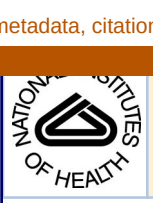

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Invasive adenoma and pituitary carcinoma: a SEER database analysis

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Abstract

Invasive pituitary adenomas and pituitary carcinomas are clinically indistinguishable until identification of metastases. Optimal management and survival outcomes for both are not clearly defined. The purpose of this study is to use the Surveillance, Epidemiology, and End Results (SEER) database to report patterns of care and compare survival outcomes in a large series of patients with invasive adenomas or pituitary carcinomas. One hundred seventeen patients diagnosed between 1973 and 2008 with pituitary adenomas/adenocarcinomas were included. Eighty-three invasive adenomas and seven pituitary carcinomas were analyzed for survival outcomes. Analyzed prognostic factors included age, sex, race, histology, tumor extent, and treatment. A significant decrease in survival was observed among carcinomas compared to invasive adenomas at 1, 2, and 5 years (p=0.047, 0.001, and 0.009). Only non-white race, male gender, and age ≥65 were significant negative prognostic factors for invasive adenomas (p=0.013, 0.033, and <0.001, respectively). There was no survival advantage to radiation therapy in treating adenomas at 5, 10, 20, or 30 years (p=0.778, 0.960, 0.236, and 0.971). In conclusion, pituitary carcinoma patients exhibit worse overall survival than invasive adenoma patients. This highlights the need for improved diagnostic methods for the sellar phase to allow for potentially more aggressive treatment approaches.

Keywords

Pituitary tumor; Pituitary carcinoma; Invasive adenoma; Treatment; Survival

Introduction

Invasive adenomas are benign pituitary tumors that infiltrate the dura mater, cranial bone, or sphenoid sinus. Gross invasion at time of operation is observed in up to 35 % of pituitary adenomas [1-3]. Although not malignant, invasive adenomas exhibit aggressive biological behavior. In contrast, pituitary carcinomas are defined as tumors of the pituitary gland exhibiting cerebrospinal and/or systemic metastasis. They are rare and account for only 0.1 to 0.2 % of pituitary tumors [4].

Differentiating locally aggressive adenomas from carcinomas in their sellar phase can be difficult because it is unusual for a patient to have metastases at the time of initial presentation. Attempts have been made to define morphologic features and molecular markers more commonly associated with invasive adenoma or pituitary carcinoma to help

predict tumor behavior and discriminate between the two prior to identification of metastatic disease. These include quantification of the degree of cytologic atypia and mitotic activity, examination of proliferation markers such as Ki-67 using the MIB-1 antibody and cell-cycle molecules such as p27 and galectin-3, and gene expression of p53, MGMT, and MMP-9 [5-9]. Several patterns have been identified. For example, Thapar et al. noted increased MIB-1 indices in carcinomas (12 %) compared to invasive adenomas (4.5 %) and noninvasive adenomas (1 %) [10]. In a separate study, overexpression of the p53 oncoprotein was found to occur in 100 % of carcinomas but only 15 % of invasive adenomas and 0 % of noninvasive adenomas examined [11]. Despite such findings, there are currently no consistent patterns in immunohistochemistry, cell histology, or radiological appearance that differentiate invasive adenoma from pituitary carcinoma [12]. The difficulty distinguishing between the tumors is highlighted by the introduction of an intermediate category of “atypical adenoma” between adenoma and carcinoma by the World Health Organization. The atypical classification is used for those adenomas exhibiting a MIB-1 proliferative index greater than 3 %, significant p53 immunoreactivity, and increased mitotic activity [13]. Recently, genetic analysis of pituitary carcinomas has shown an average of 9.3 chromosomal imbalances per tumor (7 gains vs. 1.3 losses) with the most common changes being gains of chromosomes 5, 7p, and 14q [4]. While such analysis of invasive adenomas may in the future enable better identification of those tumors likely to undergo malignant transformation and eventual metastatic dissemination, it is not routinely available in clinical practice [14].

Current treatment approaches for both invasive adenoma and pituitary carcinoma include surgical debulking, definitive or adjuvant radiation therapy, or medical management. Optimal management of these tumors is not clearly defined. Similarly, survival outcomes specifically in patients with invasive adenoma and pituitary carcinoma are relatively unknown and generally based on case reports or small single institution series [4, 9, 15-19].

