The Chemotherapy of Intrathoracic Tumors*

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THE FUNDAMENTAL PRINCIPLES OF chemotherapy of intrathoracic neoplasms are the same as elsewhere:
1. Control the primary site of the neoplasm as completely as possible with surgery or local radiation.
2. Determine the reserve of the most vulnerable tissues to chemotherapeutic agents, e.g., hematopoiesis, renal, hepatic, etc.
3. Select the agent or group of agents which offer the highest probability of cancerocidal or cancerostatic effect.
4. Evaluate the level of incapacity of intra- and extrathoracic function which might result from maximal effect of the chemotherapy.
5. Select the optimal dosage and schedule of administration to achieve maximal and prolonged regression and yet minimize toxicity and untoward reactions.

PLANNED PROGRAM
It is best to plan an overall program immediately prior to surgical attack so the combined modalities of adjunctive chemotherapy and radiotherapy as well as subsequent therapy may be programmed. The chemotherapist has the added advantage of being present at the surgery. Regions which may remain neoplastically contaminated should be outlined with radio-opaque clips to define the exact location in three dimensions for subsequent radiation therapy and also to serve as a measure of evaluating growth recession of the tumor mass. Pleural or pericardial fluid should be carefully collected prior to contamination with blood or other tissues to ascertain the presence of tumor cells with confirmation by elevated lactic acid dehydrogenase activity in the fluid and by cyto-histology. When tumor cells are present in the fluid, an in vivo assay should be performed to aid in the selection of the most effective chemotherapeutic agent.

Many tumors are comprised of a mixed population of cells which, although they have similar or identical histopathologic appearance, each population often possesses diverse biochemical reactions which determine the susceptibility to one chemical agent and resistance to another. Furthermore, as chemotherapy proceeds, the percentage and flora of the tumor cells may change as adaptive mechanisms come into play, necessitating a change of chemotherapeutic agents. Therefore, the employment and selection of chemical agents should consider such mixed populations of tumor cells and if in vivo assay is not available, it is wise to employ simultaneous and sequential blocking of biochemical pathways in the neoplastic cells by employing agents which have different modes of action, combining a DNA inhibitor with mitotic interference and other agents whose actions differ therefrom.

ADJUNCTIVE CHEMOTHERAPY
The use of chemotherapeutic agents at the time of surgery may discourage implantation of the increased number of circulating tumor cells during surgical manipulation. This therapy should be started just prior to surgery and continued at high concentrations during surgery and for two

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to three days thereafter. It is essential that the agent to be employed be effective against the neoplasm or else no benefit can be anticipated. The employment of chemotherapy during radiation enhances the effects of both modalities which may offer advantages not achieved by either alone. In general, the

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<tr>
<td>Trachea</td>
<td>Cartilage, epithelium, chromaffin cells, sympathoblasts</td>
<td>Chondroma, fibroma</td>
<td>Tracheal carcinoma, pheochromocytoma</td>
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<td>Lung</td>
<td>Bronchial wall, accessory glands</td>
<td>Chondroma, hamartoma, fibroadenoma, papilloma</td>
<td>Epidermoid carcinoma, anaplastic carcinoma (oat cell), adenocarcinoma, pleomorphic carcinoma, bronchial adenoma, grade I carcinoma</td>
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<td>Pleura</td>
<td>Mesothelium, connective tissue</td>
<td>Lipoma, xanthoma, chondroma, osteoma, angiofibroma, myxoma</td>
<td>Liposarcoma, angiosarcoma, lymphoma</td>
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<td>Connective tissue, fat cells</td>
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<td>Superior-Anterior</td>
<td>Teratoma</td>
<td>Epidermoid carcinoma, teratoma</td>
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<td>Thymus</td>
<td>Epithelial reticulum, lymphoid tissue, mixture</td>
<td>Carcinoma, lymphosarcoma, lymphoepithelioma</td>
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<td>Connective tissue, muscle</td>
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<td>Fibromyxosarcoma</td>
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<td>Pericardium</td>
<td>Metastatic</td>
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<td>Leiomyoma, adenoma</td>
<td>Rhabdomyosarcoma, adenocarcinoma (Rare), epidermoid carcinoma</td>
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<td>Lymph nodes</td>
<td>Lymphocyte</td>
<td>Giant follicular lymphoma, lymphosarcoma, hodgkin's disease</td>
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Chemotherapeutic results of other intrathoracic tumors do not achieve the dramatic response often seen with lymphoid and leukemoid neoplasms. However, there are enough instances in which significant benefit has been unexpectedly achieved in other neoplasms which demand a concerted attempt despite the poor odds. The rapid selection of the most effective chemotherapeutic agent and its prompt employment will afford the best results. Many neoplasms are years in developing before they become clinically apparent and the earliest therapy with any modality is important.

