MALIGNANT DISEASE OF THE THYROID GLAND.

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I. INCIDENCE.

It is not easy to estimate precisely the incidence of malignant disease of the thyroid, since there are hardly any vital statistics available which relate to the matter. We have to rely largely, therefore, on the figures provided by the more important thyroid clinics which enable us to deduce the incidence of malignant goitre compared with that of benign and thyrotoxic goitres. The ratio varies rather widely in different clinics, viz., 7·4 per cent.¹ (Kocher) down to 1·2 per cent.² (Coller) or less, and it appears that the larger ratios are found more particularly in areas of high endemicity for thyroid disease. So far as mortality statistics go, we are fortunate in having accurate figures for England and Wales which show for males a mean annual standardized death rate at all ages of 2·4 for the quinquennium 1931-5, and of 2·3 for the period 1936-9, whereas for women the corresponding figures are 5·3 for both periods.³

These mortality rates, when compared with those of the first three decades of the century, show a decided and steady increase in both sexes.

In my own series* of 7,039 thyroidectomies there have been 127 cases of malignant goitre verified by histological examination, the percentage 1·8 being roughly comparable with that at several other large thyroid clinics in areas not highly endemic for goitre. It has been pointed out by Pemberton⁴ that there is a fallacy in all such figures, since many patients with innocent goitres do not bother to attend the clinic, while all those with malignant goitres sooner or later present themselves for treatment, and that therefore the actual ratio of malignant to innocent goitre is always smaller than such figures as I have given would imply.

* Compiled to September 30th, 1941.

The age at death as revealed in the Registrar-General's Reports is very similar to that of malignant disease generally, being low in both sexes up to thirty-five and then rising gradually to a maximum at sixty-five and over in males and seventy-five and over in females. It is interesting to note, however, that a definite though minute number of deaths attributed to malignant goitre occurred under the age of twenty-five, and I have seen a case in a boy aged nine, while Taylor and Wilkinson⁵ described one at six years. The sex incidence in the same Reports is nearly two and a half times as high for females as for males, and my own figures based on operations is three females to one male, a much lower proportion than obtains for non-malignant goitre, whether thyrotoxic or otherwise, in this country.

II. PATHOLOGY.

It is impossible to appreciate the very varied types of neoplasms which affect the thyroid without some knowledge of the histology of the gland. The essential feature of the epithelium of the thyroid is that it is fundamentally monotypical in accord with its embryogeny, for there is little, if any, evidence that the gland has anything but a median origin from the pharynx. The view that the branchial arches contribute to the gland structure, in spite of an attempt recently to revive it by Weller,⁶ has few supporters, and much the same is true of the alleged importance of the ultimo-branchial body, which has but a transitory association with the thyroid and almost certainly takes no share in its structure.

Hürthle⁷ described two types of epithelial cells in the thyroid, and on this is based the description of certain rare thyroid neoplasms with large cells and small alveoli which are referred to as Hürthle-cell tumours. The evidence for the existence of special resting epithelial cells such as Hürthle described is extremely slender, and the careful work of Gale Wilson⁸ and Rienhoff,⁹ who used wax-model reproductions of comparatively large masses of thyroid tissue, revealed no evidence whatever of any epithelial cells in the thyroid gland, apart from those lining the vesicles.

It is, however, hardly necessary to cling so closely as some have done, to the idea of two types of thyroid epithelium based on an alleged dual origin for the two types, when it is remembered how widely the epithelial cells differ in appearance in the varied physiological and pathological changes which the gland may exhibit. Every gradation from high columnar to low cuboidal epithelium may be found in the normal gland, sometimes at one and the same time, while in the goitrous gland the cells may in addition undergo profound modification of shape, size and of staining characteristics in both cytoplasm and nucleus. The epithelium of the thyroid vesicle, which lacks a basement membrane, may lie in the closest apposition to the rich blood capillary system, and this helps to explain some of the facts observed in connexion with the spread of certain malignant adenomata. On the other hand, there is a well-developed system of lymph vessels in the gland into which certain papilliferous adenocarcinomata, as well as the less differentiated epithelial and connective tissue neoplasms, spread at an early stage.

