer un estudio que concluye que un 28 por ciento de los casos de tumores diagnosticados en estadios iniciales presentan micrometástasis -ADN tumoral circulante en la sangre- ya en el momento mismo de la detección de la enfermedad.

Evidencias

Estas evidencias avalan la hipótesis de la utilidad de la quimioterapia preoperatoria incluso en pacientes con tumores muy iniciales y ADN tumoral circulante.
"Lo convencional hoy día es operar y aplicar la quimioterapia posteriormente", ha precisado. Los estudios realizados indican que de esta manera el 50 por ciento de los pacientes presentan recidiva a distancia al año y medio después de ser tratados.
Por otro lado, los centros integrados dentro del Grupo Español de Cancer de Pulmón publicaron en 1994 su experiencia con el quimioterápico taxol en cáncer de pulmón

avanzado no quirúrgico -estadios IIIb y IV-, que es el mismo fármaco que ahora se probará en los estadios iniciales preoperatoriamente y que se ha demostrado que por sí solo tiene una actividad similar a la de las combinaciones farmacológicas con cisplatino.
"El taxol y otras moléculas como el taxotere y la gemcitabina han cambiado el panorama de la quimioterapia en el cáncer de pulmón, que hasta hace poco tiempo se basaba en el cisplatino, que es eficaz pero presenta efectos secundarios. Estos fármacos han permitido individualizar más el tratamiento, en función de los estadios y tratar incluso tumores iniciales", ha explicado Rosell. El Hospital Clínico de Madrid, el Clínico de Valencia y el Hospital Germans Trias de Badalona estudiaron los efectos del taxol en 60 pacientes con cáncer diseminado y vieron que inhibe la angiogénesis del tumor, consiguiendo un 30 por ciento de respuestas objetivas y un 50 por ciento de enfermedad estable. "La respuesta radiográfica estable durante más de un año es una buena respuesta", ha precisado Rosell.
Por otro lado, el experto ha destacado la importancia del trabajo coordinado que llevan a cabo los centros investigadores del cáncer de pulmón en España y del que se está desarrollando conjuntamente con otros países europeos. "Esto permite homogeneidad en la calidad del tratamiento en el ámbito europeo y respuestas más rápidas".

Comparación

En Sitges se han dado a conocer, por otra parte, resultados preliminares de un estudio multicéntrico internacional -16 países, entre ellos España- sobre el taxol combinado con carboplatino versus taxol mezclado con cisplatino en enfermos con cáncer de pulmón no microcítico.
Los datos confirman la hipótesis de que la primera opción es tan eficaz como la segunda y con menores efectos secundarios. Las conclusiones se presentarán en mayo durante el Congreso Americano de Oncología Médica que se celebrará en Los Angeles, en

California.
Carmen Fernández. Barcelona.