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Progesterone, Oestradiol, Somatostatin and Epidermal Growth Factor Receptors on Human Meningiomas and Their CT Characteristics

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The presence of progesterone, oestrogen, somatostatin and epidermal growth factor receptors of 24 meningiomas was related with their radiological CT appearance. Progesterone receptors were present in 16 of 21 (76%), oestrogen receptors in 4 of 21 (19%), somatostatin receptors on 23 of 24 (96%) and epidermal growth factor receptors on 17 of 19 (89%) meningiomas. There was no relationship between the presence of these receptors and the age or sex of the patients, tumour histology, tumour localisation, the presence of perifocal oedema, displacement of the midline cerebri or obstructive hydrocephalus on CT scan. There was a negative correlation ($P < 0.05$) between the number of progesterone receptors and "malignant" behaviour of the meningiomas on CT (e.g. the presence of necrosis, cyst formation, intratumoral haemorrhage, irregular surface and/or inhomogeneous attenuation of contrast). The observation that aggressive tumour behaviour on CT is accompanied by low numbers or absence of progesterone receptors makes these meningiomas less attractive candidates for medical therapy with antiprogestins.
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INTRODUCTION

IN THE last decade new information has been obtained about meningiomas, both with regard to their radiological appearance on computed tomography (CT) examination, and to the presence of hormone and growth factor receptors in these tumours. Studies into the CT characteristics of meningiomas suggest a prognostic and pathophysiological importance [1–4]. Endocrine investigations showed the presence of progesterone receptors (PR) on the majority of meningiomas [5, 6], while the presence of oestrogen receptors (ER) has been a matter of controversy [5–9]. We recently showed that somatostatin receptors (SSR) are present in various densities on virtually all meningiomas [9, 10], whilst epidermal growth factor receptors (EGFR) are simultaneously present on most of them [11, 12]. In breast cancer the presence of PR, ER, SSR and EGFR has been previously shown to be of importance both with regard to the prognosis and the choice of medical therapy [13, 14].

The clinical importance of radiological appearance as well as of the presence of hormone receptors on meningiomas is at present uncertain. However, various attempts have been made to correlate CT characteristics with histology or with the clinical course of meningiomas [1, 15, 16]. In the present study, we compared CT appearance of 24 meningiomas with the presence and quantity of PR, ER, SSR and EGFR and with histology.

MATERIALS AND METHODS

Twenty-four human intracranial meningiomas were obtained at surgery. From these tumours, a preoperative CT had been made, with and without contrast (Philips Tomoscan 310). After

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Table 1. CT characteristics of meningiomas

CT characteristics, modified, according to Lanksch [17]	
Displacement of the midline	−(absent), +(present <1cm), ++(present >1cm)
Obstructive hydrocephalus	−(absent), +(moderate), ++(severe)
Perifocal oedema	−(absent), grade I (<2cm), grade II (<half hemisphere), grade III (>half hemisphere)
Calcifications	−(absent), +(present)
Bone aberrations	−(absent), +(present)
Necrosis, cyst formation and/or haemorrhage	−(absent), +(present)
"Malignant" tumour characteristics (irregular circumscription, inhomogeneous attenuation)	−(absent), +(present)
Multiplicity	Solitary, multiple, recurrence
Receptor determination of meningiomas	
PR (fmol/mg protein)	0(absent); +(0–60), ++(60–200), +++(>200)
ER (fmol/mg protein)	0(absent or <10, +(>10)
SSR	0(absent), + (low density), ++(medium density), + + +(high density)
EGFR	0(absent), +(low density), ++(medium density), +++(high density)

In the case of multiple meningiomas the receptor determinations were carried out on the meningioma tissue removed from one localisation, as in Table 2.

removal of the tumour one part was taken for pathological confirmation. The other part was processed as described by Reubi *et al.* [11] for SSR and EGFR autoradiography. In addition, cytosolic binding assays were executed to determine the presence of progesterone and oestrogen receptors [6]. All PR and ER results were based upon Scatchard analysis of the binding characteristics, involving at least five concentration points.

