

METASTASIS FROM AN UNKNOWN TUMOUR

INGER DISSING

The diagnosis of metastasis from an unknown primary tumour always constitutes an unsatisfactory basis for treatment and usually a fatal outcome is inevitable, unless the primary tumour is found. Nevertheless, some patients survive for a long time after the treatment of metastases even without the primary tumour being detected.

Only a few authors have discussed the treatment of metastases in general (HOLMES & FOUTS 1970, AGLIOZZO & REINGOLD 1967, GEWANTER et coll. 1943). Only HOLMES & FOUTS have presented a clinical material but unfortunately they make no mention of treatment.

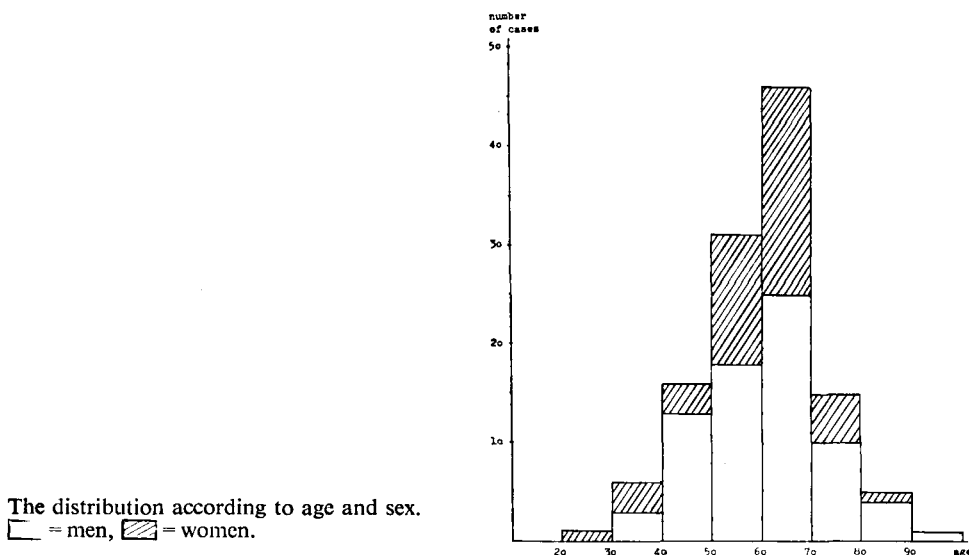
Nearly all previous authors have restricted themselves to metastases in the lymph nodes and mainly in the neck (BARRIE et coll. 1970, COMESS et coll. 1957, HENDRICH 1967, JESSE et coll. 1966, 1973, MARTIN & MORFIT 1944, PROBERT 1970). Their results are much better than those of HOLMES & FOUTS and this also applies to the present material consisting of metastases of all sites.

The purpose of this investigation was to find out if any relation existed between the nature of the malignancy and the survival rate.

Material

During the period 1955 to 1965, 228 patients out of a total of 45 000 consecutive patients were treated under the diagnosis: metastasis from unknown primary tumour. Thirteen, later found to have systemic disease, were excluded. One patient was

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excluded on the basis of the principles of MARTIN & MORFIT, having a squamous-cell carcinoma within a branchial cyst. After the material had been restricted to patients in whom no primary tumour was found within the first 6 months after treatment of the metastasis, 121 patients remained. All were included in a follow-up in December 1973.

The age distribution and sex ratio are similar to those found in other materials, 74 patients being men and 47 women, with the age peak between 50 and 70 (Figure).

In about half the cases, a painless mass made the patient seek medical advice, while tenderness, pain or functional disturbances were responsible in one third. The history ranged from a few days to several years, mean 7.7 months.

PROBERT suggested that the longer the history, the better the prognosis. In the present material, however, the 5-year survival rate after a history of less than 6 months was 21 per cent, after more than 6 months 13 per cent; the 10-year rate was 11 and 7 per cent, respectively. Thus, PROBERT's suggestion was not confirmed.