The common tumors of the intrathoracic region are both benign and malignant (Table 1). In general, benign tumors do not respond as rapidly as malignant lesions to chemotherapy alone but experience with combined chemical and radiation therapy is insufficient for any valid opinion. The chemical agent should be directed at or as near the target areas as is feasible. The less time and distance that elapses between administration of the agent and its contact with the neoplastic cells, the greater will be the effect. Chemotherapy for local or distant neoplasms is arrestive but not curative and must be employed judiciously with caution.

**INTRACAVITARY CHEMOTHERAPY**
(Intrapleural and intrapericardiac)

This route of administration is ideal for recurrent neoplastic pleural effusion after control of the primary lesion has been attempted and a mediastinal cause for the effusion has been excluded. All the attributes of radioisotope instillation have been surpassed at less cost and expenditure of effort and need for special equipment. The maximum amount of pleural effusion is removed and the total number of neoplastic, mesothelial and leukocytes determined by calculation from the concentration and differential count. The cytometry and volume of cells and debris by centrifugation with the LDH activity of the supernatant fluid will also aid in gauging the effectiveness of the agent. The rate of fluid formation generally can be estimated by the amount of fluid that must be removed per week which affords a rough estimate of the neoplastic involvement and will subsequently serve as a measure of evaluating the therapeutic effectiveness.

With the needle still in place at the conclusion of the withdrawal of fluid, the chemotherapeutic agent is instilled into the pleural space via the tubing, taking precaution that there is free ingress and that the end of the needle has not slipped into the lung or into the subcutaneous tissue or parietal pleura. It is advisable to withdraw the fluid back into the syringe at the end of the injection and then squirt it forcibly back into the pleural cavity to enhance mixing of the chemical agent with the residual fluid. The needle is then withdrawn and the patient is asked to change positions gradually and to breathe deeply to facilitate further diffusion of the chemical agent in the pleural cavity. On occasion, the knee-chest position is advised, or if possible, the head is placed on the floor with the body remaining on the bed, much as in postural drainage, to allow the chemical agent to move to the upper portion of the lung field.

Four alkylating agents have proven of great value in intracavitary chemotherapy: HN2, methyl bis betachloroethylamine (HN2) (Mustargen), 0.2 to 0.4 mg. per kg., thio-triethylene phosphoramide (Thio TEPA) 0.2 to 0.8 mg./kg., mannitol myleran (CB 2511), 0.2 to 0.4 mg./kg., and cyclophosphamide (Cytoxan), 3 to 20 mg./kg. The exact dosage is estimated on the rate of fluid formation and the tumor content. The effect upon the local tissues is minimal and pain is only rarely encountered, particularly in those instances where erosion and ulceration of the pleura is present.

The effect upon hematopoiesis is much less than that generally observed with comparable intravenous doses. With continued administration of the chemical agent by this route, however, hematodepression will eventually ensue. The removal of the
chemical agent some hours after its administration has been attempted, with no significant decrease in toxicity. It is not recommended. Intrapleural infusions may be repeated every four to ten days as determined by the response and hematopoietic depression.

**Systemic Chemotherapy**

Intravenous, intramuscular, and oral routes have proved beneficial. Intrabronchial and intratumor routes have not been employed with success.

