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MANAGEMENT OF CARCINOMA OF THE BRONCHUS

BY

NEVILLE C. OSWALD, T.D., M.D., F.R.C.P.

Physician, St. Bartholomew's and Brompton Hospitals, London

Twenty-five years ago the management of carcinoma of the bronchus was almost entirely in the hands of physicians and general practitioners. Since then considerable advances have been made in diagnosis and treatment, but the majority of patients can still be offered no more than palliative medical measures. Physicians have a duty to keep abreast of recent advances because they are largely responsible for the form that treatment shall take. This is illustrated by reviewing some 272 cases seen personally since 1947, of which 166 (61%) came to light as a result of a medical consultation; these represent a small fraction of the vast number of patients with respiratory symptoms who are referred for routine clinical and radiological examination. The remainder, having already been radiographed, were sent for diagnostic and therapeutic assessment. Clearly, physicians have a very great responsibility in relation to early diagnosis, and this becomes progressively more important as methods of treatment improve. Before considering in detail the place of the physician, it is necessary to give a brief outline of the clinico-pathological background of the disease and the present stage of development of effective surgical and radiotherapeutic measures.

Clinical Assessment

Clinico-pathological Pattern

The usual pathological sequence is spread from the primary growth to the broncho-pulmonary glands within the lung, then to the mediastinum, and finally to extrathoracic sites. In this series the growth at the time of diagnosis appeared to be limited to the lungs in 138 (51%), had obviously spread to the mediastinum in 63 (23%), and had proceeded to involve extrathoracic structures in the remaining 71 (26%). In the terminal stages the main mass may be in any of these structures, but quite often the carcinoma never extends beyond the bounds of the thorax, death being caused by extensive involvement of the lung or mediastinum, or both.

Of 46 cases in this series untreated by surgery, necropsy revealed 24 with multiple extrathoracic metastases, 9 with solitary extrathoracic spread (3 brain, 6 suprarenals), and 13 with purely intrathoracic involvement. The suprarenals were involved in no fewer than 27.

The type of cell seen on microscopy is of some consequence, the more highly differentiated varieties such as squamous carcinoma and adenocarcinoma carrying a better prognosis than the anaplastic forms.

In this series section revealed that the carcinoma was adenoid in 26, squamous in 89, and undifferentiated in 59.

Little is known of the duration of the early stages of bronchial carcinoma. Almost certainly there is a latent phase in which epithelial metaplasia or islets of immature cells occur. When such specimens are available for microscopy, considerable difficulty may arise in trying to draw the line between a simple metaplasia and an early carcinoma, particularly when invasion of the deep layers of the bronchus is indistinct. The current view is that these early changes persist for a matter of months before showing obvious signs of invasion. Occasionally these very small foci can be identified radiologically, especially if they are associated with small patches of pneumonia or collapse.

Unfortunately, symptoms tend to develop rather late and often do not become apparent before extrapulmonary metastasis has occurred. Sometimes a haemoptysis or a small pneumonic episode may enable an early diagnosis to be made. The median duration of symptoms before diagnosis is of the order of four to six months (Bignall, 1955), and 70–80% of all patients are dead within a year from the time of diagnosis, emphasizing the rapid course of the disease once symptoms have developed.

In this series the median duration of symptoms from onset to diagnosis was 3½ months. With the institution of a follow-up system, the fate of 191 patients is known. Some 79 (41%) were dead in three months or less from the time of diagnosis and 145 (76%) died within a year.

Special Investigations

The diagnosis usually presents little difficulty provided the possibility of bronchial carcinoma is considered. Of the various special investigations, bronchoscopy is the most important because it is the one most likely to supplement radiological evidence of the extent of the growth within the thorax. It is generally regarded as yielding confirmatory evidence in about 60% of cases. This figure is not as great as that for neoplastic cells in the sputum, which, in the hands of experts, can be found in 60 to 90% of cases provided they are looked for thoroughly enough (Bamforth, 1946; Jennings and Shaw, 1953; Farber, 1954). Examination of the sputum is valuable mainly in investigating radiological shadows beyond the reach of the bronchoscope and in persons unsuitable for bronchoscopy.

When the growth has extended beyond the thorax, biopsy material is often forthcoming from the affected sites.

In this series a firm histological diagnosis was made in 174 (64%) by the following means: 113 bronchoscopy, 23 thoracotomy, 16 gland in neck or axilla, 14 sputum, 3 pleural fluid, 2 skin nodule, 1 oesophagoscopy, 1 liver

biopsy, 1 secondary in rib. In addition, 42 (15%) showed confirmatory evidence on bronchoscopy but biopsy was negative. The remaining 56 (21%) were diagnosed on clinical and radiological grounds.