A protocol for the evaluation of the preoperative CT was drawn on the basis of modified criteria described by Lanksch [17] (Table 1). CT characteristics investigated were tumour localisation, attenuation with and without contrast, regularity of the tumour surface, displacement of the midline, obstructive hydrocephalus, perifocal oedema, calcification, bone aberrations, necrosis, haemorrhage or the presence of cysts and multiplicity. Special attention was given to malignant CT characteristics, which were defined as irregular circumscription, inhomogenous attenuation and bone destruction. As well, the presence of necrosis, cyst formation and/or intratumoral haemorrhage was classified separately. CT interpretation was performed by the neuroradiologist (H.T.) with confirmation by one of the other investigators, without knowledge of the results of hormonal receptor investigations.

Statistical evaluation on the possible relationships between these characteristics was done with the χ^2 test and Fisher's exact test.

RESULTS

Table 2 summarises the hormone receptor levels on the tumours, the results of the CT grading of the meningiomas and their histology.

PR were present on 16 of the 21 meningiomas investigated (76%), while ER were present on only 4 of 21 tumours (19%). SSR were found on 23 of 24 tumours (96%), while EGFR were detected on 17 of 19 tumours (89%). The only SSR negative meningioma was an intraventricular meningioma (no. 10, Table 2). Examples of the autoradiography of SSR and EGFR on two meningiomas are shown in Figs 1 and 2.

With regard to the bone lesions on the CT scans of these patients, hyperostotic abnormalities were found in patients 6, 8, 13, 15 and 24, while osteolytic abnormalities and erosions were seen around the meningiomas of patients 9, 11 and 20. In Fig. 3 the CT characteristics of "malignant" tumour behaviour are illustrated.

Statistical analysis of the possible correlations between the hormonal and CT data did not point to a relationship between the presence and/or density of PR, ER, SSR and/or EGFR and the age and sex of the patients. In addition tumour histology and localisation, the presence of perifocal oedema, displacement of the midline cerebri and obstructive hydrocephalus did not correlate with the presence of hormone receptors on these tumours. Also, no correlation was found between the presence of "malignant" CT characteristics and necrosis, cyst formation and/or haemorrhage and the presence of SSR and/or EGFR receptors.

11 of the 21 meningiomas contained none or less than 60 fmol/mg protein of PR ("0" or "+" in Table 2), while 10 of these tumours contained more than 60 fmol/mg protein of PR ("++" or "+++" in Table 2). Of the tumours with low numbers of PR receptors 7 showed necrosis, cyst formation and/or haemorrhage on CT, while only one with high numbers of these receptors had such characteristics ($P < 0.05$). Such a correlation between low or absent progesterone receptors and "malignant" CT characteristics was also statistically significant ($P = 0.05$).

Analysis of the presence of bone abnormalities suggests a relationship with the number of SS receptors. All tumours with clear evidence of bone erosion, destruction or hyperostosis contained high numbers of SSR. Bone abnormalities were observed in 8 patients. In 6, SSR were rated "+++" and in the other 2 as "++". However, the statistical analysis of the relation between the number of SSR and the presence of bone abnormalities was just not significant ($P = 0.054$, χ^2 test).

DISCUSSION

The diagnosis of intracranial meningioma especially with the aid of CT and, recently also magnetic resonance imaging (MRI) in general presents few problems. Human meningiomas are in most instances benign tumours, but a "malignant", often recurring and aggressive variant is observed in a minority of cases [15–19]. Aggressive behaviour of meningiomas was defined by these investigators as rapid recurrence after surgical removal with changes in the number of mitoses, invasion of the brain substance and/or an increase of focal necrosis. Histological features of aggression have been previously reported to be mirrored in certain CT appearances of these tumours, such as heterogeneous contrast enhancement, the presence of cystic components, an irregular outline of the tumour, sometimes with "mushrooming", bone destruction and in a minority of cases the presence of marked perifocal oedema [1, 15, 16].

