# Metastatic Patterns of Prostate Cancer: An Autopsy Study of 1,589 Patients

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**The prognosis of prostate cancer is mainly determined by the presence or absence of metastases. Nevertheless, the metastatic pathways in prostate cancer are not entirely understood. Among 19,316 routine autopsies performed from 1967 to 1995 on men older than 40 years of age, the reports from those 1,589 (8.2%) with prostate cancer were analyzed. Hematogeneous metastases were present in 35% of 1,589 patients with prostate cancer, with most frequent involvement being bone (90%), lung (46%), liver (25%), pleura (21%), and adrenals (13%). Several lines of evidence suggested the existence of a backward metastatic pathway through veins from the prostate to the spine in addition to classical hematogeneous tumor spread via the vena cava. First, there was an inverse relationship between spine and lung metastases, suggesting that metastasis to the spine is independent of lung metastasis. Second, the maximum frequency of spine involvement occurred in smaller tumors (4 to 6 cm) as compared with the maximum spread to lung (6 to 8 cm) and liver (>8 cm), suggesting that spine metastases precede lung and liver metastases in many prostate cancers. Third, there was a gradual decrease in spine involvement from the lumbar to the cervical level (97% *v* 38%), which is consistent with a subsequent upward metastatic spread along spinal veins after initial lumbar metastasis. The results of this study show that bone, lung, and liver are the most frequent sites of distant prostate cancer metastases. Besides the cava-type of metastasis through lung passage, there are strong arguments for the existence and clinical significance of a backward venous spread to the spine, which is likely to occur early in the metastatic process.** HUM PATHOL 31:578-583. Copyright © 2000 by W.B. Saunders Company

*Key words:* prostate cancer, autopsy, metastasis.

Despite the widespread use of prostate-specific antigen screening for early detection, prostate cancer remains the second leading cause of cancer-related death in Western countries.[1] There is a considerable discrepancy between the histological prevalence and clinical disease from prostate cancer, reflecting the broad spectrum of tumor behavior.[2] Although more than 30% of all men older than 50 years have been shown to harbor prostate cancer, only 9% develop clinical disease.[2] The outcome of prostate cancer is mainly determined by metastases. Hormone withdrawal therapy can initially relieve symptoms in a large proportion of patients with metastases, but long-term cure is rare because the tumors become hormone refractory after a few months or years, and efficient additional systemic therapies are not available.[3] Despite the clinical significance of metastasis in prostate cancer patients as well as the crucial role of the preoperative detection of metastases for treatment selection, the metastatic pathways are not yet fully understood. It has been suggested that besides the cava type of metastasis through the lung, alternative pathways may exist for hematogeneous tumor spread through periprostatic to prespinal veins into the spine.[4,5] Autopsies offer a unique opportunity to study the distribution of metastasis. The aim of this study was to evaluate the patterns and pathways of metastasis in a large number of routinely processed autopsies from patients with prostate cancer.

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## MATERIALS AND METHODS

### Patients

In a consecutive series of 19,316 autopsies from men older than 40 years of age performed at the Institute of Pathology of the University of Basel between 1967 and 1995, there were 1,589 men (8.2% of all autopsies) having either prostate cancer at autopsy or a history of previously treated prostate cancer. Eight hundred thirty-seven (52.7%) of these tumors were clinically known, and 741 (46.7%) were unsuspected (latent). Ten patients (0.6%) had suffered from known metastatic disease with clinically unknown (occult) primary tumor. The average age of tumor patients at autopsy was 78 ± 8.6 years (range, 40 to 100 years). Residual tumor could not be detected after local treatment in 87 of the 837 patients with clinically known disease. In most cases, histological analysis was done only in case of suspicious macroscopic findings or gross abnormality.

### Morphological Features

Tumor stage and maximum tumor diameter had been assessed macroscopically in most tumors. If not indicated, the local stage according to the TNM classification was reconstructed from the tumor extension described in the autopsy report.[6] Histological grading had subjectively been performed by different pathologists at the time of autopsy as high, intermediate, or low grade based on growth pattern and nuclear atypia. Data on local stage, histological grade, and tumor diameter were available in 1,393 (88%), 1,029 (65%), and 891 (56.1%) patients, respectively.