The thoroughness with which individual patients are investigated varies with the stage at which the disease is diagnosed. If there is a chance of their being suitable for effective surgical or radiotherapeutic treatment, any measure which is likely to assist in the accurate location of the growth is applied. In many, however, there can be no hope of a cure, and investigations are directed towards confirming the diagnosis with the least inconvenience to the patients, and making certain that no other, possibly treatable, condition exists. The 56 patients in this series who were diagnosed on clinical and radiological grounds alone comprised mainly those who had reached a terminal stage of the disease at the time of diagnosis and for whom no effective treatment was possible.

Choice of Treatment

Before deciding upon a definitive form of treatment, it may be as well to consider briefly the potentialities of surgery and radiotherapy, because these are the only two methods of combating an otherwise uniformly fatal disease.

Surgery

In general terms, pneumonectomy offers a 50% survival rate at one year and 25% at five years, with an operative mortality rate of 10%. These figures need to be modified when they are applied to individual patients. In the most favourable group the five-year survival rate is in the region of 50% and a permanent cure is likely in a high proportion of these, although long-term follow-up figures for the most modern types of operation are not yet available. Patients most likely to have a favourable outcome from pneumonectomy are those under the age of 60, with good general health and no obvious chronic bronchitis, emphysema, hypertension, arteriosclerosis, or intercurrent disease, and with a well-differentiated growth which has not spread beyond the lung. Only a few fall within this category, and full assessment must necessarily be retrospective, because metastatic spread, especially to the mediastinal glands, can be determined only at or after operation. The less favourable group comprise patients who, at thoracotomy, have obvious mediastinal involvement but in whom the surgeon feels that a radical clearance of the mediastinum and part of the pericardium is worth while. Indeed, in the most desperate cases in which such a clearance is attempted, the rather problematic position has been reached in which a "salvage" rate of about 5% at five years has been achieved at the expense of an operative mortality rate of not less than 10%.

In addition to pneumonectomy there is the less formidable operation of lobectomy, which is sometimes appropriate for those unfit to stand the larger procedure. It may also be applied palliatively to remove a septic lobe distal to an occluded bronchus.

Radiotherapy

Although the one-year survival rate for radical radiotherapy may be as high as 50%, few radiotherapists can claim a five-year survival rate in excess of 3% (Smithers, 1951; Whitfield *et al.*, 1954; Hilton, 1955). Indeed, the long-term results have been so poor in the past that some authorities have abandoned this form of treatment. The problems to be faced are indeed formidable, the greatest being that there is no method short of thoracotomy for determining the exact site and extent of the growth within the thorax. All that a radiotherapist can do is to employ all accessory aids for accurate location, irradiate a sphere of not more than 3 in. (7.5 cm.) in diameter, and hope that the carcinoma has not spread beyond

these limits. He can never hope to irradiate effectively as much tissue as a surgeon can remove, and any infection there may be in association with the growth must remain and may be aggravated by the treatment.

The question of dosage remains a problem. Until very recently, the figure of 6,000 r, given by conventional means, was regarded as the smallest effective dose. This often caused much constitutional upset, and death was undoubtedly hastened in many patients. A course of about 4,000 r spread over four to six weeks is much better tolerated and seems to be equally effective in controlling a localized carcinoma.

Management

The diagnosis of bronchial carcinoma is usually obvious on simple clinical and radiological examination, and its confirmation by bronchoscopy, biopsy, or sputum examination is a matter of routine. Patients can be divided into three groups of roughly equal size—namely, those for whom some form of radical treatment may be attempted, an intermediate group, and those who are unsuitable for any form of effective treatment. As applied to this series of 272 patients, the first group comprised 57 (21%) who underwent thoracotomy and 35 (13%) for whom a radical course of radiotherapy was prescribed. The third group consisted roughly of the 41% of patients who died within three months from the time of diagnosis, the remainder forming the intermediate group. Clearly each patient must be placed in one of these groups without delay, in order that the necessary special investigations may be arranged.

There is inevitably an interval of at least a few days between the clinical diagnosis and pathological confirmation. This is the time in which physicians do their utmost to establish an alternative, and if possible less formidable, diagnosis. The whole range of causes of pulmonary consolidation and collapse, pleural effusion, and mediastinal irregularities need to be considered together with extra-thoracic features which might be due to metastases. Amongst the commoner differential diagnoses are pneumonia, pulmonary tuberculosis, the reticuloses, and cervical adenitis.

