DOI: 10.5137/1019-5149.JTN.11759-14.1
Received: 13.08.2014 / Accepted: 31.10.2014
Published Online: 16.02.2016

Original Investigation

Treatment Results for Pineal Region Tumors: Role of Stereotactic Biopsy Plus Adjuvant Therapy vs. Open Resection

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ABSTRACT

AIM: Pineal tumors represent uncommon intracranial tumors with highly diverse histologic subtypes. There still exists a controversy in literature about what influences overall survival and outcome.

MATERIAL and METHODS: We present the results of 48 patients with pineal tumor treated either by stereotactic biopsy followed by adjuvant therapy (23 patients) or open surgical resection without (18 patients) or with (7 patients) adjuvant therapy in Shohada Tajrish Hospital, Iran (1993-2008).

RESULTS: Unremarkable pathology yield was 3/23 in the biopsy and 1/25 in the surgical group. Perioperative mortality and morbidity were 4.3% and 0% in the biopsy group and 32.0% and 4.0% in the surgical group. Analysis showed that age, gender, cranial nerve deficit, motor deficit, preoperative Karnofsky Performance Score (KPS), midbrain involvement, and brain stem involvement had no effect on neither perioperative mortality nor long-term survival, while local invasion and pineocytoma pathology increased perioperative mortality and presence of hydrocephalus and pineoblastoma pathology significantly decreased long-term survival. Hospitalization length was shorter in the stereotactic biopsy plus adjuvant therapy group.

CONCLUSION: The results of the study suggests that although gross total resection is the standard of care in most pineal tumors nowadays, stereotactic biopsy followed by adjuvant therapy may still be a safe and viable option.

KEYWORDS: Pineal tumor, Stereotactic, Biopsy, Resection, Adjuvant therapy

INTRODUCTION

Pineal region tumors represent 0.4-1.0% of intracranial tumors and can harbor highly diverse histologic tumor subtypes, including germ cell, pineal parenchymal, and glial tumors (21).

The tumor manifestations are the consequence of their pressure effects and consist of visual disturbances, headache, mental deterioration, Parinaud's syndrome, non-communicating hydrocephalus, and sometimes dementia-like behavior.

Because optimal therapeutic strategies vary with tumor type, a histologic diagnosis by either stereotactic or endoscopic biopsy or open surgery is the foundation of management decisions. Stereotactic biopsy has the advantage of ease and minimal invasiveness but is associated with more sampling errors than open surgery (19), while open resection facilitates maximal removal of tumor volume with more diagnostic accuracy. However, all surgical procedures in the pineal region, including both stereotactic biopsy and open surgery, are potentially hazardous (3,11).

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There still exists a controversy in the literature about what really influences overall survival and outcome in pineal tumors. Some have shown that only younger age and localized disease (27), tumor diameter less than 25 mm (10), and low-grade histology (5,10,12) were associated with better prognoses and that surgery and adjuvant radiotherapy may not influence overall survival (27), while others have focused on the role of gross total resection, refusing a long-term role for adjuvant therapy (9), both in benign pineocytomas (2,6-8,13) and pineoblastomas (28). Some other studies, nonetheless, have shown a beneficial role for adjuvant therapy, either alone (4) or after gross total surgical resection (15,17,22).

Here, we present the results of our patients with a diagnosis of pineal region tumor treated either by stereotactic biopsy followed by adjuvant therapy or open surgical resection without or with adjuvant therapy in Shohada Tajrish Hospital, Tehran, Iran from 1993 till 2008.

MATERIAL and METHODS

Patients who were diagnosed with a pineal region tumor and admitted to the Neurosurgery and Stereotactic Surgery wards of Shohada Tajrish Hospital (Tehran, Iran) in the 1993 to 2008 period were reviewed. We retrospectively recorded the patients' admission data including age, operation date, hospital stay length, initial signs and symptoms (including headache, decreased consciousness, cranial nerve paresis, limb paresis), Karnofsky Performance Score (KPS), neuroimaging data (presence of hydrocephalus, tumor location, and local invasion in either Computed Tomography (CT) scan or Magnetic Resonance Imaging (MRI)) in a computerized database. Patients were grouped in 3 different categories based on the treatment they had received: 1) stereotactic biopsy followed by adjuvant therapy (radiotherapy and/or chemotherapy); 2) open surgical resection alone; 3) open surgical resection followed by adjuvant therapy. Patients who received other treatment paradigms or who did not give their consent to either therapy were excluded from the study. The tumor pathology was also recorded in the database. Patients with non-neoplastic pathologies (cysts, tuberculoma, etc) were excluded from the study. All stereotactic biopsies were performed using the modified Riechert Mundinger frame (Freiburg, Germany). Surgical resections were performed under the neurosurgical microscope view. On follow-up, which was performed during 2013, the patients' current KPS, neurologic deficit (ND), and new brain MRI data (tumor control status) were evaluated and saved in the database.

