

## Recurrence of pituitary adenomas after transcranial operation

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**SUMMARY** A series of 289 pituitary adenomas operated upon transcranially have been assessed for the frequency of recurrence. Ten patients died in the postoperative period, and nine patients have been lost to follow up. Follow up data is therefore available in a series of 270 cases for a period extending up to 30 years after the initial operation. There have been 13 histologically verified recurrences (4.8%), and a further six cases are known from CT scan or air study evidence to have residual or recurrent tumour which has not necessitated re-exploration. The total recurrence or residual tumour rate could therefore be regarded as 7.4%.

The large majority (77%) of recurrences have been within 10 years of the first operation, and the rest between 10 and 20 years. Histologically, all were chromophobe adenomas, and the average age of their initial presentation was lower than the peak incidence of pituitary adenoma as a whole. Two patients showed frank malignant change in the second biopsy. In recurrent tumours, most had had only subtotal excision with some macroscopic evidence of invasion or degeneration, such as cystic change, haemorrhage or necrosis. Microscopic evidence of aggressive growth and capsular invasion by tumour cells also was relatively frequent. Postoperative radiotherapy decreased and delayed recurrence, although the vast majority of cases in the series received radiotherapy. Surgery for recurrence appeared an effective method of treatment, and no patient died following repeated operation. Initial transcranial excision in more recent years using the operating microscope followed by uniform radiotherapy, appears to have considerably reduced the already small recurrence rate of pituitary adenoma.

Despite apparently adequate macroscopic excision and radiotherapy, a definite, if small, recurrence rate of pituitary adenomas remains. The five year recurrence of large series following transcranial operation varies from 7 to 35%.<sup>1-10</sup> When transcranial surgery was combined with radiation therapy, the five year recurrence rate was 13% in contrast to 42.5% with surgery alone (Cushing's series). Visual disturbance is the commonest manifestation of recurrence.<sup>8</sup> Postoperative arachnoid cyst,<sup>11</sup> empty sella syndrome and radiation effects<sup>12</sup> may be confused with tumour recurrence. German and Flanigan<sup>13</sup>

observed that adenomas vary in their growth potential and there are reported examples of patients with many years of symptomatic freedom following minimal tumour removal and others who suffered rapid tumour recurrence after "ideal" treatment. The majority of recurrences occur within three to five years after surgery.<sup>1,2,8,10</sup> Stern and Batzdorf<sup>7</sup> reported the least recurrence in radical removal (with or without chemical corrosion of the evacuated sella), and excision of suprasellar tissue. All capsules were removed to the plane of the diaphragma sellae with intracapsular curettage of all grossly visible and palpable tumour. Partial excision showed a higher recurrence rate. McCallum<sup>10</sup> had 12 recurrences in 44 chromophobe adenomas in whom he had performed only intracapsular removal with the capsule in most cases left in place. Guiot<sup>14</sup> has stated that recurrence is due to residual tumour fragments left by the surgeon, although more likely to occur if the tumour has a greater cell density or some abnormalities in cellular morphology. He has

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further suggested that recurrence develops sooner and more seriously in young patients. Pituitary adenomas are known to grow in response to endocrine disturbances such as following adrenalectomy in Cushing's syndrome.<sup>15,16</sup> Recurrent adenomas have been reported to have a very high mortality.<sup>17-19</sup> The present retrospective study was undertaken to assess the factors responsible for recurrence after transcranial surgery, by a long follow up of a series of cases treated in a single centre by two surgeons (VL and LS). We have also reviewed the pattern of recurrence, and the role of re-operation in this group.

**Patients and methods**

The series comprised 289 patients with pituitary tumour treated during the period 1948 to 1979 at the National Hospital, Queen Square, and Maida Vale Hospital, London, by the first two authors. These cases had 304 transcranial operations, 13 cases having 15 operations for recurrence. Histological verification was available in each case. All 13 presented with delayed visual failure after initial operation. Other causes of delayed visual failure following the first operation are shown in table 1. One patient who had a recurrence with an intrasellar blood cyst and seven patients who had some evidence of recurrence on air study or CT scan were excluded from the present study, since histological verification of recurrence was not available.