When the diagnosis is established as accurately as is necessary, the management can be considered for each of the three groups already described.

First Group

Here an attempt is made to effect a permanent cure either by surgery or radiotherapy or by both. As the results of surgery are the best that can be offered, the surgeon is given first choice of the most favourable cases—that is, those in which the growth is potentially resectable and the risks of the operation are not excessive. The operative mortality rate, within a month of operation, for pneumonectomy is in the region of 10%. If capable thoracic surgeons allow their death rates to fall much below this figure in the present state of knowledge, they are probably denying many of their patients the most successful form of treatment available. The significance of the figure of 10% varies almost from year to year with the steady improvement in operative and post-operative selection and care and the gradually increasing indications for operation. The selection of patients for pneumonectomy must rest primarily with thoracic surgeons, for they, working in a limited sphere, have the problem constantly before them, but the causes of failure in terms of post-operative deaths are almost entirely medical. They can be classified roughly as "cardio-vascular" and "pulmonary," and consist nosologically of such conditions as bronchopneumonia, anoxia, embolism, infarction, coronary thrombosis, and cardiac irregularities, but perhaps one-half of them would be better regarded as errors of clinical judgment in that either the physique or the will of the patient was insufficient to withstand the procedure in the event.

In this series thoracotomy was performed upon 57 patients; 41 of these had a pneumonectomy and 4 a lobectomy. There were 5 post-operative deaths. The figures are too small for detailed analysis, but most of the patients who lived for more than two years after diagnosis were successfully operated upon.

Radical radiotherapy is applicable to patients whose carcinoma appears to be limited in extent and who for one reason or another are unfit for surgical resection. There is no doubt that radiotherapy has a specific effect upon cancer cells, and bronchial carcinomata often diminish in size or disappear, at least temporarily. Undifferentiated growths are very difficult to control, but squamous carcinomata may be held in check for many years. A full course of radiotherapy (about 4,000 r spread over four to six weeks) can cause as much constitutional upset as a pneumonectomy, and so can be given only to patients who are reasonably fit at the time. It has the advantage over surgery that it can be used safely in the older age groups; also associated cardiovascular and pulmonary disorders are relatively less important; but it has the overwhelming disadvantage that only a small volume of tissue can be effectively treated.

Of 35 patients for whom radical radiotherapy was planned, 27 completed the course; the remainder either could not tolerate the treatment or developed distant metastases during the course. Three patients having the complete course, all with histologically proved squamous carcinomata, had almost complete radiological regression which persisted for the rest of their lives; one died after 3½ years from coronary thrombosis and the other two after 3½ and 4½ years respectively from rapidly progressive distant metastases.

Second Group

These patients present many problems to physicians. They are usually fit and perfectly capable of doing a day's work, yet they are unsuitable for radical therapy. Such patients may present with no more than a blood-stained pleural effusion containing neoplastic cells, or there may be a small discrete primary growth with enlarged glands above the clavicle, or possibly there is a formidable hilar mass. A decision has to be made whether to offer the patient a form of treatment which causes a higher mortality rate than its five-year survival rate, or whether to abandon any hope of cure and treat symptoms as they arise. In coming to a conclusion, particular attention must always be paid to the patient's temperament and general social and domestic background. A serious operation will make some of them into unhappy invalids, whereas with symptomatic treatment alone they may enjoy six months to a year of good health in ignorance of the diagnosis and then rapidly go downhill as metastases develop. More stoic patients are prepared to accept risks as long as a hope of cure exists. Indeed, it is from this group that advances in effective treatment derive.

In this series 72 patients had either a resection or radical radiotherapy, leaving 200 (73%) in whom the growth was inadequately dealt with. In many patients there were several reasons for withholding treatment; the following were the principal causes—extrathoracic metastasis (65), mediastinal involvement (57), cachexia (31), bronchitis (16), pleural effusion (14), old age (10), and miscellaneous (7).

Third Group

This group comprises those for whom no more than symptomatic treatment is possible. Some survive for only a few days after diagnosis, others may linger on for many months. The diagnosis is usually obvious, and pathological proof is necessary only if there is any doubt. Indeed, there are times when confirmation by biopsy is an embarrassment when dealing with intelligent patients. Much has been said but little has been written about whether a cancerous patient should have the nature of his disease explained to him. The time-honoured British custom is to avoid letting the patient know at all costs, at the same time informing the

nearest relation. Personal experience suggests that this is the best approach, because on the few occasions when the diagnosis has been made known no advantage has resulted; in the majority it has made no difference because they did not understand the implications, but in an important minority the information caused great unhappiness and hastened death.