The study design was approved by the Ethical Committee of Shahid Beheshti University of Medical Sciences and the study was performed with adherence to the statements of the Declaration of Helsinki and regulations of IRB (Institutional Review Board).

Chi-square analysis was used for comparison of categorical variables, and independent sample t-test and one-way ANOVA for quantitative variables (14,24). Logistic regression was used to analyse the effects of variables on bimodal outcome variables (16,26,30,31). All analysis was performed with PASW Statistics 18 package (Predictive Analytics Software, SPSS inc, USA). For all analyses, p values less than 0.05 were considered statistically significant.

RESULTS

48 patients (28 males, 20 females, M/F ratio = 1.4) who were admitted to the Shohada Tajrish Hospital with the diagnosis of pineal region tumor and fulfilled the inclusion and exclusion criteria were enrolled in the study. The diagnoses were made by either brain CT or MRI. The mean age of patients was 24.6 years (range: 0-60). The mean hospitalization length was 16 days (standard deviation (SD) = 8.1, range: 6-31). The most frequent symptoms were cranial nerve paresis, motor paresis, and cognitive disturbance (63.2%, 26.3%, and 17.5%, respectively). On imaging, 91.2% had hydrocephalus. In addition to the pineal region, 36.8% had invaded the third ventricle, 22.8% the midbrain, and 10.5% the brain stem. 42 patients had been managed first by ventriculo-peritoneal shunt insertion (87.5%), either before referral to or after admission to our center. 23 patients were managed by stereotactic biopsy, followed by adjuvant therapy after discharge (group 1), which consisted of radiotherapy in all 23, and chemotherapy in 2 patients (both diagnosed as germinoma). 18 patients were treated by open surgical resection alone (group 2), which was gross total in 12, subtotal in 4, and partial in 2. 7 patients had open surgical resection followed by adjuvant therapy (group 3). In these, surgical resection was total in 2, subtotal in 4, and partial in 1. All 7 received radiation therapy after discharge and 2 patients with diagnosis of non-germinomatous Germ Cell Tumors (NGGCT) received chemotherapy. For more convenience, we would refer to group 1 as 'biopsy' group, and groups 2 and 3 as 'surgical' group. Operations were performed by 7 neurosurgeons.

The most common pathologies are presented in Table I. The distribution of pathologies was not different between the biopsy and surgical groups (p = 0.76). Unremarkable pathology yield was 3/23 (13.0%) in the biopsy and 1/25 (4.0%) in the surgical group. Preoperative KPS, cranial nerve deficit, and motor deficit were not different between biopsy and surgical groups (p = 0.99, 0.29, and 0.27, respectively). Moreover, tumors equally involved brain stem, midbrain, and third ventricle in the 2 groups (p = 0.77, 0.54, 0.74, respectively).

Only 1 patient experienced perioperative morbidity that also resulted in mortality in the biopsy group (1/23, 4.3%). In this patient, who was finally diagnosed as grade 3 pineocytoma, a post-operative intraventricular hemorrhage (IVH) occurred which caused rapid crescendo loss of consciousness and did not respond to medical and surgical attempts. No other patient experienced a morbidity or mortality. Mortality and morbidity rates were 8/25 (32.0%) and 1/25 (4.0%) in the surgical group (p = 0.024 and 0.99, respectively). the causes for death in these 8 patients included hematoma (3, either in tumor bed or IVH), meningitis (1), intra-operative vascular damage (1), brain vital parenchyma insult (1), post-operative edema (1), and pneumonia (1). The pathology in these 8 included pineoblastoma (3), pineocytoma (2), NGGCT (1), teratoma (1), and high-grade glioma (1). One patient

Table I: Pathologies of Pineal Region Tumors Observed in Our Patients

Pathology	Number
Low grade astrocytoma	11
Germinoma	8
Low grade pineocytoma	8
Non-germinoma germ cell tumor	6
Pineoblastoma	5
Ependymoma	2
Unremarkable	4
Others	4

experienced an ICH, which due to prolonged hospital stay led to deep vein thrombosis (DVT) and consequently pulmonary emboli. However, the patient survived these events and was discharged from hospital. In the 39 patients who survived the perioperative period, 23 were lost from long-term follow-up, and 16 were followed thoroughly (5 in group 1, 5 in group 2, and 6 in group 3). Among the latter 16 patients, 7 were deceased before the last follow-up, all because of their tumor and its related morbidities (mean survival = 34.4 months, range: 10-60). 9 were alive in the last follow-up in year 2013 (3 (60%) in group 1, 5 (100%) in group 2, and 1 (17%) in group 3; mean survival = 118.0 months, range: 49-190). Binary logistic regression analysis showed that age, gender, cranial nerve deficit, motor deficit, and preoperative KPS had no effect on neither perioperative mortality ($p = 0.27$, 0.68, 0.19, 0.74, 0.63, respectively) nor long-term survival ($p = 0.51$, 0.91, 0.36, 0.28, 0.33, respectively), while local invasion and pineocytoma pathology increased perioperative mortality ($p = 0.04$ and 0.06, respectively) and presence of hydrocephalus and pineoblastoma pathology significantly decreased long-term survival ($p = 0.04$ and 0.04, respectively).

