

Papers and Originals

Treatment of Isolated Pulmonary Metastases*

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Tudor Edwards was largely instrumental in establishing the journal *Thorax*, and it was fitting that the first article in the first edition should be by him, entitled "Carcinoma of the Bronchus" (Tudor Edwards, 1946). In this he gave his experiences with what, at that time, was a very large series of operations for lung cancer. He incidentally mentioned that he had removed five secondary growths with good results. In a previous memorial lecture Sir Clement Price Thomas (1959) brought the story of primary lung cancer up to date and in this one I shall consider the place of operative treatment in secondary lung carcinoma.

The series consists of an analysis of 108 cases of secondary lung cancer in which operative measures were considered justified. Eighty-six had their origin in a primary carcinoma in some other part of the body and 22 had their origin in a sarcoma of bone, soft tissue, or synovial membrane. Many of these patients had a bizarre clinical course and few firm conclusions can be drawn from what is, inevitably, a relatively small series in each subdivision. Pneumonectomy was performed in 13 cases, lobectomy in 42, local excision in 41, and imperfect removal in 12. Subsequent irradiation and chemotherapy were given in 40-50%.

The main features recorded were the interval between the removal of the primary tumour and the appearance of the lung secondary, and the survival time following the pulmonary excision. Careful note was taken of the condition of the primary site at the time the secondary was recognized. The decision to perform excision was not always easy to arrive at, largely because the recognition of a single solitary secondary might be followed by the appearance of others. There were, however, occasions in which the true state of affairs was not recognized and the shadow in the lung radiograph was suspected of being a primary neoplasm and was treated accordingly. In such cases the primary either had not been recognized or, more usually, there had been such a long period of freedom from recurrence that the possibility of a secondary seemed remote.

As has been indicated, the basic classification is into carcinoma and sarcoma, each of which can be further subdivided (see Table).

Origin of 108 Cases of Solitary Pulmonary Metastases

Origin	No.	Interval in Years		Survival in Years		
		No.	Average	No.	Average	
Bone	14	Sarcoma (22) 0-5		2	1-10	2½
Soft Tissue	5	3-8		5	2-3	2½
Synovioma	3	0-7			1-3	
Kidney	21	Carcinoma (86) 0 0-10		3	1-8	2
Colon and Rectum	17	0-13		4	0-5	2
Breast	10	1½-12		6	1-4	2
Uterus	7	0-10		5	1-7	5
Larynx	6	1-6		2½	1-5	2½
Testis	5	0-3			1-6	
Stomach	4	0-2			1-2	
Brain	2	0			1/12-7/12	
Melanoma	3	0-3			2-4	

Antrum 1, Rodent 1, Parotid 1, Thyroid 1, Oesophagus 1, Jejunum 1, Hepatoma 1, Pancreas 1, Bladder 1, Ovary 1, Prostate 1.

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Carcinoma

Kidney

There were 21 cases, 14 single and seven multiple (including three bilateral cases). At thoracotomy one case proved inoperable. There were five pneumonectomies, eight lobectomies, and 10 local excisions. The lung lesion was recognized at the same time as the renal growth on three occasions and these patients survived three, four, and eight years. Five lung secondaries were identified within two years of nephrectomy, and all these patients died within a year from further recurrences. At a longer range (four to six years after nephrectomy) there were five of whom one was well three years later. In a further five patients the interval was over six years after nephrectomy, being as long as 10 and 14 years in two surviving cases. One of these had had a nephrectomy in 1952 and remained well until he developed cough and pyrexia. The radiograph showed two opacities in the right lower lobe. Mr. Keith Ross excised these metastases, the histology of which was identical with that of the primary tumour. Six months later a shadow was noted in the left lower lobe. The patient was thoroughly investigated for the presence of other secondaries, and Dr. Mikhail felt that a waiting period of four to five months was justified before considering further operative measures. As no further change was observed, a lower lobectomy was performed. The patient was well more than 20 months later.