The purpose of this study is to use the Surveillance, Epidemiology, and End Results (SEER) database to report patterns of care and to compare survival outcomes according to patient characteristics, tumor characteristics, and treatment received in a large series of patients with invasive adenoma or pituitary carcinoma.

Methods

Study participants

The National Cancer Institute’s SEER database November 2010 submission [20] was used. Three hundred twenty-two patients with primary site pituitary tumors (ICD-0-3 Code C75.1) classified as exhibiting malignant behavior and diagnosed between January 1, 1973, and December 31, 2008, were identified. As there is no code for invasive adenomas specifically, only those exhibiting malignant behavior were included in the analysis as this is synonymous with invasion for SEER database coding. All tumors were further stratified based on pathologic extent of disease when available; otherwise, extent of disease was based on radiologic findings. Only malignant tumors with documented metastases were classified as pituitary carcinomas; all others were classified as invasive adenomas. For frequency analysis of patient demographics, tumor characteristics, and treatment received, patients

with histology other than adenoma or adenocarcinoma (M8140–M8389) were excluded, resulting in a study population of 117 (110 invasive adenomas, 7 pituitary carcinomas). From this subset of patients, the survival analysis included only actively followed patients with microscopically confirmed adenomas (*n*=90) or adenocarcinomas (*n*=7) with further exclusion of seven patients with a diagnosis of invasive pituitary adenoma obtained through death certificate or autopsy, those alive with no survival time, and those with multiple primaries. No patient in the carcinoma group required exclusion for these reasons. Therefore, 83 invasive adenomas and 7 pituitary carcinomas were included in the overall survival analysis.

Outcome measures

Overall survival was defined as the time from diagnosis until death or the time of last follow-up. Those cases lost to follow-up were censored by SEER. Non-survival included death from all causes. Prognostic factors included age (<65, ≥65), sex (male, female), race (white, non-white), histology according to ICD-0-3 codes (adenoma/adenocarcinoma NOS, neuroendocrine adenoma/carcinoma, chromophobe adenoma/carcinoma, pituitary adenoma/carcinoma NOS, acidophil adenoma/carcinoma), tumor extent (confined to gland of origin, localized, spread to adjacent connective tissue or organ, distant metastases), and treatment (surgery with and without radiation therapy, any radiation therapy, no radiation).

Surgical technique

Multiple codes are available in the SEER database for classifying the surgical approach used. For the purpose of analysis, these techniques were classified into three main groups based on the extent of resection. Those classified as incisional, needle, or aspiration biopsy include only those tumors for which surgical resection was done for pathologic diagnosis only. The gross tumor resection (GTR) group includes only those tumors that underwent complete surgical removal. The simple tumor resection (STR) category includes those tumors that underwent incomplete resection, classified in SEER as simple or partial removal, debulking, or excisional biopsy or removal.

Statistical analysis

In the absence of raw data from SEER, we compared the time-specific actuarial rates of observed survival using Fisher's exact test. Observed survival rates were obtained using SEER*Stat version 7.0.4 [21]. Statistical significance was done using Stata Statistical Software: Release 9 [22]. Statistical significance was defined as a *p* value less than 0.05.

Results

Invasive adenoma

Patient, tumor, and treatment characteristics—Patient characteristics, tumor characteristics, and treatment received for the 117 patients in our series are summarized in Tables 1, 2, and 3, respectively. There was a slight female predominance (ratio 1.12) in invasive adenoma patients. The median age at diagnosis was 52.5 (range 1–85+). Seventy-eight percent of patients with invasive adenoma were white.

Sixty-nine (76 %) invasive adenomas underwent surgical resection after 1983, with some patients having multiple resections. Thirty-four (41 %) invasive adenomas were treated with STR alone, 20 (24 %) received STR plus radiation, 2 (2 %) received radiation therapy alone, 8 (10 %) had neither STR nor radiation therapy, and 19 (23 %) were treated with a combination other than those listed above.

Thirty percent of patients with invasive adenoma received external beam radiation therapy (EBRT).

Survival outcomes—Overall survival rates for invasive adenoma were 89.1, 87.7, 79.0, and 65.5 % at 1, 2, 5, and 10 years, respectively (Fig. 1a). A statistically significant difference in survival between invasive adenoma and carcinoma was observed at 1, 2, and 5 years (p=0.047, 0.001, and 0.009, respectively). No statistically significant difference in survival was observed at 10 years (p=0.099). Similarly, the extent of disease (confined to gland, localized, invading adjacent connective tissue or organ, distant metastases) significantly impacted survival at 1, 2, and 5 years (p=0.034, 0.001, 0.025, respectively).