### Statistical Analysis

Contingency table analysis was used to analyze the relationship between metastasis, stage, and grade. Analysis of variance (ANOVA) was performed to analyze the relationship of nominal parameters with continuous variables (eg, patient age, tumor diameter). Because some of the parameters were not available in every patient, the number of patients included in particular statistical analyses varied between analyses.

## RESULTS

There was a strong relationship between patient age and prevalence of prostate cancer (Table 1). Prostate cancer was found in only 0.2% of the patients aged 40 to 49 years but in 16.1% of those older than 80 years. The tumors consisted of 1,583 adenocarcinomas, 4 small cell cancers, and 2 carcinosarcomas. Lymphatic or hematogeneous metastases were seen in 631 (39.7%) of all patients, and in 65.8% in the 837 patients with clinically known cancer. Only 9.4% of the 741 patients with unsuspected cancer had metastases at autopsy. The distribution of lymphatic metastases is shown in Figure 1. Paraaortic lymph nodes were most frequently involved, followed by pelvic lymph nodes. There was a strong association between lymphatic and hematogeneous metastasis. Eighty-four percent of the 415 tumors with pelvic or paraaortal lymphatic metastases had simultaneous hematogeneous spread, as opposed to 16% of those 996 tumors without pelvic or paraaortal lymphatic metastases ($P < .0001$). Simultaneous hematogeneous dissemination was markedly more frequent in tumors with paraaortic lymph node metastases than in those with pelvic lymph node metastases (88.9% *v* 63.9%, $P < .0001$).

Hematogeneous metastases were found in 556 (35%) of all patients. Bone metastasis was detected in 501 of these patients (90.1%). Bone metastases were predominantly present in the spine (90%), which was always grossly examined on its whole length from the lumbar to the cervical section. Interestingly, spine

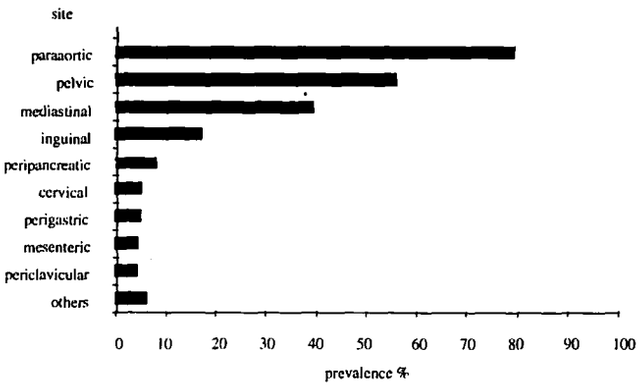


**FIGURE 1.** Distribution of lymph node metastases at autopsy ($n$ = 471 patients with lymph node metastases).

metastasis was significantly associated with paraaortic lymph node metastasis in hematogeneously disseminated tumors. Paraaortic lymph node metastases were found in 57.5% of the 447 tumors with spine metastases but in only 38.6% of the 70 tumors without ($P = .0031$). In 100 consecutive patients with detailed information about the distribution of metastases within the spine, the prevalence decreased from the lumbar (97%) to the thoracic (66%) and cervical level (38%). An exclusive involvement of the thoracic or cervical spine had been recorded in only 2% and 1% of these patients, respectively. Metastases were rarely recorded in other bones such as ribs (18.2%), long bones (15%), and skull (8%), but these sites were not systematically examined at autopsy.

Other hematogeneous metastases were most prevalent in lung (45.7%), liver (25.0%), pleura (21.0%), and adrenals (12.8%), but could be observed in nearly any organ such as the breast (1.1%), diaphragm (1.1%), skin (0.9%), heart (0.5%), penis (0.5%), testicle (0.5%), and gallbladder (0.5%) (Fig 2). Interestingly, there was an inverse relationship between lung and spine metastases. Spine metastases were found in 92.1% of 302 patients without metastases to the lung but in only 74.8% of 254 patients with ($P < .0001$). The patients