If examinations of the most probable sites for a primary tumour were negative, the metastasis was excised totally when possible, or a drill biopsy was performed.

The diagnosis of metastasis was verified microscopically in all but 9 cases in whom no biopsy was performed. Six of these patients had osteolytic bone metastases. One patient, subjected to laparotomy, had gross metastases in the liver, mesentery, and abdominal lymph nodes. Another had a mass in the mediastinum with nerve palsy and oesophageal stenosis. The last patient received preoperative irradiation to the neck; at operation no tumour tissue was found although he later developed several further metastases and died. All microscopic reports have been reviewed. In doubtful

Table 1
Microscopic diagnosis of metastases by location

Diagnosis	Location of metastases						No. of patients
	Cervical lymph nodes			Axill. lymph nodes	Ing. lymph nodes	Bones	Organs or soft tissue
	Upper	Middle	Lower				
Solid carc.	12	7	14	4	2	6	39
Squamous-cell. carc.	11	7	2	2	1	1	21
Anapl. carc.	5	2	4	0	3	2	17
Adenocarc.	3	0	2	0	2	2	13
Malignant melanoma	0	0	2	0	2	0	5
Others	5	2	2	2	1	4	17
No. of metastases	36	18	26	8	11	15	28

cases the slides were reviewed by J. Clemmesen (Senior pathologist, Finsen Institute, Copenhagen).

Location. The metastases had developed in practically all parts of the body, but in 68 patients (56 per cent) they were located in the cervical lymph nodes. SINNER (1959) found that 78 per cent of the metastases in his material involved the lymph nodes in the neck, and most previous authors have been concerned solely with metastases in this location.

In 29 of the patients with metastases in the cervical lymph nodes, 23 with lesions on the left side of the neck and 6 on the right, a primary tumour was later disclosed. Sixteen primary tumours were located above the clavicle, 13 below. The primary sites above the clavicle were: rhino-pharynx, nasal cavity, oral cavity, root of the tongue, tonsils, larynx, parotid gland and thyroid gland, while the primary sites below the clavicle were: oesophagus, lungs, pancreas, colon, liver, common bile duct, kidneys, bladder, and a malignant melanoma in the plantar skin.

Microscopy. The most common microscopic diagnoses were solid carcinoma and squamous-cell carcinoma (Table 1); the rest comprised: indeterminate malignant tumour, mucoid tumour, metastases resembling thyroid tissue and hypernephroma, but with nothing abnormal found in the thyroid gland or kidneys. As could be expected, most of the metastases of the squamous-cell type were found in the cervical lymph nodes, and the silent primary tumour later found was most often in the upper respiratory or digestive tract.

Treatment. As the metastases in this material were localized in many different regions, no special therapeutic schedule was used. Before 1962 the majority were

Table 2
Present material

Group		Males	Females	Total
1	Living without a primary tumour being disclosed	3	5	8
2	Primary tumour detected during life	14	5	19
3	Primary tumour detected at autopsy	16	11	27
4	Died without a primary tumour being detected at autopsy:			
	No tumour tissue	2	2	4
	Died of tumour	14	9	23
5	Died without a primary tumour being detected; no autopsy:			
	No clinical evidence of tumour	2	1	3
	Died of tumour	23	14	37
Total		74	47	121

treated with orthovoltage roentgen irradiation using different field sizes, in most cases including the neighbouring lymph nodes. Only a few were treated with ^{60}Co irradiation and a field size of up to 8 cm $\times$ 6 cm and a FSD of 20 cm. After 1962 nearly all patients received ^{60}Co irradiation including all the neighbouring lymph nodes.

Seventy-six patients were treated with orthovoltage irradiation and 23 with ^{60}Co . The calculated tumour doses were less than 2 500 R in 32 cases, between 2 500 and 4 500 R in 36 cases, between 4 500 and 6 500 R in 29 cases, and more than 6 500 R in 2 cases. It has not been possible to estimate the CRE (Cumulative Radiation Effect) for all treatments, and the calculated CRE values bore no relationship to the survival rate.