Table 1 Causes of delayed visual failure following transcranial operation and radiotherapy for pituitary adenoma

Total number of verified pituitary adenoma	289
Number of post operative deaths	10
Number of cases with delayed visual failure	30
Recurrence of adenoma	
Histologically verified	13
On air study or CT scan	7
Recurrence as a blood cyst	1
Empty sella syndrome	3
Radiation effect	3
Hydrocephalus	3

The follow up period extended up to 30 years after initial surgery (table 2). There were ten postoperative deaths in 289 cases (3.4%), almost all of whom had giant or large invasive lesions.<sup>20</sup> Nine cases have been lost to protracted follow up, all from overseas. Complete follow up therefore consists of 270 cases. A complete follow up consisted of collection of information regularly from the time of the first operation regarding general well-being, visual status, endocrine status, re-operation for pituitary tumour if the patients were surviving, or cause of death if deceased. A total of 34 cases were operated between 1948 and 1959 of which 30 had complete follow up for at least 20 years. Between 1960 and 1969, 80 cases were operated of which 70 had complete follow up for at least ten years. During 1970 and 1979, 175 cases were operated, of which 120 had

Table 2 Length of post operative follow up

Years	No of cases	Follow up available		No of recurrences
		Complete	Incomplete (op death)	
1948-59	34	30	4	7
1960-69	80	70	10	6
1970-79	175	170	5	0
Total	289	270	19	(10)

follow up for at least five years. Nine cases had incomplete follow up, mostly due to loss of contact in a foreign country. The large majority of this group had at least five years follow up, during which maximum recurrence is known to occur. Information regarding 47 deaths are available during this follow up study. These include four deaths that had occurred among 13 recurrent adenomas, and the rest due to natural or unrelated causes.

**Results**

Histologically verified recurrence was found in 13 cases of the 270. The symptom of recurrence was invariably delayed visual failure. Half the recurrent cases showed increase in headache and two cases ophthalmoplegia. There were seven females and six males, with a mean age of 37.7 years. Nine of the recurrent cases were aged below 40 years. The mean interval of visual symptoms at recurrence was 7.1 years. Of the recurrences, ten, that is 77%, occurred within the first ten years following initial surgery. A further three (23%) occurred after ten years, the latest being at 15 years.

The thirteen patients who had verified recurrences are shown in table 3. Two patients had a total of six operations, that is, two recurrences each. Three patients had had initial radical removal and 10 patients had partial removal of varying degrees (that is, Class 2-4 of operative procedures described by Stern *et al*<sup>7</sup>). Postoperative radiotherapy after the first operation was not given to six (46%) of the cases which subsequently recurred in contrast to only 27 (10%) of cases which did not receive radiotherapy among the cases as a whole. However, 12 of these 13 cases had postoperative radiotherapy after the second operation. A portion of this series operated upon since 1968, largely with the help of operating microscope and with invariable post-operative radiation, has been reported earlier.<sup>29</sup>

All the cases which recurred were chromophobe adenomas at the original biopsy, but two of them, cases 6 and 11, showed malignant change at the first recurrence. No case showed metastasis, though one case (case 6) showed chromophobe adenoma cells in the CSF. All cases save one showed clinical hypopituitarism, the exception being a case of Nelson's syndrome. Pertinent operative and histological