Table 2. The relationship between the presence of PR, ER, SSR and EGFR and CT characteristics of 24 meningiomas

No. (sex, age)	Localisation	PR	ER	SSR	EGFR	Bone abnormality	Calcification	Displacement midline	Obstruction	Perifocal oedema	Multiplicity	NCH	Malignant characteristics	Histological type
1 (M,73)	Parasagittal	++	0	++	ND	−	+	+	++	I	S	−	−	Sync/trans
2 (F,60)	Sphenoid	+++	0	++	+	−	−	++	+	III	S	+	+	Fibro
3 (F,55)	Convexity	0	0	+	ND	−	−	+	−	III(II)	M/R	−	−	Angio
4 (F,42)	Parasagittal	++	+	++	+	−	−	+	+	II	S	−	−	Trans/sync
5 (F,58)	Convexity	0	0	+++	ND	−	+	+	−	II	S	−	−	Trans
6 (F,40)	Convexity	++	+	+++	+	+	+	+	−	II(I)	M	−	−	Sync/fibro
7 (F,40)	Infratentorial	+	0	+++	+++	−	−	++(+)	drain	I	S/R	−	−	Trans
8 (M,56)	Convexity	++	0	+++	+	+	+	+	−	III(II)	M/R	−	+	Fibro
9 (M,59)	Sphenoid	+	0	+++	+	+	−	−(+)	−	II(III)	M/R	+	+	Sync
10 (M,66)	Intraventricular	0	0	0	+	−	−	+	+	II	S	+	+	Fibro
11 (F,62)	Convexity	+	0	+++	++	+	+	+(++)	+	II	S	+	+	Trans
12 (M,60)	Parasagittal	++	0	+++	+	−	−	+	−	II	S	−	−	Sync
13 (F,67)	Parasagittal	+++	0	++	++	+	−	−	−	I	S	−	−	Sync
14 (F,30)	Multiple	ND	ND	++	ND	−	+	+	−	—	M	−	−	Fibro
15 (M,67)	Convexity	ND	ND	++	+	+	−	+	−	—	S	+	+	Trans
16 (F,51)	Parasagittal	+++	0	+	0	−	+	++	+	II	S	−	−	Trans
17 (F,75)	Parasagittal	0	0	+	0	−	+	++	+	III	S	+	+	Fibro
18 (F,57)	Parasagittal	+	0	+	+	−	−	−(+)	−	II	S/R	−	−	En plaque
19 (F,63)	Foramen magnum	++	+	+	+	−	+	++	++	I	S	−	−	Fibro
20 (F,37)	Supra-sellar	ND	ND	+++	+	+	−	++	−	—	S	−	+	Sync/trans
21 (F,62)	Convexity	+++	+	+++	++	−	−	++	+	II	S	−	−	Trans
22 (M,58)	Parasagittal	+	0	++	ND	−	−	+	−	I	S	+	+	Fibro
23 (M,65)	Parasagittal	+	0	+++	+	−	−	+	−	I	S	+	+	Sync
24 (F,58)	Parasagittal	0	0	+++	+	+	++	++	+	II	S	+	+	Fibro

ND = not done, NCH = necrosis, cyst and/or haemorrhage, S = solitary, M = multiple, R = recurrent, Sync = syncytial, Trans = transitional, Fibro = fibroblastic, Angio = angioplastic.

In the present study we found that those meningiomas which had a CT appearance showing necrosis, cyst formation, haemorrhage and/or "malignant" behaviour contained few or no PR. This suggests that the aggressive behaviour of this type of tumour might be accompanied by a loss of progesterone-binding sites. In a previous study we reported no relation between tumour localisation and PR content in 67 meningiomas [20]. Also attempts to find a correlation between these receptors and the histological types were inconclusive. In the present study, we did not observe a relation between the presence of the various receptors and histology. Clinical follow-up was too short to know whether this related to these parameters.