**TABLE 1.** Prevalence of Prostate Cancer at Autopsy in Patients Older Than 40 Years: A Review of the Literature

| Author | Year | Method* | No. of Autopsies | No. of PCA | % PCA† | 40-49 y | 50-59 y | 60-69 y | 70-79 y | ≥80 y |
|---|---|---|---|---|---|---|---|---|---|---|
| Gaynor[8] | 1938 | S | 1,010 | 190 | 18.8 | 4.9 | 10.4 | 17.3 | 28.3 | 38.8 |
| Andrews[9] | 1949 | S | 121 | 17 | 14.0 | 4.5 | 5.3 | 17.9 | 31.8 | |
| Edwards et al[7] | 1953 | S | 173 | 29 | 16.8 | 4.3 | 9.7 | 18.5 | 25.0 | 17.6 |
| Franks[10] | 1954 | S | 198 | 69 | 34.8 | 0.0 | 29.0 | 30.2 | 40.0 | 73.7 |
| Oota[11] | 1961 | S | 239 | 46 | 19.2 | 5.0 | 6.6 | 13.6 | 35.8 | 45.5 |
| Holund[15] | 1980 | S | 220 | 57 | 25.9 | 12.5 | 8.7 | 12.5 | 32.3 | 42.5 |
| Sakr et al[14] | 1994 | S | 249 | 57 | 28.1 | 31.7 | 54.5 | 63.6 | | |
| Total S‡ | | S | 2,210 | 465 | 19.2 | 4.9 | 9.7 | 17.9 | 32.0 | 42.5 |
| Halpert et al[12] | 1963 | RH | 4,003 | 410 | 10.2 | 3.8 | 6.4 | 12.5 | 17.4 | 26.0 |
| Lundberg and Berge[13] | 1970 | RH | 3,034 | 634 | 20.9 | 0.8 | 7.4 | 14.8 | 21.9 | 35.5 |
| Total RH‡ | | RH | 7,037 | 1,044 | 15.6 | 2.3 | 6.9 | 13.7 | 19.7 | 30.8 |
| Present study | | RA | 19,316 | 1,589 | 8.2 | 0.2 | 1.7 | 4.1 | 9.2 | 16.1 |

Abbreviation: PCA, prostate cancer.

*Methods of prostate tissue processing: S = step sectioning and histology of the whole prostate; RH = routine histology (at least one histological specimen from every prostate); RA = routine autopsy (histological analysis only in case of macroscopic cancer suspicion).

†Mean values.

‡Median values.

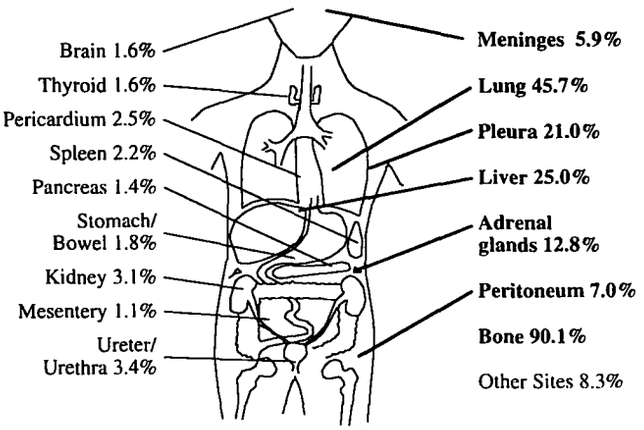


**FIGURE 2.** Distribution of hematogeneous metastases in prostate cancer ($n$ = 556 patients with metastatic prostate cancer).

with lung metastases had significantly more simultaneous metastases to other organs (92.5%) than patients with spine metastases (66%, $P < .0001$).

Histological grade was strongly linked to the prevalence of hematogeneous metastasis, which markedly increased from grade 1 (7.5%) to grade 2 (33.4%) and grade 3 tumors (60.7%, $P < .0001$). There was also a strong relationship between local stage and hematogeneous spread. Metastases were detected in 4.2% of pT2, 41.1% of pT3, and 80.3% of pT4 tumors ($P < .0001$). Accordingly, the prevalence of metastases also increased with the largest diameter of the primary tumor (Fig 3). The frequency of spine metastases was 4.2% in tumors measuring less than 2 cm, 23.7% in tumors measuring 2 to 4 cm, and 61.3% in tumors measuring 4 to 6 cm. There was no further increase of spine metastases in primary tumors larger than 6 cm. Interestingly, the maximum frequency of metastases to the lung and the liver appeared in larger primary tumors (lung, 6 to 8 cm; liver, ≥8 cm) than observed for spine metastases (4 to 6 cm, Fig 3).

