Virchows Arch. A Path. Anat. and Histol. 385, 49–59 (1979)

*Virchows Archiv A*


# Primary Malignant Melanoma of the Esophagus

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**Summary.** A case of primary malignant melanoma of the esophagus in a 74-year-old male is described. There was a diffuse pigmentation of the lower third of the esophagus macroscopically. Sections from this area revealed melanocytes in the basal layer of the epithelium. This melanosis was not caused by malignant melanoma cells, but obviously by preexisting ectopic and pigmented melanocytes a condition for which the term "esophageal melanocytosis" is proposed. It is suggested that esophageal melanocytosis as well as the presence of junctional changes may determine the primary nature of malignant melanoma of the esophagus. Furthermore, in order to outline the histologic criteria and the pathological features of primary esophageal melanomas, 64 cases have been reviewed.

**Key words:** Malignant melanoma – Esophagus – Esophageal melanocytosis – Junctional changes.

## Introduction

Primary malignant melanoma of the esophagus is an extremely rare lesion, and its occurrence at this site has been doubted for years due to the undefined histiogenesis. Moreover, the histologic criteria taken to indicate primary localization are controlversial. In the case described an esophageal melanoma occurred in the presence of preexisting melanocytosis from which the tumor may have originated. Since there is no recent review of malignant esophageal melanoma all 64 cases available in the literature have been critically surveyed and tabulated in order to outline the histologic criteria and the pathological features of this tumor.

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0340-1227/79/0385/0049/$02.20

## Case Report

A 74-year-old white male was admitted to hospital complaining of blood-stained sputum. Six weeks prior to admission, he had noted the onset of epigastric pain. He had lost 30 pounds within this period. His past history was unremarkable. On physical examination the liver was hard and plapable 19 cm below the costal margin. Laboratory data included a hemoglobin of 7.3 g per 100 ml and white cell count of 13,000/$mm^3$. The sedimentation rate and serum bilirubin, SGOT and SGPT were within normal limits. A barium swallow revealed a tumor in the lower esophagus and enlargement of the mediastinal lymph nodes. The possibility of an esophageal carcinoma was considered. However, in the view of the patients poor condition, esophagectomy was not carried out. He died 20 days after admission.

## Pathology

At *autopsy examination* of the esophagus revealed a polypoid tumor in its lower third measuring $8 \times 4 \times 3$ cm (Fig. 1). The surface of the lesion was not ulcerated and was mottled dark brown and gray. There was a diffuse pigmentation of the lower third of the esophagus. Under the esophageal epithelium, tiny dark grayish satellite nodes surrounded the central tumor mass (Figs. 1, 4). The mediastinal lymph nodes were enlarged, soft and hemorrhagic. The liver weighed 2,780 grams and showed multiple gray and brown spherical metastases averaging 1 cm in diameter. There were also metastases in the right kidney, both adrenals, the spleen and the lungs. The body was thoroughly examined for other possible primary sites, with special attention given to those where malignant melanoma is known to originate. At these sites no evidence of growth or of abnormal pigmentation was present.

*Histologically* the esophageal tumor showed extention into the submucosa and muscular layer (Fig. 3). It consisted mainly of polymorphic cells (Fig. 2). The usually large, pleomorphic nuclei were markedly hyperchromatic and contained prominent nucleoli. The stroma was scanty. Melanin pigment was frequently present in the tumor cells and often seen in macrophages. The nature of the pigment was ascertained by Masson-Hamperl's argentaffin technique and by bleaching with 40% peractic acid. Staining for iron was negative. Sections were taken from the overlying and the adjacent epithelium to the primary tumor. The epithelium overlying contained scattered tumor cells in some areas (Fig. 3). A significant finding was the presence of melanocytes in the epithelium adjacent to the primary lesion. They were localized in the basal layer and showed clear cytoplasm, dark and round nuclei, dentritic processes and melanin granules. Melanin granules were also seen in the cytoplasm of basal cells adjacent to these melanocytes (Fig. 5). The diagnosis was: primary malignant melanoma of the esophagus.