The remaining patients received radiation therapy after biopsy or excision of the metastasis, except one who was irradiated pre-operatively and 3 who were irradiated following a block dissection of the neck.

The metastases were excised totally in 10 patients as the first treatment, and radical lymph node dissection was performed in 2 patients. Four patients were not treated at all and 6 patients with advanced disease received chemo-therapy with a single drug: endoxan, erasol, or Bayer E 39.

Sixty-nine of the patients died between 6 and 18 months after the first treatment but 10 were still alive in December 1973, 8 without the primary tumour being detected, and 2 after their primary tumour had been detected and treated. Altogether, the primary tumour was disclosed during life or at autopsy in 46 patients. The entire material may then be grouped as appears in Table 2. Forty patients died without the primary tumour being detected and no autopsy was performed.

Table 3*Group 1: 8 patients still alive without detection of a primary tumour*

Age	Sex	Microscopic diagnosis	Metastases (region)	Treatment	Recurrence after treatment	Survival after last treatment (years)
53	M	Adenopap. carc.	Cerv. lphn.	Excision + 180 kV 3 300 R/23d	None	14
58	M	Melanoma	Ing. lphn.	Radical ing. dissection	None	13
50	F	Solic carc.	Cerv. lphn.	Excision + 250 kV 4 100 R/30d	None	11
30	F	Anapl. carc.	Ing. lphn.	Excision + ⁶⁰ Co 5 000 rad/25d	None	8
56	F	Squam.-cell. carc.	Cerv. lphn.	Excision + ⁶⁰ Co 6 300 rad/58d	None	8
56	M	Squam.-cell. carc.	Axill. lphn.	Axillary dissection + 400 kV 3 030 R/19d	Right lung 9 years later	1
70	F	Anapl. carc.	Thoracic subcut.	Excision	Cerv. lphn. 1 year later	9
55	F	Solid carc.	Pretracheal lphn.	Excision + ⁶⁰ Co 5 700 rad/44d	Cerv. lphn. 2 years later	6

Group 1. The first group consisted of 8 patients (6.6 per cent) who were still alive without a primary tumour being detected (Table 3). Five had no evidence of malignancy since the first treatment. Three had received treatment for a second metastasis and were then without any sign of tumour.

Within this group the microscopic diagnoses varied widely, and so did the locations of the metastases. Three patients had received orthovoltage roentgen irradiation with tumour doses between 3 030 R/19 days and 4 100 R/30 days; 3 were irradiated with ⁶⁰Co with tumour doses between 5 000 rad/25 days and 6 300 rad/58 days. The seventh patient had a radical inguinal lymph node dissection, and the eighth an excision only. Of the 3 patients with recurrences, 2 developed the second metastasis outside the primarily treated region, one had a radical operation and the other a combined neck dissection and irradiation. In the third patient the first metastasis had developed in a pretracheal lymph node on the left side and the second in the lymph nodes on the right side of the neck, partly inside the initially treated region. Radical neck dissection was then performed. All the patients in this group were surviving 8 to 14 years after the primary treatment.

Group 2. In 19 cases (15.7 per cent), the primary tumour was found while the patient was still alive. Two were still alive and well after 14 years:

Table 4*Died without recurrence or evidence of primary tumour at autopsy in group 4 a*

Age	Sex	Microscopic diagnosis	Region	Treatment	Survival (years)	Cause of death
58	M	Carcinoma	Cerv. lphn.	180 kV 3 240 R/44d	11	Cardiac failure and uraemia
70	F	Malignant cells	Cerv. lphn.	180 kV 1 300 R/28d	8	Cerebral haemorrhage
66	M	Solid anapl. carc.	Cerv. lphn.	180 kV 1 770 R/40d	2	Hepatic abscess septicaemia
68	F	Solid anapl. carc.	Cerv. lphn.	250 kV 5 200 R/39d	1	Cirrhosis and hepatic coma

Female, aged 64. In 1959 squamous-cell carcinoma in cervical lymph node on the left: excision followed by irradiation 180 kV 4 800 R/28 d. In 1963 tumour in the left tonsil and another left lymph node metastasis outside the first field; microscopy; squamous-cell carcinoma; ^{60}Co irradiation 6 217 rad/56 d. No recurrence at 10 years.