Younger age (<65) at diagnosis of invasive adenoma conferred a statistically significant survival advantage at 10, 15, 20, and 30 years with survival rates of 74.8, 60.0, 56.0, and 46.8 % compared to those aged ≥65 who had survival rates of 17.2, 0, 0, and 0 % (p<0.001, 0.001, 0.001, and =0.001, respectively) (Fig. 1b). Women had significantly better overall survival than men (79.1 vs. 54.1 % at 12 months, p=0.033, and 51.9 vs. 29.2 % at 36 months, p=0.047). White race conferred a survival advantage over nonwhite patients (93.8 vs. 68.8 % at 12 months, p=0.013, and 92.0 vs. 68.8 % at 24 months, p= 0.022). Observed survival at 5 years did not significantly differ among the various histologic subtypes (Table 4).

There was no difference in survival between patients treated with radiation therapy and those who were not (83.5, 81.4, 55.9, and 55.9 % vs. 79.1, 70.6, 46.8, and 46.8 % at 5, 10, 20, and 30 years, NS). Likewise, patients treated with radiation therapy in addition to STR did not demonstrate improved survival over those treated with STR alone at 5, 10, 20, or 30 years (82.1, 65.7, 47.9, and 38.3 % vs. 80.7, 76.0, 48.2, and 48.2 %, NS).

Pituitary carcinoma

Patient, tumor, and treatment characteristics—There was a slight female predominance (ratio 1.33) for patients with pituitary carcinoma. The median age at diagnosis was 63 (range 18–78). Seventy-one percent of patients with pituitary carcinoma were white. Three (50 %) underwent surgical resection after 1983. One patient with pituitary carcinoma received EBRT.

Survival outcomes—Overall survival rates for pituitary carcinoma were 57.1, 28.6, 28.6, and 28.6 % at 1, 2, 5, and 10 years respectively (Fig. 1a). Due to the small sample size, statistical significance of prognostic factors in patients with pituitary carcinoma was not analyzed.

Discussion

We used the SEER database to present the largest series of patients with invasive adenoma and pituitary carcinoma published to date. We found that the overall survival in patients with pituitary carcinomas was significantly worse than in patients with invasive adenomas. This finding is consistent with prior studies demonstrating poor prognosis in patients with pituitary carcinoma [4, 5, 9, 18, 19]. The difference in outcome highlights the need for improved diagnostic techniques and identification of molecular or radiological markers to differentiate invasive adenoma from early carcinoma in the sellar phase in order to allow improved therapeutic options. The ability to predict tumor behavior and modify treatment accordingly may result in improved local control and overall survival as tumor aggressiveness and increased extent of invasion have been shown to have a statistically significant association with tumor recurrence or progression [23].

The data presented in this paper suggests that prognosis in patients with invasive adenoma is related to several factors. First, reduced overall survival was found in patients with age ≥65. This is interesting as although Grossman et al. reported increased odds of death among patients >80 years old undergoing pituitary resection relative to 65–69-year olds [24], several other studies have shown that age alone does not result in increased treatment-associated morbidity in this patient population [25-27]. For example, two other studies examining the perioperative risk associated with transsphenoidal surgery for pituitary tumors in elderly patients reported that surgery was well-tolerated in all patients. No perioperative mortality or severe anesthesiological complications were reported, concluding that age alone should not be a contraindication to aggressive management of these tumors [28, 29]. The survival detriment associated with age in this study may reflect more aggressive tumor biology in these patients or perhaps a differential treatment approach such that elderly patients were treated less aggressively. Alternatively, since nonsurvival included death from all causes, elderly patients may have other medical comorbidities which are not accounted for in this SEER database analysis leading to poorer overall survival.

Second, women in this study exhibited significantly better overall survival compared to men at 12 months. This is consistent with prior studies that have demonstrated worse outcomes in men with prolactin-secreting adenomas compared to women [30, 31]. However, a separate study examining gender-related differences in nonfunctioning adenomas found significantly worse outcomes in women compared to men [32]. It therefore appears that the effect of gender may be confounded by the histology of the tumor.