## Comment

Experimental embryology has demonstrated that melanocytes originate in the neural crest (Rawles, 1953). During early embryogenesis melanoblasts migrate into the epidermis, hair follicles, uvea, chorioidea, leptomeninges, substantia nigra, oral cavity and nasopharynx. Thus, the origin of malignant melanoma at these sites is easily understood. Since melanocytes have been demonstrated in 4–8% of normal esophagi (De La Pava et al., 1963; Tateishi et al., 1974; Ladouch et al., 1976) the occurrence of primary malignant melanoma of the esophagus was not further questioned. In fact, this generally adopted neuroectodermal concept (Vaneecloo et al., 1977), accepts that melanoblasts migrating from the neural crest to their definite position may home, in rare cases, at ectopic sites, e.g. the esophagus (Masson, 1948; De la Pava et al., 1963). In contrast, the epithelial concept which claims that melanocytes originate from

**Table 1.** Summary of pathological data of the recorded cases of primary malignant melanoma of the esophagus

| Case number | Author | Age | Sex | Examined material | | | Localization of tumor | Metastases at autopsy | Junctional changes | Esophageal melanocytosis |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | B[a] | S[b] | A[c] | | | | |
| 1 | Baur (1906) | 69 | M | | | A | Upper | Satellites, Trachea | N. r.[f] | N. r. |
| 2 | Joliat[d] (1907) | 62 | M | | | A | Lower | Liver, peritoneum | N. r. | N. r. |
| 3 | Moersch and Broders[e] (1927) | 59 | M | B | | | Lower | | N. r. | N. r. |
| 4 | Voss[e] (1928) | 59 | M | | | A | Middle | Lungs, brain, intestine | N. r. | N. r. |
| 5 | Jaleski and Waldo[e] (1935) | 69 | M | | | A | Lower | Lungs, liver, spine, pancreas, satellites | N. r. | N. r. |
| 6 | Puyo and Portmann[e] (1950) | 63 | M | B | | | Lower | | N. r. | N. r. |
| 7 | Burnett and St. John[e] (1951) | 55 | F | | S | | Middle/ Lower | | N. r. | N. r. |
| 8 | Chalmagne[d] (1951) | 68 | F | B | | | Middle | | N. r. | N. r. |
| 9 | Lüdin[d] (1951) | 74 | M | | S | | Middle | | N. r. | N. r. |
| 10 | Fowler and Sutherland (1952) | 60 | F | B | S | A | Middle | Satellites | + | + |
| 11 | Garfinkle and Cahan[e] (1952) | 55 | F | B | S | | Upper | | + | N. r. |
| 12 | Bullock et al.[e] (1953) | 71 | M | B | S | | Middle/ Lower | | + | + |
| 13 | Cittero[e] (1953) | 67 | M | B | S | | Lower | | N. r. | N. r. |
| 14 | Boyd et al.[e] (1954) | 63 | M | B | S | | Middle/ lower | | + | + |
| 15 | Robertson[e] (1954) | 58 | M | | S | A | Lower | Lungs, liver, pancreas, pelvis | – | N. r. |
| 16 | Pomeranz and Garlock[e] (1955) | 48 | F | B | S | | Middle/ lower | | + | N. r. |
| 17 | Sirsat[d] (1955) | 40 | M | B | | | Middle | | N. r. | N. r. |
| 18 | Hromadova (1956) | 71 | M | B | S | A | Middle/ lower | No metastases | N. r. | N. r. |
| 19 | Loring and Zeppa[e] (1956) | 61 | F | B | S | | Middle/ lower | | + | N. r. |
| 20 | Keeley et al.[e] (1957) | 62 | F | B | S | A | Middle | Brain | + | N. r. |