Colon and Rectum

There were 17 cases, 12 single and five multiple (including one bilateral case). The average age of this group was 55-65 years, including one man who was 85 at the time of thoracotomy. On the whole these secondaries were larger than most, and two proved inoperable and four required pneumonectomy. In one case the lung metastasis was recognized at the same time as the colon growth was diagnosed, but most metastases appeared a considerable time after removal of the primary tumour (five over four years and four over six years later). One patient died following thoracotomy and nine patients died within two years, mostly from recurrence but with no further lesions in the lungs; seven have survived over three years, and five of these were patients in the long-interval category. This small series approximates with the observations of Thomford, Woolner and Clagett (1965), who gave a 40% three-year survival in 65 cases where the origin of the primary was the rectum or colon.

Breast

There were 10 cases. With one exception these were single and usually of considerable size. Three were inoperable and one required a pneumonectomy. The interval between excision of the primary and appearance of the solitary secondary was short, though two appeared 8 and 12 years after the original operation. These isolated lung secondaries were comparatively rare when compared with the incidence of pleural and general pulmonary metastases, and, as might be expected, they did badly, only one patient surviving more than four years.

Patients who developed further recurrences did not respond well to chemotherapy, radiotherapy, or any of the other accepted measures, and it is concluded that, unless there is an appreciable interval between the treatment of the primary and appearance of the lung secondary, excisional treatment has little to offer.

Uterus

There were seven cases, five single and two multiple. One patient was submitted to pneumonectomy and another to lobectomy under the assumption that the lung lesion was a primary cancer. The true nature of the position was found only after histological examination, and hysterectomy was undertaken later. These patients remained well over a short term. A further three who had a hysterectomy 6, 8, and 10 years previously were submitted to local excision of the lung secondaries and remained well for three years and over.

Larynx

One of these six cases was bilateral. In this group a laryngectomy had been successfully performed and in the course of follow-up the lung secondary was recognized, usually three to four years later. Long-term survival was observed in only one instance (five years) and the remainder died from further recurrence. It is suggested that the pulmonary secondaries might be implanted rather than blood-borne. This cannot be proved, but histologically they tended to be endobronchial rather than peripheral tumours.

Testis

One of these five patients had a bilateral lesion and all were treated by lobectomy. In one instance the lesion in the lung was excised before the primary growth was recognized, but in the others the interval was three to four years. In one patient who had had a seminoma removed four years previously there were five secondaries in the lower lobe, which was excised. The patient remained well seven years later.

Stomach

Two of these four cases were identified during routine investigation before laparotomy and were excised locally. The others were recognized in the course of routine follow-up and were excised because the abdomen was clear and the lesion was suspected of being of primary pulmonary origin. There were no survivors over 12 months.

Melanoma

There were three cases. One of the lung secondaries was multiple and required pneumonectomy for its removal. This secondary appeared three years after excision of a forearm primary and the patient has survived four years. In another case a single secondary removed from the lung was shown to be a melanoma before the small skin primary was recognized.

Brain

Two isolated tumours removed from lung were associated with cerebral lesions. The high incidence of primary lung growths with cerebral secondaries is accepted, but in these cases the lung lesion more closely resembled the biopsy that was obtained from the brain. Both patients died within a few months.

Other Cases

The remainder of the cases of carcinoma consist of single examples of secondaries arising, one each, from the antrum,

parotid, thyroid, oesophagus, jejunum, pancreas, bladder, ovary, and prostate, and one hepatoma, and one rodent ulcer.

Two cases were of special interest. One was that of the hepatoma which had been removed from a woman of 38. Three years later she was found to have a nodule in each lung. Thoracotomy was undertaken on each side and the secondaries were removed. She survived three and a half years without further involvement of the lung fields but died of metastases elsewhere.

The other case was that of an adrenal tumour removed by Professor Le Quesne from a man of 54. Four years later a group of secondaries developed in the right upper lobe. They were removed and he remained in good health for two years, when biochemical investigations indicated the further presence of active growth. The primary site was then explored and a local recurrence removed.

Sarcoma

This group of 22 cases is analysed under three headings: primary bone tumours, soft tissue sarcomas, and synoviomias.