Ansfeld, et al. report a profound benefit with combined radiation and 5-fluorouracil in non-resectable carcinoma of the lung. Actinomycin D has also been noted to accentuate the effects of radiation. HN2 will produce objective regressions in approximately 25 per cent of patients with anaplastic (oat cell) carcinoma of the lung. Intravenous cyclophosphamide will produce similar benefit (20 to 40 mg./kg.). The hematopoietic system is the limiting factor for continued therapy.

Thymic carcinoma is only temporarily benefited by this approach, in contrast to the profound regressions that may be observed with lymphosarcoma of the thymus gland or with hilar involvement of Hodgkin's disease, lymphosarcoma or giant follicular lymphoma, treated with cyclophosphamide, chlorambucil, HN2, or Vinblastine. Prolonged benefit may be obtained for many years under judicious systemic therapy with these agents used intermittently and in conjunction with local radiation.

**Supportive Therapy**

Corticosteroids, usually employed as prednisone, 15 to 30 mg. daily, may support the hematopoietic system and further aid the lympholytic response. It is of particular value when a hemolytic or thrombocytopenic component is involved. Similarly, androgens will support erythropoiesis during erythropoietic depression. Testosterone propionate at 100 mg. two to three times weekly is effective, but testosterone enanthate (Delatestryl) is less troublesome, since 400 mg. each two to three weeks is equally effective.

Transfusions, preferably with red cell mass, should be used to maintain the hematocrit above 33 per cent. Chlorothiazide and spironolactone (Aldactone) will aid in the inhibition or fluid accumulation in the body cavities and in the tissues. These diuretics may supplement the intracavitary instillation of HN2, Cytoxan, or Thio TEPA. Oxygen therapy is often beneficial and should be employed to relieve dyspnea at rest. Good nutrition and avoidance of undue exhaustion are important.

**Chemotherapy of Pulmonary Metastases**

Metastatic neoplasms of the lung often pose a difficult but not hopeless problem despite the removal of the primary site, since each of the multiple lesions will serve as secondary foci for further dissemination. Consequently, the treatment is usually aimed both locally and systemically to inhibit the rapid growth which can rapidly produce fatal pulmonary insufficiency and massive peripheral metastases.

Three types of metastatic pulmonary neoplasms have been dramatically improved by systemic chemotherapy. Metastases of endometrial carcinoma will disappear for one to four years in approximately 30 per cent of patients who receive progestosterone or hydroxyprogesterone caproate (Delalutin). Widespread metastatic choriocarcinoma in women has been shown to respond dramatically to methotrexate. About 50 per cent of the patients have shown prolonged survival in excess of two to five years. Vinblastine has been employed in methotrexate-resistant patients with limited yet definite benefit.

Pulmonary metastases from embryonal carcinoma of the kidney (Wilm's tumor) respond occasionally and temporarily to combined radiation therapy and actinomycin D. Similarly pulmonary metastases
from testicular seminomas may regress for 4 to 12 months with HN2, Cytoxan or Thio TEPA.

**Intra-Arterial Perfusion**

The administration of a chemical agent directly at a neoplasm via its major arterial supply allows the immediate contact of the chemical with the neoplastic cell at high concentrations. Intrathoracic neoplasms can be easily approached by catheter introduced at surgery or via a large peripheral artery or vein. Since the many populations of tumor cells are dividing at various rates and entering mitosis at different times, a continuous prolonged infusion at high concentrations will interfere lethally with the largest number of divisions. The optimal period of administration to destroy all cells may require weeks if the individual cell generation time is prolonged as it is in many neoplasms. Consequently, a method of continuous infusion which affords free mobility during sterility and an exact dosage schedule can be maintained. This can be achieved by infusing via indwelling catheters sutured securely on the skin.