Female, aged 68. In 1959 squamous-cell carcinoma in cervical lymph node on the left; excision. In 1967 carcinoma of the uterine cervix, squamous-cell carcinoma of the left tonsil and in a lymph node on the left side of the neck. ^{60}Co irradiation 6 600 rad/60 d. No recurrence at 6 years.

One case died one year after ^{60}Co irradiation, 5 000 rad/37 days, of a primary tumour in the larynx, 3 years after irradiation, 180 kV, 3 700 R/27 days, of a squamous-cell carcinoma in a cervical lymph node on the left side of the neck. He died of melaena from a gastric ulcer, with no evidence of tumour at autopsy. The remainder of the patients died of their tumours a few weeks to 10 years after treatment of the primary tumour with a mean survival of 20 months. The longest interval between the treatment of a metastasis and the diagnosis of the primary tumour was 10 years; in this case, another 3 metastases of the parotid tumour had occurred in the neck and mediastinum during that period. Of the 19 patients, 16 had their metastases in the cervical lymph nodes and of these, 5 had their primary tumour below the clavicle: lung, oesophagus, pancreas, colon, and bladder. The location of the primary tumours above the clavicle were: tonsils 4, rhinopharynx 1, nasal cavity 1, tongue 1, parotid gland 1, larynx 3. Skeletal metastases from a primary tumour in the lung were found in 1 case and from renal tumours in 2 cases. The metastases were treated in 9 cases with orthovoltage irradiation with tumour doses between 1 200 R/14 days and 6 200 R/41 days, and in 5 cases with ^{60}Co irradiation with doses between 4 004 rad/23 days and 6 700 rad/51 days. The lymph nodes

Table 5
Crude survival after treatment of metastases

Group	3 years		5 years		10 years	
	Recurrence	No recurrence	Recurrence	No recurrence	Recurrence	No recurrence
1		8		8		5
2	7	3	5	2	2	2
3	3	3	1			
4 a		2		2		1
4 b		1				
5		2				
5	2	4	1	2	1	
Total	12	23	7	14	3	8
Per cent	28.9		17.4		9.1	

were excised in 3 patients and radical neck dissection was performed in 2. In 13 cases curative treatment of the primary tumour was possible in spite of the previous treatment. In 6 cases the primary tumour was too widespread for radical treatment. Three patients underwent radical operation and 9 had curative irradiation. One patient died of heart failure before any treatment had been instituted.

Group 3. In 27 cases (22.3 per cent) the primary tumour was not detected until post mortem. In other words, the total number of primary tumours detected, either during life or at autopsy, was 46 (38 per cent). The longest survivals from the first treatment were 63 and 57 months. Thirteen of the 27 cases of this group had metastases in the cervical lymph nodes; in 8 of these the primary tumours were located below the clavicle: lung 4, kidney 1, liver 1, common bile duct 1, and plantar skin 1. The primary tumours above the clavicle were located in: rhinopharynx 1, tongue 1, larynx 1, and thyroid gland 2. In the cases with metastases outside the neck the primary tumours were located in: lung 4, pleura 1, thyroid gland 1, kidney 3, gastrointestinal tract 2, ovary 1, vagina 1, and testis 1. Fifteen of the patients were treated with orthovoltage irradiation with tumour doses between 600 R/21 days and 4 400 R/29 days, 3 had ^{60}Co irradiation with doses between 1 230 rad/38 days and 6 000 rad/34 days, while 3 patients were not treated at all. One patient underwent radical neck dissection, 3 merely had excision of the metastasis, and 2 received chemotherapy. In 2 cases with a tentative microscopic diagnosis of reticulosarcoma, the diagnosis was changed at autopsy. In one of these two, lymph-node recurrences had been biopsied, yielding different microscopic diagnoses, but finally autopsy established the diagnosis of seminoma. All the earlier slides were revised and proved compatible with the diagnosis of seminoma.