**Table 1** (continued)

| Case number | Author | Age | Sex | Examined material | | | Localization of tumor | Metastases at autopsy | Junctional changes | Esophageal melanocytosis |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | B[a] | S[b] | A[c] | | | | |
| 21 | Buchholz[e] (1958) | 60 | M | B | | A | Middle | Brain, other organs | N. r. | N. r. |
| 22 | Ferro et al.[e] (1958) | 64 | M | B | S | A | Lower | Now metastases | – | N. r. |
| 23 | Fleming and van Merve (1958) | 77 | F | B | | A | Middle | No metastases | – | + |
| 24 | Nègre et al.[e] (1958) | 59 | M | | S | | Middle | | + | N. r. |
| 25 | Bartsch[d] (1961) | 38 | F | B | S | | Middle/ lower | | – | N. r. |
| 26 | Minwalla and Parry[e](1961) | 67 | F | | | A | Lower | Liver | N. r. | N. r. |
| 27 | Suehs[e] (1961) | 82 | F | B | | | Lower | | N. r. | N. r. |
| 28 | Calvet et al.[e] (1962) | 53 | M | B | | | Middle | | N. r. | N. r. |
| 29 | Waken and Bullock (1962) | 47 | M | B | S | A | Middle | Liver, spleen skin pleura, bone-marrow, peritoneum | + | + |
| 30 | Raven and Dawson[e](1964) | 52 | F | B | S | | Middle | | + | + |
| 31 | Sakornpant et al.[e] (1964) | 70 | M | B | S | | Upper/ middle | | ? | N. r. |
| 32 | Sakornpant et al.[e] (1964) | 50 | M | B | S | | Lower | | + | N. r. |
| 33 | Huppe[e] (1966) | 64 | M | B | | A | Upper | No metastases | ? | + |
| 34 | Richard et al.[e] (1966) | 60 | M | B | S | | Middle/ lower | | + | + |
| 35 | Nichet and Mouchard[e] (1967) | 74 | F | B | | | Upper | | N. r. | N. r. |
| 36 | Bettini and Gori[e] (1968) | 60 | M | B | S | | Middle | | N. r. | N. r. |
| 37 | Heully et al.[e] (1968) | 57 | F | B | S | | Middle/ lower | | N. r. | N. r. |
| 38 | Witonsky[e] (1968) | 77 | M | | | A | Lower | Liver, peritoneum | N. r. | + |
| 39 | Hosoda et al.[d] (1969) | 61 | M | | | A | Middle | Liver, adrenals, skin, pancreas, bladder | + | N. r. |
| 40 | Yamasaki et al.[d] (1969) | 51 | M | | | A | Middle/ lower | Kidney, adrenals, spleen, pancreas | ? | N. r. |

**Table 1** (continued)

| Case number | Author | Age | Sex | Examined material | | | Localization of tumor | Metastases at autopsy | Junctional changes | Esophageal melanocytosis |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | B[a] | S[b] | A[c] | | | | |
| 41 | Basque et al.[e] (1970) | 7 | M | B | S | A | Middle | Mediastinum | – | N. r. |
| 42 | Piccone et al. (1970) | 70 | M | B | S | A | Lower | Lungs, liver, stomach, ureter, skin, kidney, vertebrae | + | + |
| 43 | Bingham et al.[d] (1971) | 53 | M | | S | | Lower | | + | N. r. |
| 44 | Coste et al.[e] (1971) | 65 | M | B | | | Lower | | – | N. r. |
| 45 | Broderick et al.[e] (1972) | 52 | M | B | S | | Lower | | + | N. r. |
| 46 | Frable et al.[e] (1972) | 69 | F | B | S | | N. r. | | + | N. r. |
| 47 | Moffat et al. (1972) | 54 | M | B | | A | Middle/ lower | Lungs, liver, brain, lip, stomach, adrenals, scalp | + | N. r. |
| 48 | Futonaka et al. (1973) | 61 | F | B | S | | Lower | | + | N. r. |
| 49 | Chaput et al.[e] (1974) | 57 | M | B | S | A | Lower | No metastases | + | + |
| 50 | Hendricks et al. (1974) | 55 | M | B | S | | Lower | | + | N. r |
| 51 | Musher and Lindner[d] (1974) | 73 | M | | S | | Lower | | + | N. r. |
| 52 | Holler et al.[e] (1975) | 62 | M | B | S | A | Middle/ lower | Meninges, mediastinum | N. r. | N. r. |
| 53 | Mikuz et al. (1975) | 74 | M | B | S | | Middle | | + | N. r. |
| 54 | Urbano and Fornaciari (1975) | 72 | F | B | S | | Lower | | – | + |
| 55 | Yang et al. (1975) | 56 | M | | S | | Middle | | N. r. | N. r. |
| 56 | Yang et al. (1975) | 62 | M | B | S | | Middle/ lower | | N. r. | N. r. |
| 57 | Yang et al. (1975) | 71 | M | B | | A | N. r. | ? | N. r. | N. r. |
| 58 | Gonzalez et al. (1976) | 53 | F | B | | ? | Middle | ? | N. r. | N. r. |
| 59 | Inoguchi et al. (1976) | 76 | F | | S | ? | Lower | ? | + | + |