Post-operative mean KPS (83, 90, and 80, for groups 1, 2, and 3, respectively), neurologic status, long-term survival (56.3, 49.8, and 54.7 months, considering 0 for those deceased in the peri-operative period), and tumor control status in the last MRI were not different among the 3 treatment groups ($p = 0.66$, 0.57, 0.97, and 0.49, respectively), while hospitalization length was statistically different among the 3 groups (11.5, 19.4, and 23.5 days, respectively; $p = 0.007$).

■ DISCUSSION

The pineal is a small endocrine gland in the brain, which produces the serotonin derivative, melatonin, a hormone that affects the modulation of wake/sleep patterns and seasonal functions (1,23). The pineal gland is reddish-gray and about the size of a grain of rice (5–8 mm) in humans. It is located just rostro-dorsal to the superior colliculus and behind and beneath the stria medullaris, between the laterally positioned thalami. It is part of the epithalamus. Histologically, the pineal body consists of a lobular parenchyma of pinealocytes surrounded by connective tissue spaces. Four other cell types have also been identified in the gland, which consist of interstitial cells, perivascular phagocytes, pineal neurons, and peptidergic cells (20).

The pineal region tumors represent 0.4-1.0% of intracranial tumors. The pineal region can harbor highly diverse histologic tumor subtypes. There are four main groups of tumors: 1) the germ cell tumors (GCTs), among which the most common form is germinoma (50-70%), which arise from embryonic germ cells. Other lines of germ cell differentiation include embryonal carcinomas, choriocarcinomas, teratomas, and mixed tumors (non-germinomatous germ cell tumors), 2) the pineal parenchymal tumors, which consist of pinealomas or pineocytomas. Another group is pineoblastomas which indeed are a subgroup of primitive neuroectodermal tumors (PNETs) and are highly aggressive, 3) the glial tumors, both low grade and high grade histologies, 4) and miscellaneous (21).

As evident, different types of lesions may occur in the pineal region necessitating to obtain a pathological tissue. Because optimal therapeutic strategies vary with tumor type, an accurate diagnosis is the mainstay of management decisions and tissue diagnosis is essential to predict which treatment approach is suitable in these heterogeneous pathologies. Stereotactic, endoscopic, or open biopsy is essential for securing tissue for pathologic examination. In our series, all patients had undergone diagnosis by either stereotactic biopsy or open surgery. Stereotactic biopsy has the advantage of ease and minimal invasiveness but is associated with more sampling errors than open surgery (19). Moreover, stereotactic biopsy had been considered unsafe in the pineal region because of proximity to critical vascular structures for many years. However, modern neuroimaging methods and new stereotactic techniques have been significantly improved for obtaining diagnostic tissue in this region. A review of all major series reporting stereotactic biopsy for pineal region lesions reveals a mean diagnostic yield of 94%, with a morbidity of 1.3% and a mortality of 8.1% (29). This was also shown in our series as the risk of morbidity and mortality was low in stereotactic biopsy series (0% for morbidity and 4.3% for mortality). In patients who had undergone open resection, these rates were 4% and 32%, respectively. Our analysis showed that peri-operative mortality was significantly higher in patients who underwent open resection. The most common pathologies in patients who did not survive the peri-operative period were pineoblastoma and pineocytoma. The only patient who died after stereotactic biopsy was also diagnosed as high-grade pineocytoma. These 2 tumor pathologies show increased vascularity, which makes both procedures hazardous due to the increased risk of post-operative hemorrhage. In contrast, open resection facilitates the maximal removal of tumor volume and has higher diagnostic accuracy and improved prognosis in modern series. This was shown in our series, as there was a 4% rate of pathologic diagnosis inaccuracy in this treatment group, compared to 13% for those treated by biopsy. Previously, surgery for pineal region tumors had met with poor results (which also holds for a substantial percentage of our patients, who were operated in an era with inferior surgical

utilities and techniques). However, developments in imaging, surgical approaches, and microsurgery have improved outcomes and current operative techniques allow safe, effective removal of pineal region tumors. Advances in technology, surgical technique, and post-operative care have minimized surgical complications; however, all surgical procedures in the pineal region, including both stereotactic biopsy and open surgery, are potentially hazardous (3).