Table 6*Crude survival of 88 patients according to size of palpable metastasis*

Survival (years)	Size of metastasis	No. of cases	Primary tumour found	No primary tumour found	Per cent
< 3	< 20 cm ²	29	16	13	58
	> 20 cm ²	30	6	24	79
≥ 3	< 20 cm ²	21	7	14	42
	> 20 cm ²	8	4	4	21
≥ 5	< 20 cm ²	14	4	10	28
	> 20 cm ²	3	1	2	8

Group 4. This group of 27 patients was sub-divided into (a) cases with no tumour tissue at autopsy (4 patients), and (b) cases with tumour tissue at autopsy, but with no apparent primary tumour (23 patients) (Table 4). All but one of the group (b) cases had died of their malignancy within 18 months. This one lived for 4 years with many recurrences of adenocarcinoma in the abdominal wall before dying with generalized metastases.

Group 5. No autopsy had been performed on 40 patients in whom no primary tumour was found during life. Three died of cardiovascular failure without clinical signs of tumour 2, 3, and 4 years, respectively, after treatment for metastases. The remainder of this group died of their tumour, but in 2 cases 10 and 6 years elapsed between the first metastases and the recurrences. Twenty-nine of them died less than one year after treatment of the first metastases.

Survival. Thirty-five patients survived for 3 years (a crude survival rate of 28.9 per cent, Table 5); in 23 of these no recurrences developed. The 5-year crude survival was 17.4 per cent, and of this group 14 patients developed no recurrences; 10 of them had their metastases in cervical lymph nodes. Eleven patients, constituting 9.1 per cent of the material, lived for 10 years or more (up to 14 years). At the time of follow up (December 1973) no recurrences were present in 8, including 5 whose metastases had been in the cervical lymph nodes.

Eighty-eight patients had measurable metastases when first treated. The remainder had either had their metastases totally removed, destruction in bone, or tumour tissue in the pleura. Fifty patients had metastases measuring less than 20 cm² (Table 6); 21 of these (42 per cent) lived for more than 3 years. On the other hand, only 8 (21 per cent) of the 38 patients with metastases exceeding 20 cm² lived for more than 3 years; 28 per cent with metastases of less than 20 cm² lived for more than 5 years, while 8 per cent of those with metastases exceeding 20 cm² lived for more than 5 years. Thus, the prognosis does seem to be related to the size of the metastases, as suggested by PROBERT.

Discussion

The improvements in diagnostic techniques over the years have not lessened the problems of the metastasis from an unknown primary tumour (HOLMES & FOUTS.) Destruction in a bone or a lump in an organ is not ordinarily a diagnostic problem but a palpable lymph node may be normal or it may be metastatic; a painful lymph node may be infected or it may be metastatic and affected with secondary infection. Thus, an exact microscopic diagnosis is necessary and also important for excluding systemic diseases which may sometimes be diagnosed initially as anaplastic carcinoma. Some authors do not exclude these cases, even though the exact nature is revealed later (BARRIE et coll., PROBERT). In the present material all such cases were excluded.

The reported treatment of metastases from an unknown primary tumour has varied widely, but most often it consists of irradiation, alone or combined with operation. By irradiation of extensive fields, covering all neighbouring lymph nodes, the unknown primary tumour may be treated as well. This may be the reason why some patients survive for a long time without their primary tumour being detected.