Table 3 *Verified recurrent pituitary adenomas associated with visual failure*

Serial No	Name	Age yr	Sex	Duration of initial symptoms	No. and interval of operations	Op findings		
						1	2	3
1	RW	50	F	5/12	2, 1948-49	C	S & C	-
2	SG	28	M	12/12	3, 1951-59-67	SH	SInv	SInv
3	IW	53	F	36/12	2, 1957-72	Vas SC	SInv Vas	-
4	EB	30	F	3/12	2, 1957-71	C	S	-
5	FD	35	M	14/12	2, 1959-62	SC	S	-
6	THM	27	M	4/12 Chrm cells in CSF	2, 1958-68	Vas SInv PFC	S Haem	-
7	PHS	19	F	4/12	2, 1958-61	S	S Haem	-
8	LH	46	M	12/12	3, 1964-72-76	S Vas Haem PFC	S Haem Inv	SInv
9	LR	31	F	1/12 (had adrenalectomy for Cushing's Syndrome '52)	2, 1960-69	S	S Haem	-
10	RH	24	M	15/12	2, 1962-66	SC PFC	S Vas Haem	-
11	SH	30	M	1½/12	2, 1962-74	SInv Giant	SInv Giant	-
12	VLI	33	F	3/12	2, 1969-70	SC Vas Haem	C Haem	-
13	DS	59	F	24/12	2, 1963-68	S Vas	S Vas	-

Chrm = Chromophobe adenoma; Cap Inv = Capsular invasion by tumour; CVA = Cerebrovascular accident; CF = Cardiac failure; C = Cystic; FU = Follow up; Inv = Invasive; Radiotherapy "-" = not given; Radiotherapy "+" = given; Haem = Haemorrhage; Malig = Malignant; PFC = Prefixed chiasm; P = Partial; R = Radical; Pleo = Pleomorphic; Vas = Vascular; S = Solid.

findings in 28 operations (including the primary operation) upon 13 recurrent cases is shown in table 4. Macroscopic degenerative changes were noted in 14 cases (50%), increased vascularity in eight (27%) and invasive features in seven (25%). Histological evidence of capsular invasion by tumour cells was seen in six cases (23%), but since capsule was not available in all histological specimens, this incidence is quite inexact. Microscopic haemorrhage was noted in four specimens (14%).

Table 4 *Operative and histological findings*

Total number of verified recurrent adenomas	13
Radiation not given after first operation	6
Total number of operations performed	28
Partial excision	25
Macroscopic degenerative changes (cystic, necrotic haemorrhagic)	14
Invasive	7
Vascular	8
Capsular invasion	6
Pleomorphism	7
Haemorrhage	4
Malignant change	2

Re-operation in this group of 13 cases carried no mortality. The mean survival period after the second operation was 11.5 years. After the second operation, seven of the 13 patients showed significant improvement in vision. All recurrent tumours that were operated on before 1970, were operated without the help of the operating microscope. The ten recurrences of the early portion of the series had what we would now regard as partial excision, and nearly half of them did not receive postoperative radiotherapy.

## Discussion

Pituitary adenomas are usually benign, slow-growing tumours and malignant change is extremely rare.<sup>21</sup> When they extend beyond their capsular limits into adjacent structures by local spread, they are termed malignant<sup>22</sup> or invasive.<sup>5 23</sup> The term carcinoma is generally reserved for those cases having distant metastasis, either blood borne or spread along CSF pathways.<sup>24 25</sup> Of the thirteen recurrent

Extent of excision			Post-op		Histology			Follow-up since first operation
1	2	3	1	2	1	2	3	
P	R	-	-	+	Chrm	Chrm		Lived 29 yr died in sleep
P	P	P	+	+	Chrm	Chrm	Chrm	Lived 24 yr Died CVA
R	P	-	-	+	Chrm	Chrm		Alive 23 yr
R	P	-	-	+	Chrm	Chrm		Lived 13 yr Died CF
P	P	-	+	+	Chrm	Chrm Pleo		Alive 19 yr
P	P	-	+	+	Chrm Nec	Chrm Pleo		Lived 17 yr Lost to F/U
P	P	-	-	+	Chrm Pleo	Chrm Pleo		Lived 18 yr Lost to F/U
P	P	P	+	-	Chrm Chrm Haem	Chrom Haem	Chrm Haem	Lived 17 yr Died Rec
P	P	-	-	+	Chrm	Chrm Haem		Alive 21 yr
P	P	-	-	+	Chrm Cap Inv	Chrm Pleo Cap Inv		Alive 18 yr
P	P	-	+	+	Chrm Pleo Inv	Chrm Cap Inv Malig		Lived 12 yr Dead Rec
P	P	-	+	+	Chrm Haem	Mixed cell		Alive 11 yr
P	P	-	+	+	Chrm Cap Inv	Chrm Cap Inv		Alive 17 yr 3rd rec on CT scan

