

The projected donor rates for New South Wales calculated by two different methods are contained in table VI. The differences in the rates are due to differences in the sizes of the potential donor pool—that is, the realistic medically suitable potential donor rate. If it is assumed that the realistic medically suitable potential donor rate for New South Wales is the same as that in the study hospitals then the actual donor rate would be as high as 18/million population/year. On the other hand, the pool of potential donors implied by the actual donor rate (assuming the same conversion rate as observed in the study hospitals) is smaller than that projected in the first method (51/million population/year *v* 76/million population/year). It is derived from an actual donor rate of 13/million population/year. The same explanation applies to differences in rates for missed potential donors and potential donors with permission refused for the two methods of projection. It is important to note, however, that even if the donor rate is 13/million population/year there is opportunity to increase it by converting missed potential donors to actual donors (an increase of nine donors/million population/year) and by overcoming refusal of permission (an increase of 13 donors/million population/year). If both are overcome the projected rate would be 45/million population/year. Neither calculation of donor rates takes into account the possibility of potential donors created by interventional ventilation—that is, unrealistic potential donors in whom resuscitation would be solely for the purpose of organ retrieval.

It has been calculated that to satisfy the demand for cadaveric renal transplantation in New South Wales in 1990 and to catch up with the backlog over five years the supply rate needs to be increased 117%; the actual donor rate needs to be increased by 15/million population/year.<sup>1</sup> Assuming current community attitudes towards retrieval and our low projection of the potential for cadaveric retrieval, conversion of missed potential donors to actual donors would increase

supply by about 70% (9/13, table VI). If our high projection of the potential for cadaveric retrieval is assumed then the increase would be about 80% (15/18, table VI).

In conclusion, this study has shown that there is significant unused potential for cadaveric organ retrieval in New South Wales. The two major obstacles are reluctance on the part of medical practitioners to resuscitate potential donors and refusal of permission by the next of kin. This study creates hope that by overcoming these two obstacles, cadaveric organ supply can be increased sufficiently to satisfy demand for all types of organ transplantation. It will be important to find out whether the first obstacle can be overcome by educational intervention among health care providers, and for this the second phase of this study is now in progress.

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## Risk of second brain tumour after conservative surgery and radiotherapy for pituitary adenoma

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### Abstract

**Objective**—To assess the risk of second brain tumour in patients with pituitary adenoma treated with conservative surgery and external beam radiotherapy.

**Design**—Long term follow up of a cohort of patients with pituitary adenoma and comparison of tumour occurrence with population incidence rates.

**Setting**—The Royal Marsden Hospital.

**Subjects**—334 patients with pituitary adenoma treated with conservative surgery and radiotherapy (median dose 45 Gy) and followed up for 3760 person years.

**Main outcome measures**—Second intracranial tumour and systemic malignancy.

**Results**—Five patients developed a second brain tumour: two had astrocytoma, two meningioma, and one meningeal sarcoma. The cumulative risk of developing a second brain tumour over the first 10 years after treatment was 1.3% (95% confidence interval 0.4% to 3.9%) and over 20 years 1.9% (0.7% to 5.0%). The relative risk of a second brain tumour compared with the incidence in the normal population

was 9.38 (3.05 to 21.89). There was no excess risk of any other type of second primary malignancy.

**Conclusions**—There is an increased risk of second intracranial tumour in patients with pituitary adenoma treated with surgery and radiotherapy. Although radiation is likely to be the most important factor contributing to the excess risk, further study is required in a cohort of similar patients not receiving radiation.

### Introduction

Pituitary adenomas are successfully treated with a range of treatment modalities, which include surgery, radiotherapy, and medical treatment.<sup>1-7</sup> Radiotherapy is principally employed to reduce the recurrence rate of incompletely excised non-secreting adenomas and in secreting pituitary tumours where hormonal control cannot be achieved with surgery and medical therapy. In these situations radiotherapy combined with limited surgery is successful in controlling pituitary adenoma, resulting in a 90% 10 year progression free survival.<sup>1,3,4</sup> Radiotherapy is relatively safe, with less than 1%

incidence of optic nerve and chiasmal damage, provided that it is delivered accurately and follows well established principles of radiation tolerance.<sup>8,9,10</sup>

Radiation has been implicated in the causation of brain tumours,<sup>11</sup> and many individual cases of a second brain tumour have been reported after treatment of pituitary adenoma and other brain lesions. However, the risk to an individual of developing a second tumour either of the central nervous system or at peripheral sites is not known. We have followed a cohort of patients with pituitary adenoma treated with limited surgery and radiotherapy and report the incidence of second tumours by site and the relative risk compared with tumour incidence in the normal population. This information defines the risk for individual patients and should provide a basis for comparison with other treatment approaches.