The connective tissue of the gland, too, has its neoplastic potentialities, as will be mentioned later, but there is one peculiarity which requires special mention, viz., the tendency to lymphoid changes in the thyroid gland under many different conditions, sometimes to such a degree that a close simulation of neoplasia may be mimicked, to say nothing of those cases in which the process has appeared in fact to lead on to the development of reticulo-endothelioma.

Thyroid epithelium has an inveterate tendency to form vesicles into which colloid is secreted, and this tendency is exhibited, though in varying degrees, by nearly all carcinomata of the gland. This proclivity may be manifested exclusively by the metastatic growths, in lymph nodes, bones, lungs, etc., and not at all by the primary tumour (very exceptionally the reverse is true). Sometimes the colloid-containing vesicles of metastases are of very regular formation and almost or entirely indistinguishable in parts from normal thyroid tissue, which they resemble also in that the colloid substance contains the active thyroid hormone (Engelstad 1936).¹⁰

III. CLASSIFICATION.

The special difficulties in the classification of malignant thyroid neoplasms follow from the brief introduction above and concern mainly the epithelial tumours. Langhans (1907) and (1911)¹¹ did much to sort out the various types accurately, but he failed to simplify the position adequately, and it was not until 1924 that Graham introduced a satisfactory basis for grouping all thyroid epithelial tumours. There are still a few exceptional neoplasms which can only be fitted into this simplified scheme with difficulty, if at all, unless full allowance

is made for the anaplastic and metaplastic capabilities of the thyro-epithelial cell, but with this proviso it is possible to group the epithelial malignant neoplasms of the thyroid as follows:—

1. Malignant Adenoma (including "Benign Metastasising Goitre").
2. Papilliferous Adeno-carcinoma.
3. Carcinoma Simplex.
4. Hürthle-cell Tumours.

1. Malignant Adenoma.

This tumour variously known as wuchernde struma or proliferating adenoma is the malignant neoplasm *par excellence* of those countries in which endemic goitre prevails, but while this type preponderates greatly in such districts, it is also the commonest type in this country, at least it is so in my own series, for among 127 operation cases there were 58 malignant adenomas, or approximately 45 per cent.

This tumour is closely related to those solid neoplasms which are often called "foetal adenomas," a term employed by Wölfler,¹² but probably a misnomer, since there is no satisfactory evidence of its foetal origin. Unlike the common colloid nodules of "simple" goitre, they are encapsuled and are probably true neoplasms. They can be found in such goitres among the colloid nodules and occur not very rarely in hyperplastic, diffuse colloid and indeed in most other types of goitre. The minute structure of these solid tumours is varied, and includes tubular, trabecular and micro-follicular forms. The malignant adenoma has similar features, sometimes exhibiting a solid mass of undifferentiated epithelial cells in one part, an alveolar structure in another, and a papilliferous arrangement in a third, but always with a tendency to lobulation. In the lobules the periphery is composed of solid masses of cells arranged in one or other of the formations above mentioned, but with a central area in which the typical vesicular thyroid structure prevails, the vesicles themselves often containing colloid, which stains characteristically. The criteria of malignancy are extremely difficult to lay down in these tumours, since they usually appear definitely encapsuled, not only to the naked eye but microscopically. Graham¹³ has, however, emphasized the importance of the intimate association between the tumour cells and the vessels of the smaller intrathyroid blood vessels, and he holds that evidence of the penetration of these cells into the lumina of the vessels is essential to enable one to differentiate between the solid innocent adenoma and the true malignant adenoma. This view, which is the accepted one in my own clinic, is borne out by the fact that the malignant adenoma, if it spreads outside the thyroid gland, invariably does so *via* the thyroid blood vessels, particularly, if not exclusively, by the veins, the secondary growths therefore appearing in the lungs, bones, etc. De Quervain¹⁴ (1935) stated, however, that venous invasion may occur in innocent adenomata!

Relationship between Malignant Adenoma and Benign Metastasizing Goitre.

Occasionally certain tumours of bone which may be found in almost any part of the skeleton, not excluding the skull, prove to have a structure similar to that of a malignant adenoma, i.e., there may be solid masses of cells of thyroid epithelium with, however, the significant tendency to the formation of colloid-containing vesicles. These tumours may be shown to possess the active iodine-containing constituent of the thyroid gland. Examination of the thyroid gland itself may fail to reveal any abnormality, and therefore it has been assumed that the normal thyroid epithelium, because of the closeness of its proximity to the lumina of the smaller blood vessels, may occasionally penetrate into them, thus providing the conditions necessary for the appearance of these bone tumours, which are usually single and slowly growing.