**Table 1** (continued)

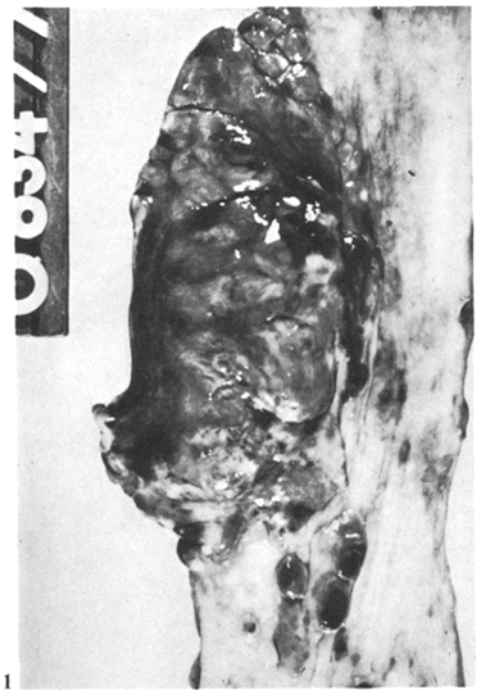
| Case number | Author | Age | Sex | Examined material | | | Localization of tumor | Metastases at autopsy | Junctional changes | Esophageal melanocytosis |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | B[a] | S[b] | A[c] | | | | |
| 60 | Kurzban et al. (1976) | 55 | F | B | S | | Middle | | N. r. | N. r. |
| 61 | Ladouch et al. (1976) | 62 | M | B | S | A | Middle/ lower | Pleura, meninges, mediastinum | N. r. | N. r. |
| 62 | Montgomery (1976) | 58 | M | B | S | | Lower | | N. r. | N. r. |
| 63 | Mansson and Berge (1977) | 74 | F | B | | A | Middle | Pleura | + | + |
| 64 | Vaneecloo et al. (1977) | 54 | M | B | S | | Upper | | + | + |
| 65 | Kreuser (1979) | 74 | M | | | A | Lower | Liver, lungs, spleen, kidney, adrenals, satellites | − | + |

[a] B = Biopsy specimen
[b] S = Surgical specimen
[c] A = Autopsy specimen
[d] References see: Vaneecloo et al. (1977)
[e] References see: Urbano and Fornaciari (1975)
[f] N. r. = not recorded

basal cells by a process of in situ transformation and metaplasia (Allen and Spitz, 1953) seems less convincing, since the migration of neural crest cells to all regions of the body is now well established by embryological studies (Rawles, 1953).