Benzel and Gelder [21] previously found a correlation between PR binding activity on meningiomas and the presence of peritumoral oedema. Such a relationship was not observed, however, in our group of 24 meningiomas.

Recently, it has become clear from *in vitro* as well as from preliminary *in vivo* studies that chronic therapy of meningioma patients with the PR blocking drug RU 486 (Roussel UCLAF, Paris) results in control of tumour growth in some of these patients [22, 23]. This beneficial effect was observed even in view of the expected problems of the simultaneously occuring glucocorticoid receptor-blocking activity of the drug. The observations described in the present study suggest that those meningiomas which show CT scan characteristics of necrosis, haemorrhage and cyst formation and irregular outline contain the lowest numbers of PR. This would imply that especially relatively benign, slowly-growing meningiomas contain high numbers of receptors, making patients with aggressively growing meningiomas less attractive candidates for medical therapy with PR antagonists.

Our study confirms the virtual absence of oestrogen receptors on most human meningiomas. This is in accordance with our previous observations, as well as with those by others [6–8].

Virtually all meningiomas contain high numbers of high affinity SSR [10, 11]. At present the pathophysiological implication of this observation is not known. Preliminary studies do not suggest a consistent direct antimitotic effect of somatostatin (analogues) on cultured human meningioma cells [11]. Our present data suggest that those tumours which cause clear evidence of bone erosion, destruction or hyperostosis in particular contain the highest number of SSR, albeit that no statistically significant correlation was obtained. Previous studies on meningiomas suggested that bone proliferation might be the result of progressive dilatation of blood vessels near the meningioma, secondary to the secretion of vasoactive factors by the tumour [24]. The subsequent infiltration of these vessels by the tumour might then be responsible for secondary bone destruction. Schenk *et al.* [25] showed in a series of 115 meningiomas that relatively avascular meningiomas are usually associated with hyperostosis and bone thickening, while the vascular tumours are often associated with bone erosion. Our studies show that somatostatin itself is not produced by meningioma cells [26], suggesting that this peptide is not the potential vasoactive-meningioma substance, which might be involved in causing the characteristic bone lesions.

EGFR are present on most meningiomas [11, 12]. Our previous studies suggest that SSR and EGFR are in a minority of meningiomas present on the same tumour cells [11]. We did not find a relationship between the presence of EGFR and the histological type or biological behaviour of meningiomas, or to the CT characteristics of these tumours. In addition we found