I formerly adopted this view, but more extended experience has convinced me that these tumours are essentially malignant, for two reasons:—

- (1) The absence of a palpable tumour in the thyroid gland is no proof that such a tumour does not in fact exist. It may be that the primary neoplasm lies in some part of the thyroid which it is not possible to see or feel, i.e., the retrosternal or retro-oesophageal regions, and in any case it may be of such a small size that it defies palpation. The latter explanation is the more likely because, histologically, some of the smallest tumours of the thyroid may have a structure typical of what has been already described as constituting a malignant adenoma. There is no reason whatsoever why such a minute tumour should not produce a metastasis in bone or elsewhere.

In one of my own cases¹⁵ the absence of a thyroid tumour in a patient with a clavicular neoplasm, the structure of which closely simulated normal thyroid gland

tissue, seemed to support the conception of a benign metastasizing thyroid, yet some year or two later a very definite left-sided thyroid mass became palpable, and still later evidence of pulmonary metastases.

(2) The destructive action of these tumours on the bony tissue in which they develop seems to be conclusive evidence that they are not normal thyroid tissue which certainly does not possess osteolytic powers.

The logical conclusion, therefore, is that there is no such thing as a benign metastasizing goitre, but that tumours so described are merely atypical instances of malignant adenomas in which the bony metastasis happens to be conspicuous and the primary growth obscure.

2. The Papilliferous Adeno-carcinoma.

This tumour is *relatively* more common in areas in which goitre is not markedly endemic. In my own series of 127 operation cases there were 34 of papilliferous carcinoma, or 27 per cent. A papilliferous structure is not very commonly found in a purely innocent tumour, but it is seen not uncommonly in small foci in certain nodular goitres and it is also not unusual in certain malignant adenomata. The true papilliferous adeno-carcinoma has, however, characteristics which differ widely from those of the malignant adenoma. It is even more slowly growing than the latter, it appears never to spread by the blood stream, and it has a special tendency to involve lymph nodes, without apparently much predilection to more remote metastasis; in fact, the remoter lymph nodes are only involved very late.

One of the special peculiarities of the papilliferous carcinoma is that it may appear to be multifocal. It is extremely difficult to decide as to the justification for this view, since it is possible that what has been described as multifocal papilliferous adeno-carcinoma may be merely the result of metastases in outlying or ectopic masses of thyroid tissue, or in certain lymph nodes which are not normally involved in thyroid neoplasms.

Many displaced or ectopic masses of thyroid tissue, including lingual thyroids, have a more or less papilliferous structure, as Dunhill states,¹⁶ and therefore when multiple masses of papilliferous adeno-carcinoma are found in the triangles of the neck, sometimes without palpable evidence of disease of the thyroid gland proper, it is understandable why the multifocal view has been advanced. There is a good deal of evidence, however, that the association is similar to that described for the alleged benign metastasising goitre, i.e., there is almost certainly a small or obscure primary papilliferous carcinoma in the thyroid gland, and the multiple tumours are probably multiple metastases.

The papilliferous adeno-carcinoma may produce a very large tumour and is sometimes cystic. It nearly always is engrafted on an existing goitre and is slow in its growth. It produces pressure effects, and though it may involve lymph nodes early, shows little tendency to infiltrate in the strict sense, so that, in spite of a noticeable tendency to local recurrence after operation, relief by further operation is often possible over a long period of years, for the very reason that the trachea, œsophagus and great vessels are pushed aside or compressed rather than invaded.

The naked-eye appearance of these tumours is nearly always characteristic, the well-marked capsule enclosing pale opaque grey or pinkish, very friable tumour material which contrasts with that of the goitrous semi-translucent tissue in the neighbourhood. The lymph nodes are often very much enlarged and yet show little tendency to matting together or to involvement of the overlying skin, and the lymph nodes in the posterior triangle of the neck may be affected more obviously than those in the anterior triangle. Recurrent papilliferous tumours tend to be more solid and less friable than the original, and they also have a more infiltrative quality. *Microscopically* the papilliferous carcinoma may consist of stout polyp-like masses with little branching or there may be a complicated arrangement of delicately branched processes, the stroma in the former group predominating over the epithelium in bulk and vice versa. The epithelium may be single layered and highly columnar or there may be several layers of cells of columnar, cuboidal, stratified, or even syncytial character.