64 published cases of alleged primary malignant melanoma of the esophagus are available in the literature and have been reviewed and listed in Table 1. On the contrary, the review of the literature on secondary malignant melanoma of the esophagus revealed 9 cases (Spiegelberg, 1895; Ranieri, 1941; Das Gupta and Brasfield, 1964; Butler et al., 1975; Dedeurwaerder, 1975; Wood and Wood, 1975) which are not included in Table 1. However, there may be doubts as to the validity of the diagnosis in those cases in which the primary site was not substantiated by histologic criteria (45%, Table 1), or the diagnosis was established only by biopsy (12%, Table 1). Autopsy was performed in 40% of all cases and surgical specimes of the esophagus were examined in 63% (Table 1). We do not wish to reject these cases because histologic criteria might have been present, but they were not recorded (Table 1). But we simply regard the published evidence as unconvincing. In order to obtain the right criteria for diagnosing this entity, we listed all available cases in Table 1.

Histologic criteria for primary malignant melanoma of the esophagus have



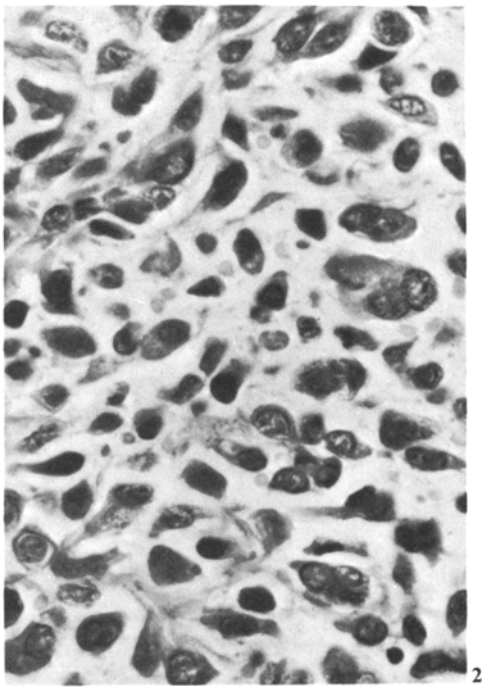
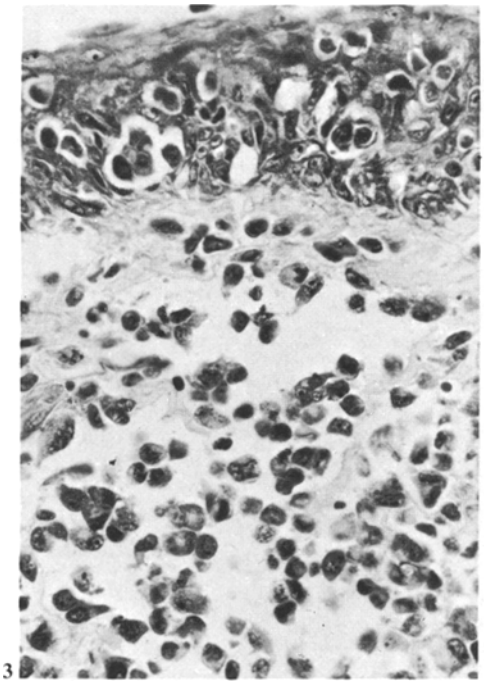


**Fig. 1.** Gross photograph of autopsy specimen showing primary malignant melanoma of the esophagus. The lesion measures 8 × 4 × 3 cm. Note the pigmentation and the satellites of esophageal mucosa

**Fig. 2.** Photomicrograph of the primary lesion showing a wide range of nuclear variation of malignant melanoma cells. HE; × 250

been developed by Allen and Spitz (1953) emphasizing the presence of junctional changes: "Therefore, the prelude to a melanocarcinoma of mucous membranes – just as of the skin – is an activated junctional nevus". The junctional changes concept is now generally adopted to demonstrate the primary nature of malignant melanoma. But, one must realize that on review of literature junctional changes of the overlying or adjacent epithelium occured in only 40% (Table 1). This could possibly be due to growth of the tumor destroying any preexisting lesion. Furthermore, careful examination of the photomicrographs from some of the reported cases suggests that intraepithelial invasion by tumor cells may have been taken for junctional changes. In fact, the overlying epithelium in the present case (Fig. 3) can be considered as an example in which such misinterpretation could be made. Therefore, it seems necessary, to look for further histologic criteria.