Among the explanations for not detecting the primary tumour HOLMES & FOUTS mentioned: a primary tumour too tiny for diagnostic examinations, too small to be detected at autopsy, no autopsy, early malignant melanomas or endometrial adenocarcinomas destroyed without microscopy or spontaneous regression (EVERSON & COLE 1966). As an example of a tiny primary tumour GIKAS et coll. (1967) mentioned a case in which a primary tumour in the thyroid gland, measuring $0.6 \text{ mm} \times 0.3 \text{ mm} \times 0.2 \text{ mm}$ had given a metastasis in a cervical lymph node.

The reported survival rates have varied widely, but so have the materials. The material of HOLMES & FOUTS included similar metastases as in the present one, but their crude survival rates for 3, 5 and 10 years were 7.8, 5.1 and 3.3 per cent, respectively, while the corresponding survival rates in the present material are 28.9, 17.4 and 9.1 per cent.

Others, dealing only with lymph-node metastases in the neck, have presented much higher crude survival rates. BARRIE et coll. found a 30 per cent 3-year, a 25 per cent 5-year and a 15 per cent 10-year survival, but they had excluded all cases of anaplastic carcinoma. COMESS et coll. stated that 12.4 per cent of their patients were alive at 11 years without having had the primary tumour detected. HENDRICH (1967) found 17.3 per cent surviving at 3 years without any sign of tumour while JESSE et coll. (1973) had 48 per cent surviving at 3 years. However, they had excluded advanced localized tumours as well as disseminated tumours. MARCHETTA et coll. (1963) found a 30 per cent 4-year survival and PROBERT an 8 per cent 3-year survival. In the present material the survival rates for patients with metastases only to the cervical lymph nodes were 30.6 per cent at 3 years, 19 per cent at 5 years and 12.4 per cent at 10 years.

The size of the metastasis plays an important prognostic role, as apparent from the present material and as pointed out by PROBERT. A large metastasis has either been

growing through a long time or contains fast-growing, highly malignant tumour tissue, factors spelling a poor prognosis. PROBERT suggested that anaplastic carcinoma has a better prognosis than other types, and HOLMES & FOUTS found that 8 of their anaplastic cases survived for 5 years or longer. In the present material 17 patients (14 per cent) had microscopically proven anaplastic carcinoma. Among the 5-year survivors they constitute 19 per cent and among the 10-year survivors 27.3 per cent.

Conclusion

Since 14 out of 121 patients survived for more than 5 years after treatment of their metastases without any primary tumour being detected, it seems justifiable to treat these patients by curative measures. It is also advisable to continue to search for the primary tumour, as it may be curable, even when found several years later. The best treatment is difficult to decide, as the measures in the literature have varied and the treatment also must be appropriate to the site of the metastasis. The preferred treatment seems to be irradiation, sometimes combined with operation, and such treatment may by chance include the unknown primary tumour. In the present material, however, 5 of 12 patients having received only local surgery, survived for more than 5 years.

The metastasis should be removed totally to afford the best possible microscopic information. It has been suggested that anaplastic carcinoma has a better prognosis than other types; this cannot be disproved by the present findings. The site of the metastasis as well as the size is important and the best results are encountered among patients with metastases to the lymph nodes, especially in the neck, while metastases to organs and bones give a low survival rate.

SUMMARY

A total of 121 patients were treated under the diagnosis: metastasis from an unknown primary tumour; 99 were irradiated. In 46 cases the primary tumour was detected from 6 months to 10 years after the primary treatment. The 3-year survival was 28.9 per cent, the 5-year 17.4 per cent and for 10 years or longer (up to 14 years) 9.1 per cent, after the primary treatment. The prognosis is correlated to the size of the metastases, their site and also their microscopic appearances.

ZUSAMMENFASSUNG

Insgesamt 121 Patienten unter der Diagnose: Metastase eines unbekannten Primärtumors wurden behandelt; 99 wurden bestrahlt. Bei 46 Fällen wurde der Primärtumor 6 Monate bis zu 10 Jahren nach der Primärbehandlung entdeckt. Die 3-Jahres Überlebensrate betrug 28,9%, die 5-Jahres Überlebensrate 17,4% und die für 10 Jahre oder länger (bis zu 14 Jahren) 9,1% nach der Primärbehandlung. Die Prognose ist zur Lage, der Grösse und dem mikroskopischen Bild der Metastase korreliert.