The management of these patients calls for considerable skill and judgment if the distressing effects of the disease are to be minimized and confidence in the medical attendants is to be maintained. The relationship between physicians and general practitioners is somewhat nebulous, and the question of routine attendances at out-patient clinics and consulting-rooms arises. Physicians are able to supply clinical and radiological progress reports and are conversant with recent trends in local symptomatic treatment; general practitioners are equal if not more competent judges of the range of analgesics. The determining factor in whether specialist opinion is regularly sought is often the attitude of the patient. Some demand it, others are content to trust the family doctor in the knowledge that a further opinion can be sought if necessary. Sometimes the maintenance of hope in the face of increasing symptoms and unacquaintance with the diagnosis is best ordered by one man, the family physician, the specialist having previously convinced the patient that he is having the correct treatment, that he may become worse before he improves, and that further consultations can be arranged if necessary. As the problems of each patient are different, the happiest solution is often for the specialist to inform the family doctor fully of the prognosis and possible symptomatic treatment and leave to him the question of further consultations.

Symptomatic treatment consists of local measures, such as palliative radiotherapy and pleural aspiration, and analgesics. The former tend to be used while a reasonable good general health persists, and the latter in the terminal stages. Radiotherapy, which is unpredictable in its effect, is most likely to afford relief when there is obstruction of the superior vena cava; it can also benefit recurrent haemoptyses, intractable cough, and metastases in bone. Radioactive gold often checks the formation of metastatic effusions. There is considerable individual variation in the effectiveness of analgesic drugs. At first, preparations containing codeine and phenacetin are usually tried, with a barbiturate at night. When these fail to relieve pain, pethidine and methadone hydrochloride should be given before morphine and its derivatives are finally relied upon. In the last category, "nepenthe," heroin, and the Brompton cocktail (morphine, cocaine, and gin) are usually tolerated best.

Of the supportive measures during the terminal stages the following should be mentioned. Cyanosed patients benefit most from oxygen; it should be given intermittently through a "polythene" bag attached loosely to the head. Nausea, especially during radiotherapy, is often relieved by pyridoxine, 60 mg. thrice daily, with a fluid intake of 2,500 ml. a day. Frequent moving of position lessens the chances of pressure sores and bronchopneumonia; this may be facilitated by using a cardiac bed. Pressure on the spine may be relieved by air rings and feather pillows. Much encouragement is needed to combat mental depression; for this reason, patients with this disease should never be nursed in adjacent beds.

Discussion

The present position with bronchial carcinoma is that, of 100 patients, 70 to 80 die within a year of diagnosis and not more than 10 survive five years. This appalling state of affairs is mainly due to two causes. Firstly, the disease has spread too far by the time the diagnosis is established, and, secondly, many patients are unable for one reason or another to tolerate radical treatment. In the future, improvements will undoubtedly be made, as they have been progressively over the past 25 years. The following would seem to be the main lines of advance: prophylaxis, earlier diagnosis, better selection for radical treatment, improve-

ments in surgery and radiotherapy, and possibly some entirely new approach through hormones or chemotherapeutic agents.

Prophylaxis, so far as is known, is concerned with pollutants in the inspired air. There can no longer be any doubt but that tobacco-smoking carries an added risk for those who are susceptible to cancer. Equally, the atmosphere of industrial towns predisposes to bronchial carcinoma (Waller, 1952; Stocks and Campbell, 1955; Clemon *et al.*, 1955). Far more needs to be known about the carcinogens involved before effective prophylactic measures can be firmly recommended.

Earlier diagnosis may be achieved either by periodic radiography of selected groups of the population or by shortening the interval between the onset of symptoms and treatment. Mass radiography is an expensive undertaking for this purpose. A review of some 750,000 persons examined by this method showed that only 66 previously unknown carcinomata were brought to light, and of these only 38 were resectable (McNulty, 1954; Bondi and Leites, 1952), and the suggestion that all heavy smokers should have a routine chest x-ray examination every six months after the age of 40 (Ochsner *et al.*, 1954) is hardly practicable at present. Undoubtedly, mass radiography is a valuable means of detecting carcinoma in its early stages; indeed, 24 or nearly 10% of the present series were detected in this way; but not all fresh cases are chance findings, as people with recent respiratory symptoms tend to offer themselves for group surveys and the facilities are sometimes available to general practitioners for use in selected cases. However, mass radiography, which is primarily designed to detect pulmonary tuberculosis, will continue to contribute to the earlier diagnosis of bronchial carcinoma.