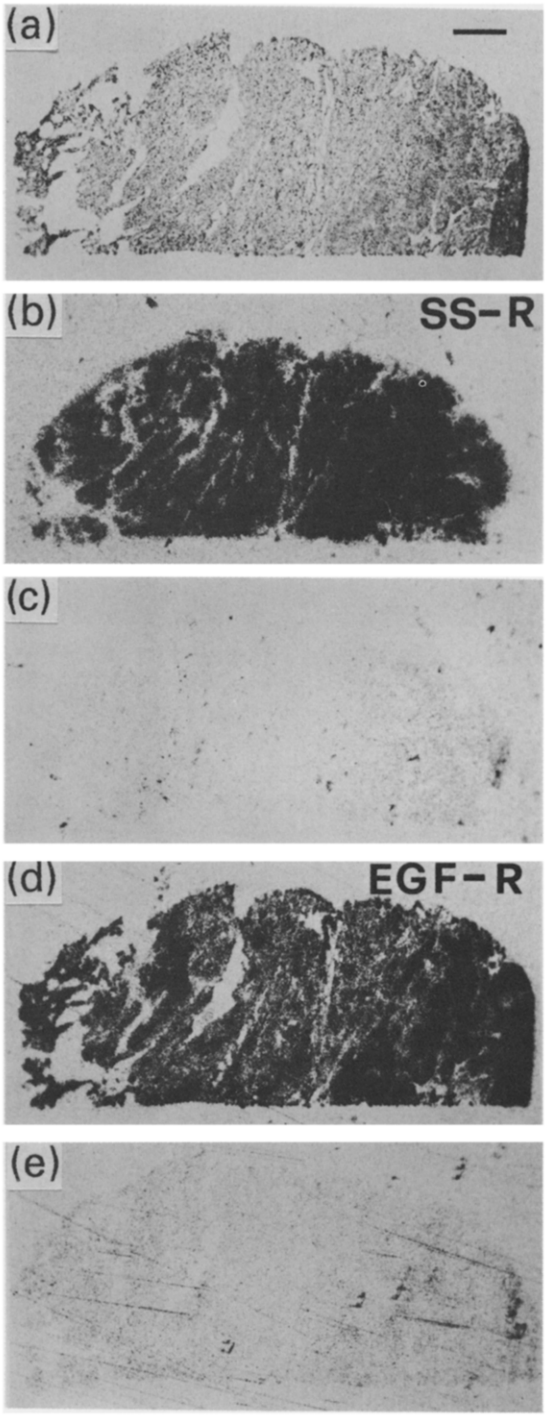

Fig. 1. The presence of SSR and EGFR in adjacent sections of a meningioma. (a) haematoxylin–eosin stained section. (b, c) Autoradiograms of SSR labelled with ^{125}I-Tyr^3-octreotide: (b) total binding, (c) non-specific binding in the presence of 1 μmol/l Tyr^3-octreotide. (d, e) Autoradiograms of EGFR labelled with ^{125}I-EGF: (d) total binding, (e) non-specific binding in the presence of 0.1 μmol/l EGF. Exposure times were SSR: 1 week, EGFR: 3 weeks. Bar = 1 mm.

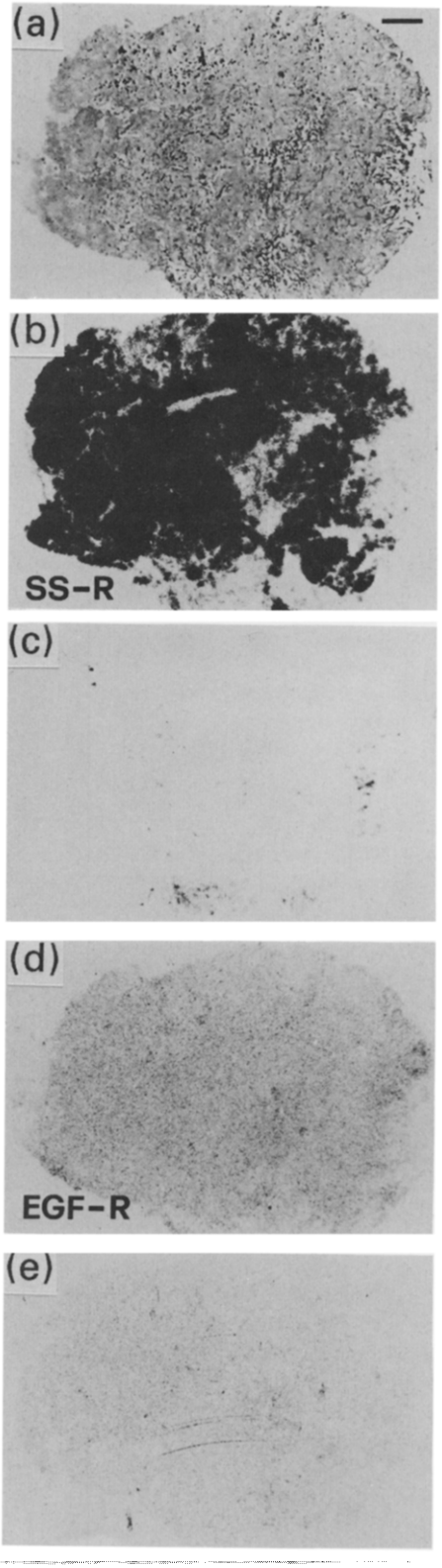

Fig. 2. The presence of SSR and the absence of EGFR in adjacent sections of another meningioma.

no relationship between the presence of these receptors and those for progesterone, oestradiol and/or somatostatin. In other human brain tumours e.g. glioblastomas [27], as well as in human breast cancer [28], the presence of EGFR often predicts very aggressive behaviour of the tumours and a bad prognosis.