3. Carcinoma Simplex—or (more exactly) undifferentiated Carcinoma.

In my own series this type occurred 28 times, i.e., approximately 22 per cent. It is, on the whole, the most malignant and least curable of the epithelial thyroid neoplasms. Unlike the malignant adenoma and papilliferous adeno-carcinoma, it appears to arise more commonly in the normal than in the goitrous gland. It is often extremely rapidly growing and has a far greater tendency to spread into vital structures such as trachea and œsophagus

than have the other malignant thyroid growths. These tumours are usually solid and pale in section, with a variable amount of fibrous stroma, and may be hard or soft accordingly. They show no trace of encapsulation, rarely reach anything like the size of the papilliferous carcinoma, yet may perforate into larynx or trachea while still of comparatively trivial size. They spread into lymph nodes fairly early and the latter tend to mat together. Invasion of the blood stream is rare. The carotid sheath and its contents are engulfed and the vagus and sympathetic nerves relatively soon become affected. Death occurs from pressure effects or from ulceration through the skin and secondary hæmorrhage. *Histologically* the cells vary widely in size, shape and staining character, being often highly anaplastic. In some areas their epithelial nature is obvious, in others the resemblance to small round-celled sarcoma is so strong as to have led to errors of ascription. Giant-cell types may occur. The difficulty in classification of such neoplasms is enhanced when the tumour is composed almost wholly of such undifferentiated cells. On the other hand, where there is a wide range of cell structure from area to area these tumours have been grouped as sarcoma-carcinomatodes or carcinoma-sarcomatodes, terms which are *a priori* suspect, since the simultaneous or contiguous appearance of epithelial and connective tissue neoplasms is extremely unlikely anywhere in the body.

It must not be forgotten that *squamous* carcinoma may occur, though very rarely, in the thyroid as a primary growth. This anomaly has been explained as due to malignant development in thyroglossal duct remnants of even to the ultimo-branchial body, but there is ample evidence that squamous metaplasia occurs in the epithelium of certain nodular goitres which would more reasonably account for these growths.

4. Hurthle-cell Tumours.

It is probable that these rare large-cell small-alveolar carcinomata arise by parathyroid cell inclusions in the thyroid and not from thyroid epithelium or from the ultimo-branchial body as Getzowa¹⁷ postulated. Eisenberg and Wallerstein (1932)¹⁸ regard these neoplasms as innocent.

Connective tissue tumours. It is generally agreed that malignant thyroid connective tissue tumours are far less common than the carcinomata, but Ewing goes so far as to maintain that the conclusive evidence of the occurrence of sarcomata of the thyroid is wanting. He bases his view largely on the lack of satisfactory criteria in differentiating anaplastic epithelial cells from certain connective tissue cells and believes that the tumours labelled sarcomata of the thyroid are really examples of epithelial tumours showing a striking degree of anaplasia. It is, however, probable that Wegelin and the Continental school of pathologists are correct in estimating the sarcomata of the thyroid as constituting approximately 10 per cent. of all malignant thyroid tumours. In my own series of malignant goitres, even after applying the strictest scrutiny, it was impossible to classify seven cases (5·7 per cent.) otherwise than as sarcomata, and even in the U.S.A., although the recorded percentage is low compared with Europe, there are reliable records of thyroid sarcomata. All histological types are represented. In my own series reticulum cell sarcoma is the commonest, but Wegelin¹⁹ has met with more examples of the polymorphic-celled type. *Endotheliomata* are rare, yet twenty-two examples of one variety, the hæmangio-endothelioma, were recorded from the Berne material by Simon (1939).²⁰ Macroscopically, sarcomata are often large, rapidly growing, unilateral tumours replacing the greater part of the thyroid tissue and tending eventually to involve both lateral lobes. They are often of a uniform pale pinkish or greyish in colour, but sometimes there are whorls of fibrous tissue breaking up the mass into a pseudo-lobular formation. Occasionally yellowish opaque foci of necrosis are visible, as are sometimes hæmorrhagic and cystic areas. The lymph nodes are often enlarged but discrete. The endotheliomata are similar, with, however, a special liability to form large hæmorrhagic cysts in the hæmangio-endotheliomata.