### Patients and methods

The cohort under study consisted of 436 patients with pituitary adenoma who received radiotherapy at the Royal Marsden Hospital between 1962 and 1986 after surgery at the Atkinson Morley's Hospital, the National Hospital, and other referring neurosurgical hospitals. The diagnosis of pituitary adenoma was either confirmed histologically or based on clinical and radiological features and endocrine abnormalities. The median dose of radiotherapy was 45 Gy in 25-30 fractions, and treatment was delivered by using a three

TABLE 1—Characteristics of patients with pituitary adenoma. Except where stated otherwise figures are numbers of patients

	Patients with pituitary adenoma
Total in series	334
Median age (years) (range)	49 (15-78)
Primary referral	319
Referral at recurrence	15
Tumour type:	
Hormone secreting	104
Non-secreting	210
Unknown	20
Histological confirmation	260
Radiation dose (Gy):	
<40	7
40-44	104
45-49	146
≥50	77
Radiotherapy apparatus:	
Linear accelerator	331
Cobalt	3
Extent of surgery:	
Complete	8
Incomplete	245
Biopsy/no surgery	68
Not known	13
Medical treatment:	
Bromocriptine	53
No bromocriptine	281
Years of follow up	3760

TABLE 2—Details of five patients with pituitary adenoma who developed second intracranial tumours

Case No	Age at diagnosis of pituitary adenoma (years)	Sex	Years since radiotherapy	Second tumour	Site
1	54	M	6	Astrocytoma (Kernohan grade IV)	Left frontal
2	40	F	7	Astrocytoma (Kernohan grade IV)	Right temporal
3	48	F	7	Meningeal sarcoma	Sella
4	19	F	10	Meningioma	Right sphenoidal
5	58	F	21	Meningioma	Right temporal

TABLE 3—Incidence and relative risk of second intracranial tumours (334 patients; 3760 person years)

Tumour	No of second tumours observed	No of second tumours expected	Relative risk (95% confidence interval)	Two sided p value
Astrocytoma	2	0.25	7.92 (0.96 to 28.61)	0.06
Meningeal tumour	3	0.08	37.33 (7.69 to 109.08)	<0.001
All	5	0.53	9.38 (3.05 to 21.89)	<0.001

TABLE 4—Incidence and relative risk of second intracranial tumours

Years since radiotherapy	No in group	No of person years	No of second tumours observed	No of second tumours expected	Relative risk
0-4	334	1493.35	0	0.18	0
5-9	261	1088.78	3	0.15	20.01
10-19	173	1029.71	1	0.17	5.80
20-29	49	148.54	1	0.03	34.26
Total	334	3760.37	5	0.53	9.38

field technique with an anterior oblique and two lateral fields.

Patients were followed up at the Royal Marsden Hospital or in an endocrine clinic attended by a neuro-oncologist. Patients who had last been seen more than one year before the date of analysis were traced through a postal questionnaire addressed to the general practitioner and referring hospital. In addition, the cohort was flagged for second tumours through the Thames Cancer Registry.

Of the 436 patients, 102 were resident overseas and were excluded from analysis. Their follow up was poor and they contributed only 427 of the total 4187 person years. The absence of second tumours at any site in that group of patients, who constituted almost a quarter of the cohort, also suggested that their data may be incomplete. The characteristics of the remaining 334 patients, who are the subject of this study, are shown in table 1.