Primary Bone Tumours

Of these 14 cases four were multiple and three were recognized at the time the primary tumour was treated, but most appeared after an interval of two to three years (five years being the longest). The average survival time was two and a half years, though one patient had survived more than 10 years. Sweetnam and Ross (1967) analysed the cases of 12 patients with solitary metastases from bone primaries and found that four had died from the disease and that the average survival after the lung operation was six and a half years. It should be mentioned that two patients included in that series are also in this series.

Soft Tissue Sarcomas

These five cases had a fairly long interval before secondaries appeared, the range being between three and eight years. There was one bilateral case in which cannon-ball-type secondaries were excised from each lower lobe and the patient remained well two and a half years later. The average survival has been between two and three quarter and three years. One patient, a woman of 49, had had a retroperitoneal sarcoma excised by Sir Eric Riches in 1949. Eight years later, quite by accident while the efficiency of an x-ray plant was being tested, her chest was x rayed and a secondary found. This was excised and she remained well for two years, at the end of which time she developed a secondary at the base of her tongue, and this, in spite of treatment, proved fatal.

Synoviomias

There were three cases. One patient whose secondary was recognized a year after a wrist primary had been excised has survived three and a half years after lobectomy, and another, who had an amputation for an ankle joint primary, was well for seven years before a single secondary appeared. This was removed by lobectomy, and the patient remained well for three years before dying of multiple secondaries. The third case proved an interesting diagnostic problem. A woman of 43 came from the Middle East and was referred with a presumed diagnosis of hydatid disease. One large and two smaller rounded shadows were seen in the right lung and the Casoni test was positive. Just before entering hospital she coughed up some blood and a membranous substance said to be like a grape skin. On examination she was found to have a small lump the size of an almond on the tip of her left shoulder. This was infiltrating skin but was not adherent to deep structures. At operation the objective of enucleating the cysts

was unsuccessful because they were very adherent to lung tissue. They were excised and found to contain clear fluid. The nodule on the shoulder was also excised; and pathological examination showed that the nodule and the lung cysts were identical in appearance and were synoviomias. Some months later the patient developed multiple secondaries.

Mackenzie (1966), reviewing 58 cases of synovioma, quoted a 50% five year survival but did not indicate the incidence of lung involvement.

Discussion

From the above short summaries it would appear that there is no real relationship between the interval following excision of the primary and appearance of the secondary and the survival time. But it does appear that excision of a single or isolated group of secondaries is not necessarily followed by a shower of further metastases. This and the occasional long survival is the most encouraging aspect of the exercise.

The whole question centres around the problem of why in some cases there should be single secondaries and not multiple ones. Before discussing this it is useful to consider Willis's (1967) analysis of 500 necropsies for malignant disease. Among his figures he showed that the lung was the site of metastases in 11 out of 26 sarcomas, in 28 out of 48 cases of breast cancer, in 8 out of 10 renal growths, but in only 8 out of 65 intestinal cancers. Involvement in the case of the kidney is fairly obvious, since the growth has a predilection to grow along the renal vein and into the vena cava and, similarly, sarcoma might be assumed to have ready access to the venous system. These are simply figures which indicate the proportion of patients who may die with involvement of the lung.

Schmidt (1903) observed that malignant cell emboli may be found in the lung without any visible metastases, and in fact this observation was also made by Andrée as long ago as 1874. In other words, a metastasis is something more than a malignant cell embolism; it implies growth of cells at the point of lodging, and the size of the cell mass that can be impacted in the lung varies from 50 to 200 μ . This can be demonstrated experimentally if a fine suspension of carcinoma cells is injected slowly—they pass through the pulmonary capillaries. But if the same number of cells is injected in intermittent clumps a malignant embolism is much more likely. Takahashi in 1915, experimenting with mice, showed that the number of "takes" with different strains of tumour varied, but he did show that less than 3% of the mice that had had malignant cells injected had metastases in the lung—the lung capillaries presumably act as an efficient filter, preventing circulating malignant cells producing emboli.