RÉSUMÉ

Un total de 121 malades ont été traités sous le diagnostic de: métastase d'une tumeur primitive inconnue; 99 ont été irradiés. Dans 46 cas la tumeur primitive a été décelée entre

6 mois et 10 ans après le premier traitement. Le taux de survie à 3 ans a été de 28,9%, à 5 ans de 17,4% et pour 10 ans ou plus (jusqu'à 14 ans) de 9,1% après le premier traitement. Le pronostic est en rapport avec la taille des métastases, leur localisation et leur aspect microscopique.

REFERENCES

- ABRAMS H. L., SPIRO R. and GOLDSTEIN N.: Metastases in carcinoma. *Cancer* 3 (1950), 74.
- ACQUARELLI M. J., MATSUNAGA R. S. and CRUZE K.: Metastatic carcinoma of the neck of unknown primary origin. *Laryngoscope* 71 (1961), 962.
- AGLIOZZO C. M. and REINGOLD I. M.: Scalene lymph nodes in necropsies of malignant tumours. *Cancer* 20 (1967), 2148.
- BARRIE J. R., KNAPPER W. H. and STRONG E. W.: Cervical nodal metastases of unknown origin. *Amer. J. Surg.* 120 (1970), 466.
- COMESS M. S., BEAHR O. H. and DOCKERTY M. B.: Cervical metastases from occult carcinoma. *Surg. Gynec. Obstet.* 104 (1957), 607.
- DEUEL H.: Metastasen am hals bei zunächst unbekannt gebliebenem primär tumor. *Radiol. clin.* 14 (1945), 202.
- EVERSON T. C. and COLE W. H.: Spontaneous regression of metastatic cancer. Chapter 13. London 1966, Saunders Comp.
- FEIGENBERG S., POPPE E. and ROMANUS R.: Tumörsjukdomar. (In Swedish.) Almqvist & Wiksell. Uppsala 1963.
- FRANCE C. J. and LUCAS R.: The management and prognosis of metastatic neoplasms of the neck with an unknown primary. *Amer. J. Surg.* 106 (1963), 835.
- GEWANTER A. P., MITCHELL N. and ANGRIST A.: A.: Latent primary carcinoma. *Arch. Path.* 35 (1943), 66.
- GIKAS P. W., LABOW S. S., DIGIULTIO W. and FINGER J. E.: Occult metastasis from papillary carcinoma of the thyroid. *Cancer* 20 (1967), 2100.
- GREENBERG B. E.: Cervical lymph node metastasis from unknown primary sites. *Cancer* 19 (1966), 1091.
- HENDRICH J. W.: Differential diagnosis of neck tumors. *S. med.* 45 (1952), 1019.
- Occult cancer with cervical lymph node metastasis. *In: Cancer of the head and neck*, p. 41. Edited by Conley, J. Butterworths, Washington 1967.
- HEUSON J. C.: Addison's disease secondary to occult metastatic seminoma. *Cancer* 19 (1966), 1754.
- HOLMES F. F. and FOUTS T. L.: Metastatic cancer of unknown primary site. *Cancer* 26 (1970), 816.
- JESSE R. H., PEREZ C. A. and FLETCHER G. H.: Cervical lymph node metastasis: unknown primary cancer. *Cancer* 31 (1973), 854.
- — — and NEFF L. E.: Metastatic carcinoma in cervical nodes with an unknown primary lesion. *Amer. J. Surg.* 112 (1966), 547.
- KEIM W. F.: The occult primary in head and neck surgery. *Arch. Otolaryng.* 84 (1966), 566.
- KINSEY D. L., JAMES A. G. and BONTA J. A.: A study of metastatic carcinoma of the neck. *Ann. Surg.* 147 (1958), 366.
- KLOPP C. T.: Metastatic cancer of axillary lymph node without a demonstrable primary lesion. *Ann. Surg.* 131 (1950), 437.
- KRANZFELD I. M.: Irrtümer in der diagnose bösartiger Neubildungen bei lebzeiten. *Z. Krebsforsch.* 26 (1928), 146.
- LEVINE W. and WEINER S.: Spontaneous regression of metastatic cancer, primary unknown. *In: Spontaneous regression of cancer*. Edited by Everson, T. C. and Cole, W. H. Saunders Comp. London 1965.