The capability of a tumor, however, to cause metastatic spread is obviously not defined by only its local stage or diameter. Despite the strong association between tumor stage and hematogeneous metastasis, 71

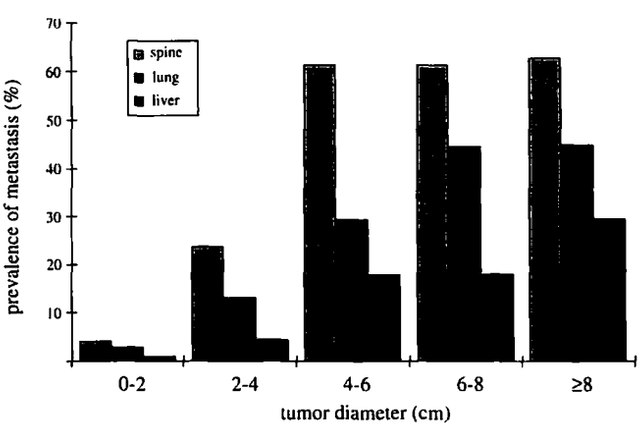


**FIGURE 3.** Tumor diameter and metastasis to spine, lung, and liver ($n$ = 891 patients).

pT4 carcinomas had no detectable metastases (19.7% of pT4 tumors), and there were also 42 tumors ≤2 cm that already had detectable hematogeneous metastases (7.9% of tumors ≤2 cm). These small tumors are able to use both hematogeneous metastatic pathways. Simultaneous metastases to spine and other distant sites were found in 48% of these tumors, and metastases limited to the spine or other distant sites were found in 33% and 19%.

## DISCUSSION

Prostate cancer had been detected in 8.2% of our patients. This is less frequent than in previous autopsy studies reporting a frequency between 8.8% and 20.6%.[7-14] This discordance between different autopsy studies can partly be attributed to different patient populations or different criteria of malignancy, but most of all to different methods of tissue processing. The rate of prostate cancer was highest in studies in which the whole prostate was cut in serial sections (median, 19.2%)[7-11,14,15] (Table 1). The frequency of prostate cancer was clearly lower in studies in which only 1 or a few prostate sections were histologically examined at autopsy.[12,13] This decrease in frequency is consistent with the results of Scott et al,[16] showing that serial sectioning of the whole prostate can double the number of detected prostate cancer as compared with routine procedures. The even lower prevalence of prostate cancer in the current study is attributable to the fact that histological analysis was done only in case of suspicious macroscopic findings. This suggests that a considerable number of microscopic carcinomas have remained undetected in this series. This does not, however, affect the analysis of the metastatic spread. The distribution of hematogeneous metastases, with bones, lungs, liver, pleura, and adrenals being most frequently involved was in agreement with previous studies.[17,18]

More than 50 years ago, Batson[4] had suggested that a backward venous metastatic pathway from the prostate to the lower spine existed. This hypothesis was based on the observation of an unusually high prevalence of lower spine metastasis in prostate cancer and also on cadaver experiments showing that contrast liquid could flow from the prostatic veins to the lower spine and subsequently also to higher segments of the spine in case of an increased intraabdominal or intrathoracic pressure. These results were subsequently contradicted by several other authors, who reported a similar prevalence of lower spine involvement in other tumors such as lung, bladder, and kidney cancer by means of bone scintigraphy.[19,20] Therefore, Batson's concept has not been generally accepted, despite the fact that the specificity of scintigraphy for the detection of metastasis is not satisfactory, especially in the lower spine, where degenerative changes prevail.[21]

This study provides strong additional evidence for the existence and clinical significance of the "Batson pathway." First, there was an inverse relationship between the prevalence of spine and lung metastases,