Microscopically the thyroid sarcomata show very considerable variety, as already indicated, and absolute diagnostic criteria are difficult to lay down.

Teratomata of the Thyroid. Pusch and Nelson (1935)²¹ were able to collect twenty-eight cases which they regarded as authentic. They are practically invariably tumours of the newly-born, and may be big enough to cause dystocia and stillbirth, though a few cases of survival are on record. They form large and often bilateral tumours which compress the trachea and necessitate early surgical intervention in the rare cases born alive. The thyroid is occupied by a partly solid, partly cystic, mass, which on section reveals a great variety of tissues derived from epiblastic, mesoblastic and hypoblastic sources.

Metastatic Tumours of the Thyroid are relatively common and from a large variety of primary foci (Willis, 1931²²). For practical purposes it is desirable to be prepared for them in order to avoid unnecessary surgical or other treatment. The really important example is found in association with carcinomata of the upper œsophagus and hypopharynx, which, without producing any characteristic local symptoms may involve the posterior aspect of the thyroid gland, and eventually produce a relatively *smooth* but very hard tumour which presses on the trachea and thus causes dyspnœa rather than dysphagia. I have seen several such secondary neoplasms operated on in error, occasionally with disastrous results. Myxœdema may follow widespread destruction of thyroid tissue by metastatic neoplasms (Willis, 1931²²).

IV. DIAGNOSIS.

It is perhaps inevitable that anterior to operation the correct diagnosis of malignant thyroid neoplasm in a curable or even treatable stage is made in only about half the cases, even in well-organized thyroid clinics. Advanced cases with involvement of extra-thyroid structures, deposits in lymph nodes, etc., are, on the other hand, painfully obvious and their diagnostic features need no elaboration. We have, for example, nothing to guide us as to when the cells of a malignant adenoma begin to find their way into the blood vessels, so that potential metastases may already exist in the extrathyroid blood stream when the tumour is exposed. Furthermore, when the tumour is actually viewed its nature may be overlooked, not so much in the infiltrating types of neoplasm as in those which are apparently encapsulated, for the critical criteria of malignancy in these are mainly histological. Special difficulty exists in those patients who have already been perhaps for many years goitrous, since physical changes in these dwellings are often unnoticed by the patient and not always recognisable by the skilled diagnostician.

The main diagnostic points of value are:—

1. Functional.
2. Physical.

1. Functional. In certain cases, mainly of malignant adenomata, but also in secondary metastatic deposits, there are indications of associated thyrotoxicosis, sometimes at an early stage. Thus, rapid loss of weight, tachycardia and palpitation leading on sometimes to auricular fibrillation are occasionally observed, and with them a rise in the basal metabolic rate. Coller (1929)² believes that these toxic phenomena are of great importance, but they are often absent even in large well-advanced malignant tumours, and similar symptoms are seen not only in ordinary nodular goitres ("secondary" thyrotoxicosis) but also in the rare tuberculous and some other inflammatory lesions of the thyroid. Very rarely malignancy does arise in an established thyrotoxic goitre, but this can account for only a fraction of the cases of malignant thyroid tumour associated with a raised B.M.R. The raising of the B.M.R. cannot be regarded as necessarily indicating thyrotoxicosis, for it is met with in any dyspnoic patient and dyspnœa is very frequently found in any malignant goitre large enough or sufficiently invasive to obstruct breathing. It should also be mentioned that widespread destruction of the thyroid tissue as from a rapidly spreading sarcoma may so reduce thyroid function that the patient's condition actually suggests a certain degree of myxœdema. Thus, summing up, it may be said that functional changes, though they may occur in thyroid malignancy, are rarely significant or of diagnostic value.

2. Physical. Certain physical changes, though not entirely reliable, should always be looked upon with suspicion in an existing thyroid tumour, viz., *rapid increase in size* (the increase which results from hæmorrhage into a cyst or from inflammation of a cystic or solid area is sudden rather than rapid), noticeable change of shape or *increase in hardness*. Mere hardness of a thyroid swelling which is not known to be of recent onset may signify old standing calcification or a cyst with fibrous or calcified walls, but doubts about these are resolved by skiagraphy. Intense hardness with a relatively small unilateral tumour suggests Riedel's thyroiditis—such a degree of hardness is never seen in malignant disease, in my experience. Moderate firmness and a bilateral swelling is seen in Hashimoto's disease, which should never be mistaken for a malignant growth, which even when bilateral is not symmetrical.