As pineal region tumors are uncommon, deep-seated, heterogeneous group of mass lesions of the brain, the management strategy of any types of these tumors remains controversial and there still exists a controversy in literature about what really influences overall survival and outcome in pineal tumors. Some have shown that only younger age and localized disease (27), smaller tumor sizes (diameter less than 25 mm) (10), and low-grade histology (5,10) were associated with better prognoses and surgery and adjuvant radiotherapy may not influence overall survival (27).

In contrast, some others have focused on the role of surgery, refusing a long-term role for adjuvant therapy. In a group of studies in papillary pineal tumors, only gross total resection and younger age were associated with a longer overall survival, radiotherapy and chemotherapy having no significant impact, which emphasizes the importance of gross total resection and not adjuvant radiotherapy or chemotherapy in the treatment of these tumors (9). Moreover, in patients with benign pineocytomas, it was shown that gross total resection was associated with significantly increased tumor control and survival compared with subtotal resection combined with radiotherapy. When gross total resection was not possible, adding radiotherapy to subtotal resection was not associated with increases in either tumor control or survival (6-8). The benefits of gross total resection (GTR) are also shown in pineoblastomas (28).

Some other studies, nonetheless, have shown a beneficial role for adjuvant therapy. Craniospinal irradiation with tumor boost and chemotherapy were shown to be of significant influence on long-term survival in patients with malignant NGGCTs (4). Other studies showed that both gross total surgical resection and craniospinal irradiation plus multi-agent chemotherapy appeared to correlate with improved survival (17,22).

As a general recommendation, benign pineal tumors should be cured with surgery alone. Malignant tumors should be treated with aggressive resection followed with irradiation and chemotherapy (18, 25). Pure germinomas represent a considerable percentage of the tumors in the pineal region. They are exquisitely radiosensitive and are not treated by surgical debulking. They can be cured by conventional radiation therapy and chemotherapy alone if histological diagnosis can be obtained with stereotactic biopsy (21). If α-fetoprotein (AFP) and/or beta-human chorionic gonadotropin (HCG) are positive, a highly malignant NGGCT must be suspected. An initial course of chemotherapy without biopsy is recommended to avoid tumor seeding. After the "markers" are normalized, operative removal of the residual tumor and radiotherapy should be carried out (21,22).

In the current study, 3 treatment paradigms were exerted for the patients. First, patients would undergo either stereotactic biopsy or open surgical resection. Stereotactic biopsy was always followed by radiation therapy, and sometimes by chemotherapy (group 1). Those who had undergone open resection and had survived the surgery would not (group 2) or would (group 3) receive adjuvant therapy, based on tumor pathology and tumor state. The most frequent pathologies in our series were glioma, GCT (both germinoma and NGGCT), pineocytoma and pineoblastoma. In accordance with most series, open resection had a higher diagnostic yield than stereotactic biopsy (96% vs. 87%). However, it was associated with a significant higher perioperative mortality (32% vs 4.3%). Moreover, stereotactic biopsy was associated with a significant lower hospital stay length (11.5 days vs 19.5 and 23.5 days). In the percentage of patients who could be followed for a long period (mean = 12 years, range: 5-20), it was shown that there was no significant difference between the treatment paradigms in terms of survival, KPS, ND, or tumor control. Local invasion caused a higher peri-operative mortality, while presence of hydrocephalus was associated with a higher long-term mortality (perhaps because of increased tumor sizes).

Our interpretation may suffer from some limitations of our study. The first limitation is the relatively low sample size of the study. As stated before, pineal region tumors are not prevalent; therefore, providing a large sample size may be difficult for any study regarding these tumors. Moreover, we suffered from a substantial patient lost in follow-up, which is common in referral facilities that lose their connection with the initial referring system. Second, our design was retrospective and non-randomized. Prospective designs may suffer from the low patient number, and real randomization is extremely difficult, if not impossible, in such patients. However, we could show that patients' neurologic and functional status, tumor pathology and location (involvement of structures other than pineal region) were not significantly different between the comparison groups. Third, a substantial percentage of our patients were operated in an era with inferior imaging techniques, and inferior surgical utilities and techniques. This may be responsible for the higher peri-operative mortality of our surgical group and the lack of superiority of more aggressive approaches over more conservative ones. This may not hold true for the current era with more modern and delicate surgical techniques.

■ CONCLUSION

Considering all these, the results of the current study suggest that although gross total resection is the standard of care in most pineal region tumors nowadays, stereotactic biopsy followed by adjuvant therapy (radiation therapy with or without chemotherapy) may still be a safe and viable option. Its long-term effects on survival and Karnofsky represents those obtained by GTR, if not superior.

■ ACKNOWLEDGMENT

The authors would like to thank Drs. K. Parsa, S.M. Tabatabaie, F. Borzouyeh, M. Shirvani, M. Mohseni, A.R. Zali.

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