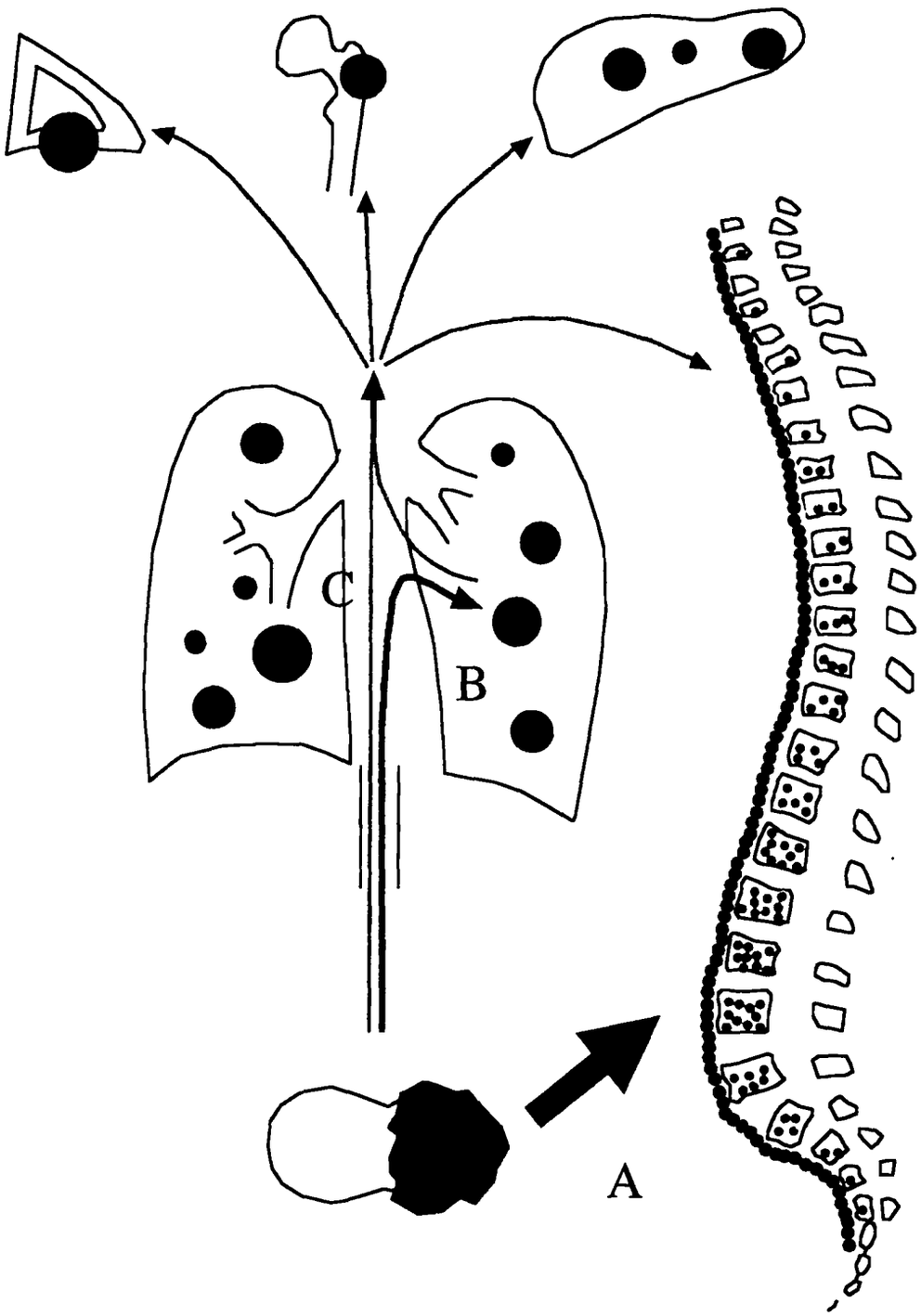


**FIGURE 4.** Pathways of hematogeneous metastasis in prostate cancer. (A) Backward venous spread to the spine; (B) Cava-type metastasis into the lung, and from there to other organs; (C) Cava-type metastasis without lung involvement.