In the more *infiltrative tumours* with signs of involvement of the trachea (by compression, distortion and displacement, or by invasion of its lumen) dyspnœa is out of proportion to the size of the thyroid mass, while *dysphagia* may result from pressure on or spread into the walls of the œsophagus. Pupillary changes from infiltration of the sympathetic may be simulated

by a purely inflammatory involvement, such as is sometimes found in association with certain deeply placed simple cysts in and about the walls of which an obscure type of subacute inflammation sometimes occurs. *Pain* of a referred character may also be complained of in the corresponding ear or side of the head in rapidly spreading forms of carcinoma or sarcoma, but is also met with in certain purely inflammatory lesions. *Fixation* of a thyroid tumour may indicate infiltration of deep structures or overlying muscles, but it is also seen in Riedel's disease and in certain obscure inflammations; it is an early phenomenon with carcinoma simplex and relatively late in malignant adenoma and papilliferous adeno-carcinoma.

Large discrete lymph nodes accompanying a thyroid tumour are more suggestive of a papilliferous neoplasm or certain rapidly growing sarcomata, than of the undifferentiated carcinomata in which the lymph nodes involved are hard, small and tend to mat together. Innocent swellings of the thyroid, however large or hard, rarely surround or *obscure the pulsation of the carotid vessels*, while in the later stages of carcinoma simplex and also the papilliferous adeno-carcinoma this phenomenon is frequently observed. Metastases in connexion with malignant adenomata may affect bones, lungs, etc., and sometimes, as already stated, the metastases in bone may be noticed before the thyroid tumour, while in other cases the latter may appear trivial when the secondary growths are already conspicuous.

V. PROGNOSIS.

This has materially improved in recent years as the result of combined surgical and radiological methods of treatment. It must be admitted that in the undifferentiated carcinoma and in the sarcomata the eventual outlook is usually bad, but it is not nearly so hopeless as formerly. In malignant adenoma the prospect of cure is very good if treated before metastases have developed, while in papilliferous carcinoma the immediate outlook is better than the final prospect, for many survive five, ten or more years, only to succumb eventually to recurrence.

A good many cases of malignant disease of the thyroid are, however, inoperable and untreatable when first seen because of extensive involvement of the skin with ulceration, or because of the widespread infiltration of the cervical tissues; such cases rarely survive more than a few weeks or months, and there are cases both of carcinoma and sarcoma in which the rate of progress is so rapid that the inoperable stage is reached almost in a week or two. In my own series of 127 cases, the details of which are to be published elsewhere, one case of sarcoma has survived over ten years in spite of the hopeless prognosis generally ascribed to this form of malignancy. Several of my cases of undifferentiated carcinoma have lived over five years, and the five-year and ten-year cures of the papilliferous carcinomata are nearly as good as those for malignant adenoma.

VI. TREATMENT.

(a) Surgical.

There can be no doubt that, whenever feasible, malignant tumours of the thyroid should be extirpated with the same thoroughness as in connexion with carcinoma of the breast and elsewhere. This is a counsel of perfection, since the problem of radical extirpation in such a gland has special dangers and difficulties, particularly the tendency to involvement of structures which are virtually irremovable. It has been claimed that affected portions of the trachea and oesophagus have been removed successfully in operations for thyroid neoplasms, but such cases must be rare indeed.

With the *malignant adenoma* the diagnosis is usually a matter of suspicion only, and it is therefore wise to include some of the surrounding thyroid tissue in the extirpation of all adenomata so as to avoid the danger of leaving behind minute metastases in the capsular veins. If extensions into the capsular veins of the adenoma are *visible*, then a much wider extirpation is called for. I described an operation in 1932¹⁵ which permits the removal of the tumour with the whole of the venous plexus in the neighbourhood, including the internal jugular vein and the main cervical muscles. A somewhat similar operation was devised in 1936 by G. Crile, Jnr.²⁴

In all other types of malignant goitre the removal of affected lymph nodes must be included with the primary neoplasm, and in the papilliferous adeno-carcinoma it is often found that, though these deposits may be large and numerous, the tendency to early recurrence in neighbouring lymph nodes is comparatively slight.