In conclusion, our study shows that "malignant" CT characteristics of meningiomas, which are generally considered as a step in the process towards rapid recurrence and aggressive behavior, are accompanied by a significantly lowered number of PR. These observations might limit the success of medical treatment of this type of meningioma patients with antiprogestins.

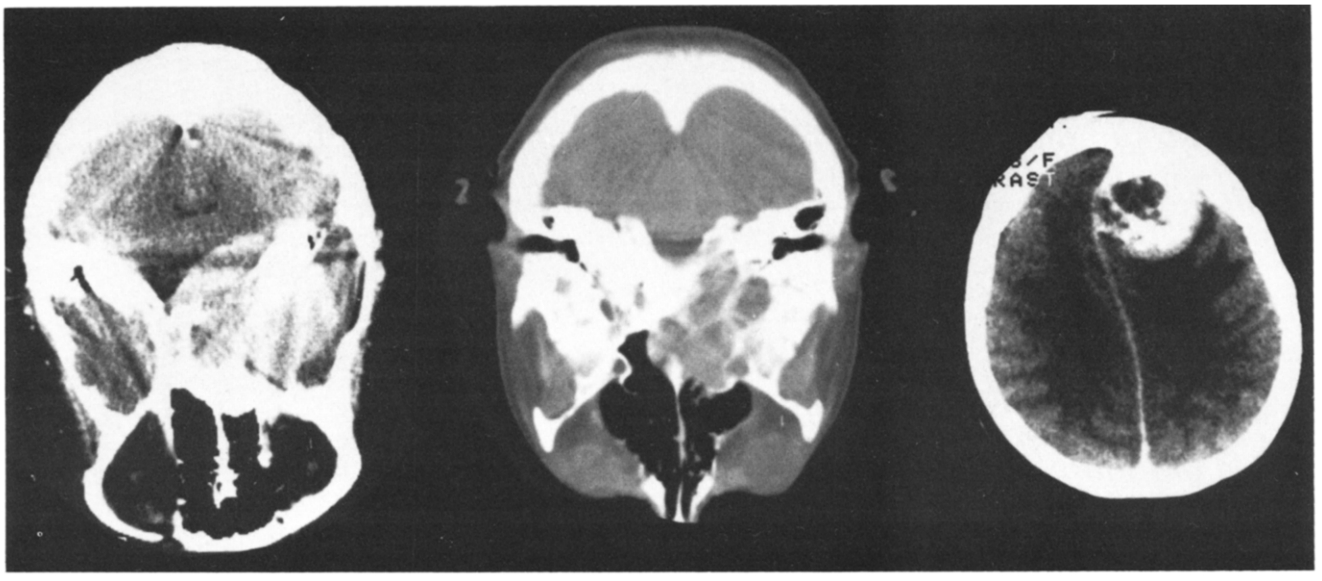

Fig. 3. Three CT pictures showing "malignant" tumour behavior (left and middle), or necrosis and cyst formation (right). On the left the suprasellar tentorium meningioma of patient 20 is shown: there is inhomogeneous contrast enhancement and irregular circumscription of the tumour. The same tumour is shown at a higher level in the middle panel. Extensive bone destruction of the apex of the os petrosum, as well as of the pituitary fossa is seen. The CT of the parasagittal falx meningioma of patient 24 is shown on the right. There is inhomogeneous enhancement of contrast, as well as evidence of cyst formation and/or necrosis.

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