pituitary adenomas studied by us, none had distant metastases, although in one case, chromophobe adenoma cells were found in CSF. Histologically, only two cases showed malignant change at the second biopsy. However, pleomorphism and capsular invasion by tumour cells were frequently observed.

Most of the recurrences have been reported to occur within five years following treatment<sup>1 2 18 19</sup> and only rarely are they known to occur later. In Cushing's series,<sup>2</sup> the latest known recurrence occurred eight years after surgery and in another report<sup>19</sup> eight of the 24 recurrences occurred after five years (at six, eight, ten, eleven, twelve and thirteen years). In the present series, three cases recurred after ten years, the latest one being 15 years after initial operation. There is no mention of recurrence after 15 years in published literature.

Factors which may contribute to local recurrence are surviving fragments of the tumour left by the surgeon, capsular invasion,<sup>14</sup> aggressive growth potential<sup>13</sup> or morphological changes in the adenoma cells.<sup>14 25</sup> It is possible, however, that large,

giant or invasive adenomas might have aggressive growth spurts as in these tumours necrosis, cystic degeneration and haemorrhage are common features.<sup>25 26</sup> Our observation reveals that the vast majority (89%) of recurrent adenomas had only partial excision. The presence of a pre-fixed chiasm, unusual vascularity or large or giant adenomas with involvement of adjacent vital structures, and the cavernous sinus, were important factors limiting a radical excision, particularly in the pre-microscope era. On the other hand, peculiar biological behaviour of recurrent adenomas were the higher incidence of degenerative changes and aggressive features in what is generally a benign, slow-growing tumour.

Growth stimulation is known to occur in the adeno-hypophyseal cells following adrenalectomy<sup>15 16</sup> implicating a hormonal factor in the growth of adeno-hypophyseal tumour. One of the recent adenomas in our series had Nelson's syndrome, but the others clinically and endocrinologically showed hypopituitarism. Host-tumour relationship and

immunological aspects of pituitary adenomas may reveal further factors in recurrence, but so far definite information on such considerations is lacking.

Martin<sup>5</sup> and Guiot<sup>14</sup> have stated that invasive pituitary adenomas are curable by radiation. Our observation agrees very well with earlier reports of decrease or delay of recurrence following radiotherapy.<sup>10,14</sup> The inhibition of further tumour growth and subsequent elimination of invasive properties may be better accomplished by alpha particles or the proton beam.<sup>21</sup> The location of x-ray ports and dosimetry can be more accurate with CT guidance. CT has been helpful for early detection of recurrence before visual disturbances occur. However, the use of radiation is not without the hazards of radionecrosis and carcinogenesis. There are no documented reports on the therapeutic efficacy of chemotherapy and immunotherapy for recurrent adenomas.<sup>21</sup> Complete clinical and biochemical remission of a growth hormone producing tumour which was locally invasive has been reported with bromocriptine.<sup>28</sup>

It is interesting to note that despite the high post-operative mortality quoted<sup>18,19</sup> for recurrent adenomas, no operative deaths occurred in this group of 13 cases, having in total 28 operations. Over half the cases had fair to excellent visual recovery, a mean survival period of 11.5 years after re-operation, and a good quality of life. Irrespective of the approach, whether transphenoidal or transcranial, total excision of an invasive adenoma may not be feasible. The former approach has been recently popular, yet recurrence has been reported<sup>14,29</sup> in a much shorter follow up. However, transcranial operation using the operating microscope during the last decade has facilitated initial radical excision of the adenoma and, combined with postoperative radiotherapy, appears to have reduced recurrence drastically.<sup>20</sup>

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