- LUMB G.: Tumours of lymphoid tissue. E. & S. Livingstone Ltd. Edinburgh & London 1954.
- MARCHETTA F. C., MURPHY W. T. and KOVARIC J. J.: Carcinoma of the neck. *Amer. J. Surg.* 106 (1963), 974.
- MARTIN H. and MORFIT H. M.: Cervical lymph node metastasis as the first symptom of cancer. *Surg. Gynec. Obstet.* 78 (1944), 133.
- MOERTEL C. G., REITMEIER R. J., SCHUTT A. J. and HANH R. G.: Treatment of the patient with adenocarcinoma of unknown origin. *Cancer* 30 (1972), 1469.
- OLSEN G.: The malignant melanoma of the skin. Thesis, Copenhagen 1966.
- PROBERT J. C.: Secondary carcinoma in cervical lymph nodes with an occult primary tumor. A review of 61 patients including their response to radiotherapy. *Clin. Radiol.* 21 (1970), 211.
- REINGOLD I. M.: Cutaneous metastases from internal carcinoma. *Cancer* 19 (1966), 162.
- RHOTON A. L., EICHLING J. and TER-POGOSSIAN M. M.: Metastatic tumors. Localization by radioisotope scanning. *Neurology* 16 (1966), 264.
- RIDENHOUR C. E., YEUN P. F. and SPRATT J. S.: Metastatic carcinoma in cervical lymph nodes from occult primary sites. *Missouri Med.* 64 (1967), 988.
- ROBINSON D. W.: The management of metastases in lymph nodes when the primary tumor cannot be found. *Plast. reconstr. Surg.* 23 (1959), 27.
- SINNER W.: Cervicale, inguinale und axilläre lymphknotenmetastasen bei zunächst unbekannten primärtumor. Thesis, Zürich 1959.
- Lymphknotenmetastasen bei vorerst nicht entdecktem primärtumor. *Oncologia* 14 (1961), 264.
- SKANDALAKIS E., GRAY S. W., TAKAKIS N. C., GODWIN J. T. and POER D. H.: Tumors of the neck. *Surgery* 48 (1960), 375.
- SMITH P. E., KREMENTZ E. T. and CHAPMAN W.: Metastatic cancer without a detectable primary site. *Amer. J. Surg.* 113 (1967), 633.
- TAYLOR G. W. and NATHANSON I. T.: Lymph node metastases. Incidence and surgical treatment in neoplastic disease. Oxford University, City Press, London 1942.
- WALTHER H. E.: Krebsmetastasen. Schwabe & Co., Basel 1948.
- WARD G. E. and HENDRICH, J. W.: Metastatic tumors of the neck. *In: Diagnosis and treatment of tumors of the head and neck.* The Williams & Wilkins Company, Baltimore 1950.
- VIACAVA E. P. and PACK, G. T.: Significance of supraclavicular signal node in patients with abdominal and thoracic cancer. *Arch. Surg.* 48 (1944), 109.
- WILLIS R. A.: Latent primary tumors. *In: The spread of tumors in the human body*, p. 130. Butterworths, London 1952.
- WORATZ G.: Lungenmetastase oder bronchialkarzinom? *Radiol. diagn.* 6 (1965), 609.
- ZEIDMAN I.: Metastasis: A review of recent advances. *Cancer Res.* 17 (1957), 157.