Certain tumours, as already mentioned in the section on the kidney, are apt to invade the venous system directly, but most invading carcinomas will in time involve veins of a greater or lesser magnitude and either produce growth emboli or a continuous scatter of growth cells into the blood stream. Metastases from other organs whose blood supply does not drain into the systemic veins may reach the lungs indirectly. Blood-borne secondaries from the large bowel tend to lodge in the liver, where their mitotic activity might be 5 to 10 times as great as that of the primary lesion. Portosystemic anastomosis may explain some cases of direct embolism into the systemic veins, but it would appear probable that lymphatic involvement plays a much greater part.

With every malignant growth there is a possibility of lymph node involvement. It has been considered that lymph nodes had a defensive role in malignant disease and passed on viable tumour only when unable to deal with the invasion. But probably, as Willis suggested, the lymph nodes form a receptive soil for cancer cells. It is known that growth cells injected into the afferent lymphatic can appear in a matter of

minutes in the efferent channel. It is not difficult to conceive that the main lymphatic trunks will be involved, and indeed 3% of all cancer fatalities show invasion of the thoracic duct. Growths in this structure can permeate local tributaries and enter the blood stream at a low level or else discharge their cells directly into the subclavian vein.

Finally there is the question of implantation. Pryce (1946) showed good examples of this when secondaries of primary bronchial origin were found in the small intestine, but this method of involvement of the lung is not commonly accepted, though it might occur readily in the case of the larynx or oropharynx. It can be explained by reaching the lungs by vascular channels.

To turn to the malignant emboli that become lodged in the lung capillaries, most are surrounded rapidly by fibrin and platelets and degenerate, leaving only a microscopic scar. A metastasis characterized by continuous proliferation probably helped by mutual adhesiveness of the cells and their motility and the invasive property of the tumour itself. Some tissues are more and some are less favourable to cell growth, as witnessed by the high mitotic activity of liver and the extreme rarity of secondaries in muscle. The biological and biochemical function of the organ or tissue must play a large part in determining proliferation or abortion of a lodged malignant cell.

The problem of immunity must also be considered. Cellular immunity may well be a vital factor in the host's response, and it seems probable that tumour-specific antigens play an important part in the ability of the host to recognize a tumour, whether primary or secondary, as self or non-self. The malignant cell, having so much likeness to its forebears in the early proliferative stage, tends to be regarded as self and thus ignored; whereas a more abnormal cell might be recognized as non-self and initiate an immunological response. The explanation of the long interval before the appearance of the lung secondary is not easy, particularly if the site of the primary has remained for years free from recurrence. Presumably the lung metastasis was liberated before the primary growth was excised or at the time of operation, and has since remained dormant.

The observation of Collins (1962) was based on the doubling theory, where the growth rate is an exponential curve related to the frequency with which cells multiply. For example, a cell mass of 10 μ would require 20 doublings to produce a tumour 1 mm. in diameter; but it would take only another 10 doublings to produce a mass 1 cm. across with a possible cell count of 10⁷—and a further 10 doublings would increase its size a thousandfold. A 1-mm. mass would not be readily recognized on a radiograph but one of 1 cm. diameter certainly should, and Collins used this fact to refute the term "early growth" and suggested that the growth may have been present for an appreciable time before being recognized, but when this happens there is acceleration of the visible increase. Cell multiplication by malignant cells could account for the apparent latent period, but it seems reasonable to assume that there are other factors which retard or accelerate the doubling.

When one is faced with the problem of a possible single secondary there is no doubt that its removal should be considered, subject to due regard to the patient's health, etc. Many of these patients did not have further recurrence in the lung and some survived a considerable period. It might be argued that chemotherapy would exert its effect on other potential secondaries, not clinically recognized; but in cases outside this series we have seen little long-term success with this or with radiotherapy. That these measures undoubtedly should be used if further recurrences develop is certain. The other aspect is that a number of secondaries have been removed on the assumption that they were a different type of lesion altogether, and in such cases later surgery and treatment of the primary is necessary.