Attempts to shorten the interval between the onset of symptoms and treatment will always be a challenge. Men developing fresh respiratory symptoms after the age of 40 should certainly be radiographed; but this is by no means the whole story: far too much time has been wasted in the past between the radiological diagnosis, pathological confirmation, and effective treatment. One of the most difficult aspects of early diagnosis is the interpretation of minimal radiological changes. Not infrequently a film shows an opacity measuring 3-5 mm. in a lung field which may not have been present in a previous film, should one be available. The question that arises is whether or not the lobe or lung should be removed. In the present state of knowledge, there is a tendency to wait for further films after an interval. Perhaps future refinements in tomography, especially near the hilum, and in the examination of sputum for malignant cells will lead to more accurate assessment of these cases.

In selecting patients for surgical treatment, a balance must be kept between the extent of the operation and the resistance of the patient. The most formidable operation of radical pneumonectomy, which involves extensive mediastinal dissection and intrapericardial ligation of the great vessels, can be carried out with a mortality within two months of operation of 10% in expert hands (Brock and Whytehead, 1955). Further surgical innovations are unlikely to be dramatic, but there is room for improvement in dealing with metastatic glands in the region of the superior vena cava and the base of the neck. Obviously some patients cannot tolerate these radical procedures, but benefit from a lobectomy. On the whole it is not the purely surgical aspect which causes early post-operative deaths, provided the resuscitation and transfusion services are efficient. More important are cardiac irregularities, coronary thrombosis, venous thromboses, inadequacy of the remaining lung, and the toxic effects of anaesthetics. A better appreciation of these hazards is slowly developing.

Radiotherapy, the Aunt Sally of radical treatment, has overcome many obstacles. Burns of the skin have been virtually eliminated, necrosis of the growth from overdose rarely occurs, and treatment beyond the point of systemic

tolerance is no longer carried out. Massive fibrosis and radiation pneumonitis, which have been so troublesome in the past, may well be alleviated by cortisone (Whitfield *et al.*, 1954; Levitt, 1955). When and how much cortisone should be given is uncertain. If it is given within six weeks of radiotherapy, it may interfere with the cancericidal effect of the deep x-rays, but certainly in some cases it seems to be remarkably efficient even if given after a lapse of many weeks. Some advances may derive from the newer and more powerful high-voltage units, but the difficulty of giving an effective dose to more than a small volume of the thorax which can be tolerated will remain.

A succession of chemotherapeutic agents, such as the nitrogen mustards, have been tried, but none seems to have the slightest beneficial effect upon bronchial carcinomata (Smithers, 1951). Attempts to find an effective substance continue.

Summary

A general review is presented of the management of carcinoma of the bronchus from the point of view of a physician, incorporating the findings in 272 cases seen personally since 1947.

Despite considerable advances in surgery, and to a less extent in radiotherapy, in the last 25 years, the prognosis remains very poor for the majority of these patients. Of 191 patients in this personal series who have been followed for at least a year 41% died within three months and 76% within a year of diagnosis. These figures differ little from most published series. The most encouraging feature of treatment is the success of surgical resection in patients having well-differentiated carcinomata which have not spread outside the lungs; for these, a 50% survival at five years has been achieved, and longer follow-ups will probably reveal that a high proportion have been cured. Unfortunately the results of radical radiotherapy have been disappointing so far, partly because patients in the most favourable group have generally been treated surgically. Few radiotherapists can claim a five-year survival rate in excess of 3%.

Palliative treatment, in the form of radiotherapy and analgesics, does much to relieve distress and calls for considerable judgment in its administration.

Advances in therapy are bound to continue, as they have done in recent years. Prophylaxis, by reducing pollutants in the inspired air, is being studied, and carcinogens, such as 3-4-benzpyrene, are being isolated. Earlier diagnosis is made possible by modern methods of investigation of respiratory symptoms in the older age groups and by mass radiography. Better selection of patients for radical treatment, with a view to reducing the complications of treatment, is likely. Improvements in surgical and radiotherapeutic technique continue. Perhaps some entirely new approach through hormones or chemotherapeutic agents may be developed.

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