Interestingly, we found no difference in survival between patients who received radiation therapy and those who did not. The 5, 10, 20, and 30-year survival rates were higher in patients treated with EBRT compared to those who did not receive EBRT (83.5, 81.4, 55.9, and 55.9 % vs. 79.1, 70.6, 46.8, and 46.8 %), but this difference was not statistically significant. Survival rates were lower at 10, 20, and 30 years for those patients treated with adjuvant radiation therapy (RT) compared to those not receiving RT (65.7, 47.9, and 38.3 % vs. 76.0, 48.2, and 48.2 %). This may reflect a preferential administration of therapy in patients with more aggressive tumors.

This study has several limitations based on the limitations of the SEER database. For example, information on secretory function or molecular characteristics of the tumors is not available. Thus, this study is restricted to invasive adenomas and carcinomas rather than the hormonal type or atypical variant. However, the significance of tumor molecular characteristics as a prognostic marker should not be overlooked. For example, estimation of Ki-67 percentage has been shown to correlate best with invasiveness and prognosis with the majority of invasive adenomas having Ki-67 index of less than 10 % [10]. Thus, a Ki-67 index greater than 10 % should raise concern for the malignant potential of a tumor as a high Ki-67 percentage appears to predict rapid tumor progression [14, 33]. Additionally, the presence of p53 expression should be determined as the predictive value of this, and an increased Ki-67 percentage is likely superior to either alone [14].

An additional limitation of the SEER database is that the data collected is based on coding from patient medical records. With no pathological data available for review, there is no means of confirming a diagnosis. Also, there is no code for invasive adenomas specifically. We were therefore required to identify pituitary tumors likely to be invasive based on tumor behavior and extent of disease. Moreover, given that metastases are usually not present at first recognition of a pituitary carcinoma, it is unknown if an initial diagnosis of an adenoma was ever later revised to reflect the discovery of metastases. If not, many of the tumors in this study identified as invasive adenomas may actually be carcinomas in their sellar phase. Similarly, given the relatively long survival of these patients, it is possible that many patients ultimately succumb to alternative diseases.

Similarly, several important treatment details are not included in the SEER database. As such, we do not report data on medical therapy or chemotherapy. Furthermore, not all variables that are available in SEER are reliably reported. This combined with the small sample size limits the power for possible analyses.

Nonetheless, to our knowledge, this study is the largest study to report long-term survival outcomes in patients with invasive adenoma and is the second largest series to date of patients with pituitary carcinoma. It highlights the need for improved diagnostic methods to distinguish invasive adenomas from pituitary carcinomas in their sellar phase. Due to differences in prognosis between invasive adenoma and pituitary carcinoma, earlier diagnosis with treatment modification could potentially result in improved outcomes for these patients.

Accordingly, based on the findings of our study as well as review of the current literature, we suggest an aggressive management strategy for these patients. Such a strategy would likely include surgical resection of the primary tumor followed by determination of the Ki-67 index with or without identification of p53 expression to evaluate for malignant potential. Radiation therapy should be considered for those patients with high Ki-67 percentage, especially for an incomplete surgical resection as invasive adenomas tend to reoccur multiple times [4, 33]. Although our results fail to show a statistically significant difference in overall survival between patients treated with radiation therapy and those who were not, there was a trend towards improved survival. Additionally, data in SEER was only available for external beam radiation therapy and not for newer technologies such as

stereotactic radiosurgery. Ultimately, prospective studies are needed to determine the best management strategy.

Conclusion

We use the SEER database to report patterns of care and compare survival outcomes according to patient characteristics, tumor characteristics, and treatment received in a large series of patients with invasive adenoma or pituitary carcinoma. These data demonstrate worse overall survival in patients with pituitary carcinoma compared to invasive adenoma, highlighting the need for improved means of differentiating between the two tumors to allow for earlier diagnosis and treatment modification.

Comments

Ludwig Benes, Arnsberg Germany

This well-written and interesting article deals with the rare pathologies of invasive pituitary adenomas and carcinomas collected over a 35-year time period. The data from a large series of 117 individuals suffering from these pathologies is illustrated comprehensively. Information is given regarding the role of genetic studies on this topic and also the prognostic significance of molecular markers. The authors nicely point out the differences in survival outcomes in these patients during a long follow-up period of 10 years underlining what most of the readers may have thought but could not really prove on the basis of a robust data analysis.