Possibly the real lesson to be learned is that because a pulmonary secondary has appeared it does not mean that the clinicians must remain passive on the assumption that further trouble is bound to develop. Boldness, as Tudor Edwards showed more than 20 years ago, has its rewards.

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Induction of Labour with Prostaglandins E₁ and E₂

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Summary: The use of intravenous infusions of prostaglandin E (E₁ or E₂) for the induction of labour was studied in 25 patients at or near term. Labour was successfully induced in 23 patients. The pattern of uterine motility produced resembled that of normal labour. No hypertonus was recorded nor were there any undesirable side-effects.

Introduction

The prostaglandins, first recognized for their effects on the contractility of uterine and other smooth muscle, are now known to comprise a group of chemically related long-chain hydroxy fatty acids. Each is derived from the basic (but not itself active) prostanoic acid, consisting of a 5-carbon (cyclopentane) ring with two hydrocarbon chains attached to neighbouring carbon atoms. Depending on the configuration of the 5-carbon ring, each belongs to one of four groups (F_a, E, A, or B), while for each group a suffix numeral (1, 2, or 3) describes the degree of unsaturation of the side chain (see formula below).

The prostaglandins are widely distributed in mammalian

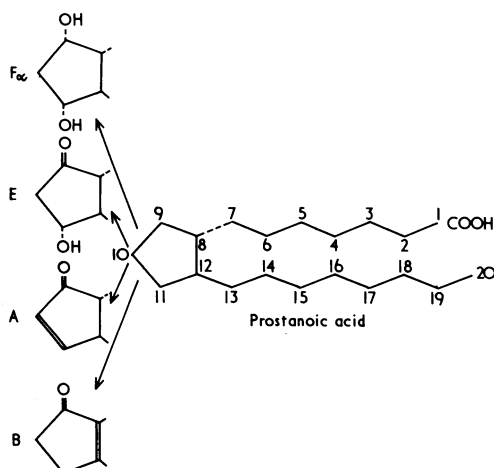
tissues and are believed to be responsible for an extensive range of biological activity (Bergström *et al.*, 1968; Pickles, 1969). Hitherto, on the basis of laboratory experiment—concentrated on non-pregnant myometrium—it was generally believed that prostaglandins belonging to the F_a series stimulated while E prostaglandins inhibited uterine myometrium (Bygdeman and Eliasson, 1963; Pickles and Hall, 1963; Bygdeman, 1964; Pickles *et al.*, 1965). Recently, however, it was shown that in the human uterus in pregnancy the E prostaglandins possess even more striking stimulatory properties than those of the F_a series. The uterotonic effects observed in vitro (Embrey and Morrison, 1968) were soon corroborated in a preliminary study of the pregnant uterus in situ (Embrey, 1969). That study showed, moreover, that the intravenous infusion of only small amounts of prostaglandins—especially E prostaglandins—was often followed by the successful induction of labour.

The present study explores further the potential value of the E prostaglandins (E₁ and E₂) in the induction of labour.

Patients and Method

Studies were undertaken in 25 women at or near term (36–42 weeks) who were recommended for induction of labour. The indications for interruption of pregnancy were: post-maturity 7, pre-eclampsia 7, hypertension 3, unstable lie 3, breech 1, hydramnios 1, diabetes 1, anencephaly 1, and intrauterine death 1. Immediately before the study a careful assessment of the obstetric findings was made, noting particularly the station of the presenting part and the state of the cervix. The membranes were already ruptured in four patients.

Pure prostaglandins (E₁ and E₂) in solution in normal saline (2 µg./ml.) were administered by continuous intravenous infusion. The prostaglandins were first dissolved in a small volume of ethanol and diluted with sodium carbonate 0.2 mg./ml. to provide a stock solution of 100 µg./ml. The solution was sterilized by filtration and kept frozen when not in use. The stock solution was further diluted with normal saline before use. Uterine contractility was recorded either internally by means of a small intrauterine balloon or in some cases by external means with the Oxford tocograph. Spontaneous contractility was observed for at least 30 minutes before beginning the infusion, and throughout the study



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