suggesting that metastasis to the spine is independent from lung metastasis. Second, the maximum frequency of spine involvement occured in smaller tumors as compared with the maximum spread to lung and liver. This suggests that spine metastases precede lung and liver metastases in many prostate cancers. Third, metastasis to the spine occurred much more frequently in prostate cancer than in kidney or urinary bladder neoplasms in our autopsy series. Spine metastases were found in 87% of the patients with metastatic prostate cancer, whereas only 36% of 247 patients with disseminated kidney cancer and 39% of 206 patients with metastatic bladder cancer had bone metastasis (our unpublished data). This latter finding could be explained by a particularly high affinity of prostate cancer cells to the bones ("dependence of the seed on a fertile soil" hypothesis), but such a model could hardly explain the gradual decrease in spine involvement from the lumbar to the cervical part, which in turn would fit well with a subsequent upward spread along spinal veins

after initial lumbar metastasis. Taken together, these results strongly suggest that prostate cancer can follow 2 different hematogeneous metastatic pathways: a backward venous spread to the spine occurring early, and a dissemination through lung passage happening later in the disease (Fig 4). To identify early lumbar spine involvement, more sensitive and more specific techniques are necessary. This may be even more useful when combined with a technology for early detection of dissemination through the cava-type pathway (such as identification of circulating cancer cells), because our data suggest that even small but highly metastatic tumors can disseminate through both the cava type and "Batson" pathway independently.

The strong association between nodal status and distant metastases fits well with the poor prognosis reported for node-positive prostate cancer even if radical prostatectomy and lymphadenectomy is performed. It confirms that presence or absence of lymph node metastases can serve as an important indicator for the metastatic potential of prostate cancer. This further emphasizes the importance of a thorough preoperative or intraoperative lymph node staging. This particularly strong association between paraaortic lymph node involvement and distant metastasis supports the inclusion of these tumors in the M1 stage as proposed by the UICC.[6] Although this finding is in agreement with a previous report,[17] the higher frequency of lymph node metastases in paraaortic than in pelvic nodes is somewhat surprising. This phenomenon could be explained by different models. First, it is possible that some metastases can skip the pelvic lymph nodes and involve the paraaortic lymph nodes first. It is also possible that in locally extensive disease pelvic lymph nodes had become part of a pelvic tumor mass, or had been overlooked in some cases with prominent paraaortic involvement. Alternatively, it can be speculated that in some cases, paraaortic lymph node metastases can originate from spine metastases. This hypothesis is supported by the significant association between paraaortic lymph node and spine metastasis in this study. Independent of the mechanism of metastatic spread, the high prevalence of paraaortic lymph node metastases and the strong association with hematogeneous metastatic spread suggests that paraaortic lymph nodes should be closely examined before radical surgery.

The strong association of histological grade, local stage, and tumor diameter with metastasis confirms the well-established role of these histopathologic parameters as major prognostic factors in prostate cancer,[22] although the retrospective collection of these data from autopsy reports may not be as accurate as a standardized assessment in a prospective setting. However, there are prostate carcinomas that metastasize despite a small tumor size, whereas others fail to do so despite extensive local tumor growth. Given the rapid development in molecular medicine, there is hope that in the near future a better prediction of a tumor's metastatic potential will be possible at the time of the initial diagnosis. It would be particularly beneficial to identify tumors with a poor metastatic potential resulting in a lack of detectable metastases even at stage pT4. These patients could be cured by extensive surgery or would be candidates for new therapeutic strategies even at a late stage. Alternatively, radical treatment could be avoided in some N0M0 patients with a high probability of micrometastases on the basis of molecular examinations.

Finally, this study shows that autopsy series are a useful tool to elucidate the distribution and mechanisms of metastasis in prostate cancer. In addition, autopsy tissue specimens from distant metastases can provide a unique target to study molecular alterations underlying metastasis or hormone-refractory disease. For example, archived specimens from this autopsy series have been used to examine the role of gene amplifications during prostate cancer progression by fluorescence in situ hybridization on a prostate tissue microarray.[23]

In summary, the results of this study show that lymph nodes, bones, lung, and liver are the most frequent sites of prostate cancer metastases. Histological grade, tumor diameter, and local tumor stage are important predictors of metastatic spread. Besides the cava type of distant metastasis through lung passage, there is unquestionable evidence for the existence and clinical significance of a backward venous spread to the spine that is likely to occur early in the metastatic process.

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