*Statistical methods*—The date of entry into the cohort was taken to be the date of start of radiotherapy at the Royal Marsden Hospital. The risk to patients of a second brain tumour after commencement of radiotherapy was estimated by the Kaplan-Meier survival method.<sup>12</sup> The computer program Person-Years<sup>13</sup> was used to compute and compare observed and expected numbers of second malignancies. Expected numbers were calculated from the observed number of person years at risk and population based incidence rates broken down by sex and five year intervals of age and calendar period. Patients were censored on reaching age 85 since tumour incidence rates for the very elderly may be unreliable.<sup>14</sup> Expected numbers of brain tumours, in total and by specific tumour type, were computed by using incidence rates in the South Thames region (available from the Thames Cancer Registry for 1961-88). Expected numbers of other second tumours were computed by using incidence rates for England and Wales (supplied by the Office of Population Censuses and Surveys; data available for 1971-84). In all analyses patients who had had a second tumour of a different type from the one under consideration were censored at the date of that tumour. All calculated p values are two sided and based on the Poisson distribution. The 95% confidence intervals for relative risk (observed to expected ratio) are exact.<sup>15</sup>

### Results

Five of the 334 patients with pituitary adenoma treated with conservative surgery and radiotherapy developed a second intracranial tumour (table II). Two patients had astrocytoma, two a meningioma, and one a meningeal sarcoma. The diagnosis of second brain tumour was confirmed histologically in four patients (cases 1-4). In case 5 meningioma was diagnosed by computed tomography three days before death (fig 1). Postmortem examination was not carried out. As far as could be determined the sites of tumour were within the region of entry of anterior or lateral radiation fields, and one tumour arose from within the pituitary fossa (table II).

The cumulative risk of second brain tumour over the first 10 years after radiotherapy was 1.3% (95%

confidence interval 0.4% to 3.9%) and over 20 years 1.9% (0.7% to 5.0%) (fig 2). The observed risk of five intracranial tumours per 3760 patient years compared to an expected risk of 0.53 ( $p < 0.001$ ). This implied a relative risk to patients of 9.38 (95% confidence interval 3.05 to 21.89) compared with the risk of a brain tumour in the general population (table III). The results were analysed by tumour type (table III). Two

TABLE V—Details of 19 patients with pituitary adenoma who developed second tumours outside cranial cavity

Case No	Age at diagnosis of pituitary adenoma (years)	Sex	Years since radiotherapy	Second tumour
6	35	F	0.2	Malignant melanoma
7	79	M	0.6	Basal cell carcinoma
8	73	M	1	Adenocarcinoma colon
9	52	F	2	Breast cancer
10	62	M	3	Basal cell carcinoma
11	69	F	3	Uterine adenocarcinoma
12*	48	F	4	Cervical cancer
13	55	M	6	Adenocarcinoma pancreas
14*	49	F	7	Pancreatic cancer
15*	74	F	8	Breast cancer
16*	62	F	10	Breast cancer
17	65	M	11	Transitional cell bladder carcinoma
18*	50	F	11	Breast cancer
19	53	M	13	Adenocarcinoma caecum
20*	47	F	13	Breast cancer
21*	70	M	15	Lung cancer
22*	46	M	17	Pancreatic cancer
23*	53	M	21	Lung cancer
24	47	M	23	Lung cancer

\*Identified at death.

TABLE VI—Incidence and relative risk of other second malignancies

Second malignancy (ICD 9 codes)	No observed	No expected	Relative risk
Lip, oral cavity, and pharynx (140-149)	0	0.41	0
Stomach (151)	0	1.49	0
Colon and rectum (153-154)	2	2.84	0.70
Other digestive organs (150,155-159)	3	1.51	1.98
Respiratory and intrathoracic organs (160-165)*	2	5.69	0.35
Female breast (174)	5	2.41	2.08
Female genitourinary organs (179-184)	2	1.50	1.33
Male genitourinary organs (185-187)	0	1.28	0
Lymphatic and haematopoietic tissue (200-208)	0	1.26	0
Other and unspecified sites (170-173, 175, 180-190, 193-199)	4	5.78	0.69
Total	18	24.17	0.74

\*A second lung cancer was diagnosed at death in a patient aged 85 (case 21; table V). All relative risks  $p > 0.05$ .