Bronchiogenic carcinoma is supplied primarily by the bronchial arteries, and the remainder derived from the smaller branches the pulmonary arteries. Occasionally a catheter can be introduced into the bronchial artery at surgery, but the results are, as yet, equivocal. Supply from the pulmonary artery is increased the more peripheral the lesion. Metastatic neoplasms in the periphery derive practically their entire blood supply from the pulmonary artery. Consequently, in the perfusion of neoplasms supplied by the pulmonary artery, a double-barreled catheter with two openings, one at the end and the other 10 to 15 cm. proximal to the end, is inserted via the cubital vein through the right atrium and right ventricle into the pulmonary conus. If both lungs are to be infused, the proximal opening of the catheter is located in the pulmonary conus so that the turbulent flow leaving the right heart will mix the chemical agent to reach both lungs. If either the right or left side is to be treated, the catheter with the shorter distance separating both openings is selected and the proximal opening is situated well into the major pulmonary artery of the selected side. The distal opening of the catheter is first wedged into a small pulmonary arterial branch which can be detected roentgenographically by a bend in the otherwise straight line of the catheter. The tip is then withdrawn slightly to admit blood flow beyond the catheter to avoid an infarction.

In most instances, arterially administered chemical agents will fix in neoplasms in amounts approximating 50 per cent or less on the first circulation. The unbound chemical which traverses the area may then circulate freely and cause early toxicity at the high levels of concentration of chemotherapeutic agents that are necessary for significant benefit. Therefore, the procedure of infusion-neutralization has been developed in which a counteracting group of chemicals is administered into the bloodstream leaving the tumor bed, neutralizing the unbound anti-neoplastic chemical. This can be accomplished at surgery by placing a catheter in the pulmonary vein, but can be achieved more simply via selective arterial catheterization. The wedged tip of the double-barreled catheter carries the neutralizing chemicals which pass through the pulmonary arteries in a small segment of the lung and which end up in the pulmonary vein. The anti-cancer chemical is administered simultaneously through the proximal opening. In this manner, extremely large doses of chemical agents may be administered over prolonged periods directly to large areas of the lung with little hematodepression, since the neoplastic bed is isolated, as it were, between two chemical agents. Temporary benefit may be achieved with anaplastic neoplasms, which can be further enhanced by radiation therapy simultaneously administered. Although many attempts have been made to isolate the upper thoracic aorta between obstructing balloons and via chemical isolation in a similar manner as described across the pulmonary arterial bed, no significant prolonged effects have been observed as yet.
REFERENCES


INTRACARDIAC PHONOCARDIOGRAPHY IN MITRAL STENOSIS

A study was made of 33 patients with mitral valve disease by means of left and right heart catheterization, conventional phonocardiography and intracardiac phonocardiography of the right and left heart. The intracardiac phonocardiogram was recorded by the electronic method from the catheter used for recording pressures. Fourteen cases were operated upon, and two of them were examined at necropsy.

A minor delay (10 milliseconds) was found in the vibrations of the intracardiac phonocardiogram over those of the external phonocardiogram. These are inherent in the method used. The intracardiac phonocardiogram proved of great utility in identifying the murmurs, their point of origin, their phase and mechanism. Greater amplitude of the third or fourth sound, and of the opening snap, was often found.

OBJECTIVE ASSESSMENT OF BRONCHIAL OBSTRUCTION CAUSED BY HISTAMINE INHALATION

The clinical data and lung volumes of 21 patients with known hyperreactivity to histamine were selected. The latter was determined beforehand by inhalation of aerosols with successively increasing concentrations of histamine during 30 seconds. The concentrations of histamine phosphate in the solutions were: 0.25, 0.5, 1, 2, 4, 8, 16 and 32 mg. per ml. The solutions were aerosolized with an air flow of 4 liters per minute. The lowest concentration which caused a change in the vital capacity more than 10 per cent was used in the comparative study.

Data were collected concerning the lung volumes, the intrapulmonary mixing of gases and the mechanism of breathing before and after histamine inhalation. It appears that VC and FEV, are the best lung volumes to demonstrate bronchial obstruction. Also, the data derived from the volume-pressure-diagram (viscous work of breathing and compliance) are suitable in this respect. The same holds true for the number of breaths needed for 95 per cent washout of the alveolar nitrogen. This conclusion is derived from the material as a whole. If the material is divided into two groups with the RV/TLC ratio as criterion, the data suggest that in the group with a low ratio, the FEV, viscous work and compliance are the best test, whereas in the groups with a high ratio, the number of breaths for 95 per cent washout is the best criterion for demonstrating bronchial obstruction as a result of histamine inhalation. It appears that simple spirometry as a rule is to be preferred to the more modern and refined methods.