As early as 1952, Fowler and Sutherland in a case of esophageal melanoma noted pigmented areas in the epithelium away from the tumor where they observed melanocytes. Fleming and van der Merwe (1958) published a case of esophageal melanoma demonstrating non-malignant pigmented cells in the basal layer at some distance from the primary tumor. In a case reported by



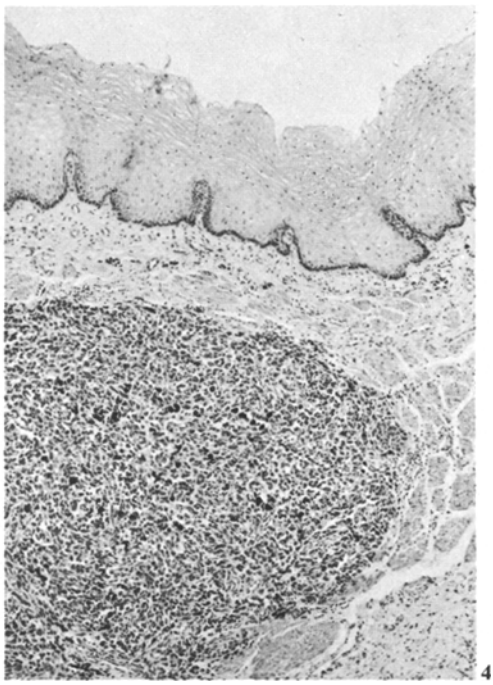


**Fig. 3.** High power illustration of esophageal malignant melanoma. Note the intraepithelial tumor cells. HE; ×200

**Fig. 4.** Photomicrograph of the adjacent epithelium of the primary lesion with a satellite metastasis. HE; ×40

Piccone et al. (1970) the primary malignant melanoma occurred in an esophagus which showed melanosis along its total length. These authors found abundant melanocytes in the basal layer in sections from all parts of the esophagus. For the first time, De La Pava et al. (1963) succeeded in demonstrating ectopic melanocytes in 4 of 100 (4%) nonselected esophagi. Later, Tateishi et al. (1974) detected areas with foci of melanocytes in 4 of 50 (8%) of normal esophagi.

In the light of these findings it is interesting to note that the case described here showed macroscopically diffuse pigmentation of the lower third of the esophagus (Fig. 1). In fact, melanocytes with melanin granules and dendritic processes were found microscopically in the basal layer in these areas (Fig. 5). Moreover, melanin granules were seen in the cytoplasm of the basal cells adjacent to the melanocytes (Fig. 5). This may be caused by incorporation of melanosomes into basal cells. In a case of primary malignant melanoma of the gallbladder Hatae et al. (1978) demonstrated this transfer of melanosomes into epithelial cells as well. In order to distinguish melanin pigmentation caused by malignant melanoma cells from that caused by preexisting melanocytes, we suggest this condition be termed "esophageal melanocytosis". This feature was reported in 25% of cases of esophageal malignant melanoma (Table 1). If one accepts that esophageal melanocytosis may be a precursor lesion for the development