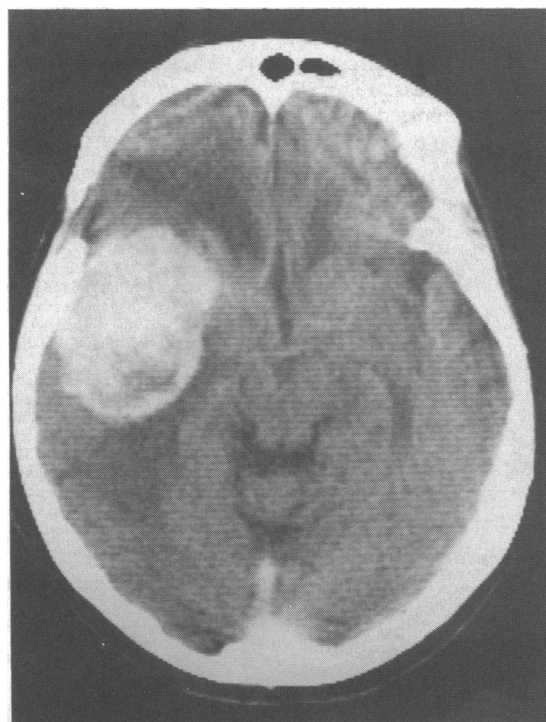


FIG 1—Contrast enhanced computed tomogram in case 5 showing uniformly enhancing right temporal tumour

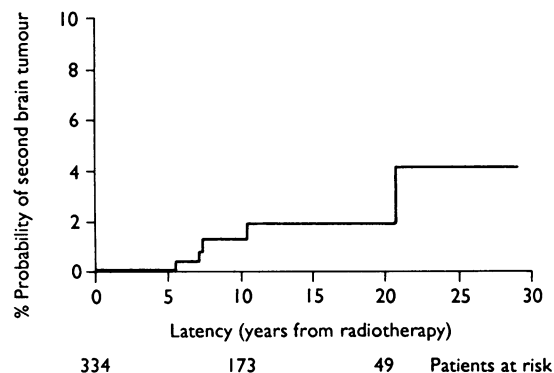


FIG 2—Cumulative actuarial risk of second brain tumour in cohort of 334 patients with pituitary adenoma

astrocytomas were observed compared with 0.25 expected ( $p = 0.031$ ). Compared with the risk of an astrocytoma in the general population the relative risk to patients was therefore 7.92 (95% confidence interval 0.96 to 28.61). Three meningeal tumours were observed compared with 0.08 expected ( $p < 0.001$ ). Compared with the risk of a tumour of the meninges in the general population the relative risk to patients was 37.33 (7.69 to 109.08).

There was insufficient information to provide evidence of either an increasing or a decreasing trend in risk by time since radiotherapy (table IV). However, both astrocytomas occurred relatively soon after treatment (six and seven years respectively) whereas meningeal tumours occurred later. None of the five patients had received bromocriptine.

Nineteen patients developed other second tumours at peripheral sites; nine of these were identified at time of death. The details are shown in table V. No evidence of excess risk of second malignancy at non-cranial sites was seen in these patients (table VI). However, it is worth noting that three patients developed pancreatic cancer compared with 0.67 expected ( $p = 0.06$ ). When considering mortality from other second tumours no cause specific or overall excess risk was observed. Eleven cancer deaths were observed compared with 15.84 expected ( $p = 0.27$ ).

## Discussion

We have found a substantially increased risk of second brain tumours in patients with pituitary adenoma treated with limited surgery and radiotherapy. Many cases of second tumours after treatment of pituitary adenoma, acute lymphatic leukaemia, and other, unrelated brain tumours have been reported, but the number of patients at risk during follow up is not known. The data presented define the overall and relative risks, although small numbers of events have resulted in lack of precision with wide confidence intervals. As a guideline we observed an absolute excess of 4.47 second brain tumours over 3760 patient years, which translates to an excess of 2.4 brain tumours in a group of 100 patients treated in this manner and followed up for 20 years.

As the population under study consisted of patients under close surveillance there was a possibility of bias. We recognise that meningiomas are underreported in the general population since a proportion of tumours are asymptomatic and found only at postmortem examination. It could therefore be argued that the detection of meningiomas in this study was due to close observation. There was, however, no policy of routine scanning, and only symptomatic tumours were recorded. The risk of other malignancies, which was comparable to that expected at national rates, also argues against a serious bias. The high relative risk of second tumours cannot therefore be explained by

overreporting of cases. Because of the small number of events it is not possible to draw reliable conclusions concerning the effects of possible predisposing factors such as sex, age at the time of treatment, or the secretory status of the tumour.

It is generally assumed that second tumours in the brain are radiation induced. This is based on the recognised increased risk of tumours after low dose irradiation for tinea capitis<sup>11</sup> and on data from animal experiments.<sup>14</sup> In addition, there are a number of individual reported cases of second tumour. Gliomas have been reported in leukaemia survivors,<sup>16,17</sup> and this has been postulated to be due to prophylactic cranial irradiation,<sup>18,19</sup> although there is a possible association between central nervous system tumours and haematopoietic malignancy.<sup>20</sup> In addition to glial tumours, meningiomas and sarcomas have been described after irradiation,<sup>11,21</sup> which may be considered akin to sarcomas developing at other sites after therapeutic radiation.<sup>22,23</sup>

Information concerning family history was not routinely collected for this cohort. It is believed, however, from the information contained in the hospital records of the five patients who developed a second brain tumour that none of the five had a family history of cancer or a genetic syndrome which might increase susceptibility to brain tumours. A familial risk of gliomas is known to exist (D F Easton, personal communication) but there is no evidence of any link with pituitary adenoma. However, the possibility of an association such as a genetic or environmental predisposition between pituitary tumours and second brain tumours which is independent of irradiation cannot be excluded. In order to estimate the risk of a second tumour which can be ascribed to radiation the results should be compared with those in a group of control patients with pituitary tumours treated without radiotherapy. As yet such a series of control patients with long term follow up is not available.

Although it is not possible to define the time course of development of second brain tumours from this study, there is a suggestion that astrocytomas occur earlier and meningiomas later. To examine this in more detail we reviewed all available world literature on cases of second intracranial tumour after treatment of pituitary adenoma and craniopharyngioma. Overall 57 cases of second brain tumour, including five patients from this series, had been reported in 45 publications. There were 12 meningiomas, 24 soft tissue sarcomas, three osteogenic sarcomas, and 18 gliomas. Figure 3 shows the cumulative frequency of reported cases of

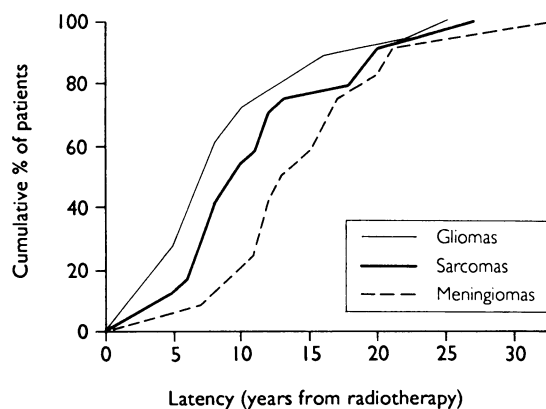


FIG 3—Summary of 54 cases of second brain tumour after treatment of pituitary adenoma and craniopharyngioma from review of case reports published in world literature (18 gliomas, 12 meningiomas, 24 sarcomas, including patients in this study). Cumulative percentage of cases plotted against time since radiotherapy

second brain tumours. The median time to detection of glioma was 7.0 years (range 1-22), sarcoma 9.7 years (range 5-27), and meningioma 13.8 years (range 7-33).

We conclude that there is an increased risk of second brain tumour in patients with pituitary adenoma treated with surgery and radiotherapy. Second tumours are not conclusively due to radiation, although this is likely to be the most important contributing factor. The data presented should provide a guideline to the risks of therapy in patients with pituitary adenoma, but at present they should not be used as a reason to withhold radiotherapy, which remains an effective treatment modality, particularly in patients with residual or recurrent tumour. For a full comparison of different therapeutic approaches it is necessary to know the risks of all the adverse events after surgery alone, and this would include incidence of second tumours.<sup>24</sup>

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