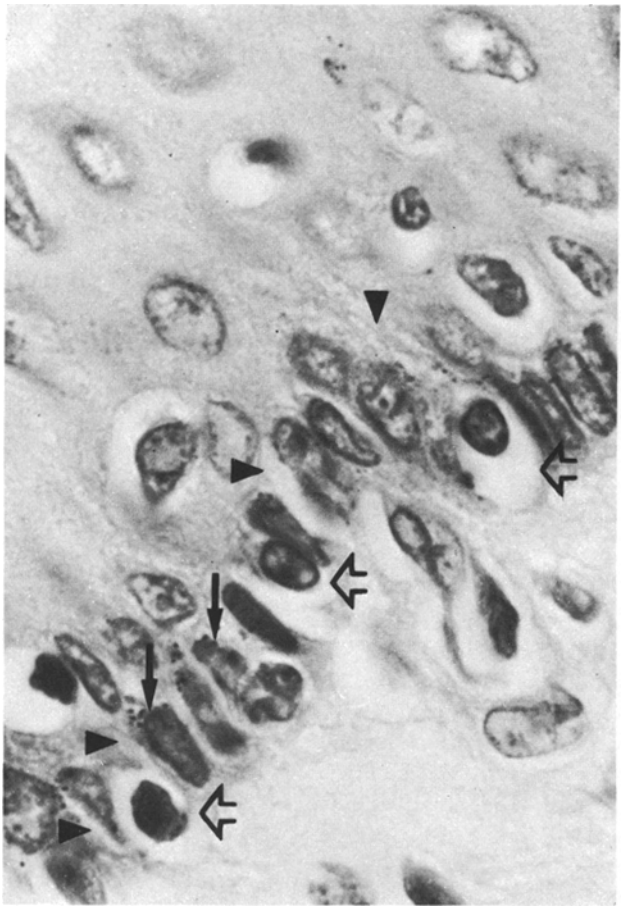


**Fig. 5.** High power illustration of the adjacent epithelium. Note the melanocytes (⇨) with clear cytoplasma, melanin granules and dendritic processes (▶). Melanin granules are also seen in the cytoplasm of the adjacent basal cells (➡). HE; ×400

of junctional changes as well as of primary malignant melanoma of the esophagus, this change deserves due attention. Accordingly, it is suggested that in any case of a pigmented esophageal lesion the epithelium adjacent and even distant from the primary tumor is examined histologically tu substantiate the diagnosis of primary melanoma of the esophagus by esophageal melanocytosis and/or by junctional changes.

It is of some interest to compare squamous carcinoma and malignant melanoma of the esophagus. In the reported cases esophageal malignant melanoma was seen in the lower third of the esophagus in 57% and in the middle third in 31% (Table 1). In contrast, carcinoma of the esophagus is most frequently localized in the lower third (Chiari and Wanke, 1971). Malignant melanoma of the esophagus affects females in 32% (Fig. 6) and the mean age is 60.4 years in males and 62.7 in females (Table 1).

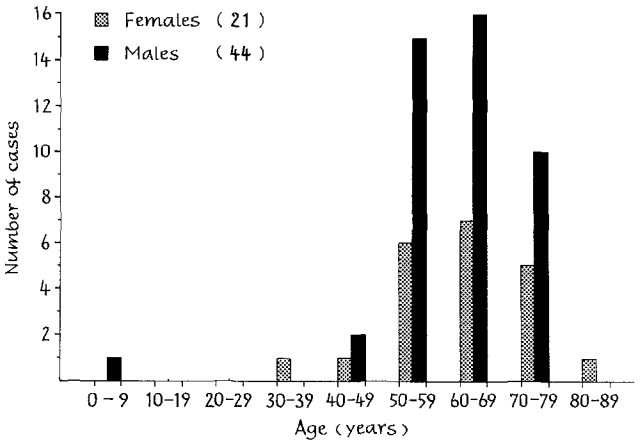



**Fig. 6.** Age and sex distribution of 65 cases of primary malignant melanoma of the esophagus

On the other hand, the mean age for squamous carcinoma of the esophagus is higher (69 years, Sjöström, 1971) and the incidence is considerably lower in females 4.9–12.2% (Chiari and Wanke, 1971). Postmortem examination revealed haematogenetic metastases in 81% of esophageal melanomas (Table 1) with the liver (38%) and the lungs (23%) most frequently involved. However, metastases from esophageal carcinoma occur in only 40–75% (Chiari and Wanke, 1971). Comparing cutaneous and esophageal malignant melanomas, esophageal melanoma affects females in 32% (Table 1), but cutaneous melanoma in 54% (Sjöström, 1971). While the mean age for cutaneous melanoma is 54.9 years in males and 53.7 in females, it is about 7 years more for esophageal malignant melanoma (Fig. 6). These epidemiologic findings underline the specific nature and at least some particular features of primary malignant melanoma of the esophagus.

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Received June 30, 1979