Paolo Cappabianca, Teresa Somma, Naples, Italy

The authors present a retrospective analysis pointing out the differences in terms of survival outcomes in patients with invasive pituitary adenomas and carcinomas over a 10-year follow-up period. Once again, the importance of early differential diagnosis has been emphasized to provide patients with an adequate treatment.

Though, this manuscript offers the possibility to draw many considerations.

The invasive adenoma is identified as a benign pituitary tumor, even if it exhibits an aggressive biological behavior, infiltrating the dura mater, cranial bone, or sphenoid sinus. Our experience constantly teaches us to warn these “false benign” lesions; they, indeed, require difficult management to achieve an adequate disease control. The pituitary carcinoma is defined as a tumor of the pituitary gland exhibiting cerebrospinal and/or systemic metastasis.

In our opinion, clinical evaluation of the patient needs to be completed by head and spinal MR and total body PET/CT to diagnose the presence of eventual metastasis indicative of a neoplastic progression. The metastatic dissemination more commonly involves the CSF axis, including virtually any site within the supratentorial, infratentorial, and spinal compartments. Extradural dissemination occurs less frequently and also exhibits less

geographic restraint; bone, liver, lymph nodes, lung, kidney, and heart have all been reported as evidence of malignancy.

Furthermore, we believe that the genetic analysis can be useful not only to evaluate the biological behavior, as affirmed in the article, but also to define the therapeutic efficacy.

In the manuscript, the authors affirm the need of an aggressive treatment for these lesions.

We think that surgery must be completed by medical and radiation therapy.

The drug temozolomide has recently been documented to be effective against these lesions (1, 5, 7) especially if they show low levels of MGMT expression or present the immunopositivity of MSH6 (2, 4, 8), though new targeted therapies have been studied for lesions resistant to temozolomide (3, 6, 9). Finally, the radiotherapy plays an important role in the management of these lesions, especially in those of incomplete surgical resection and low effectiveness of medical treatment.

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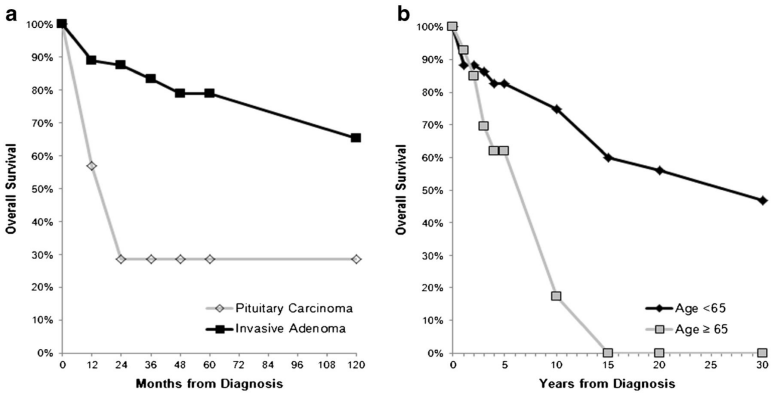

Fig. 1.

Overall survival (**a**) of all patients included in survival analysis in this study (*N*=90) and (**b**) in patients with invasive adenoma stratified by age <65 and age ≥65

Table 1

Demographic characteristics of the 117 patients with pituitary invasive adenoma or carcinoma included in this study

	Total (%) *N*=117	**Invasive adenoma (%) *N*=110**	**Pituitary carcinoma (%) *N*=7**
Age			
<65	90 (77)	86 (78)	4 (57)
≥65	27 (23)	24 (22)	3 (43)
Median (range)	52 (1−85+)	52.5 (1−85+)	63 (18−78)
Gender			
Male	55 (47)	52 (47)	3 (43)
Female	62 (53)	58 (53)	4 (57)
Race			
White	91 (78)	86 (78)	5 (71)
African-American	15 (13)	14 (13)	1 (14)
American Indian/ Alaskan Native	1 (1)	1 (1)	0 (0)
Asian/Pacific Islander	7 (6)	6 (5)	1 (14)
Unknown	3 (3)	3 (3)	0 (0)

Table 2

Tumor histology based on ICD-0-3 codes and disease extent of the 117 pituitary tumors included in the study

	Total (%)	Invasive adenoma (%)	Pituitary carcinoma (%)
Histology[a] (ICD-0-3 code)	*N*=117	*N*=110	*N*=7
Adenoma/adenocarcinoma, NOS (8140)	38 (32)	37 (34)	1 (14)
Neuroendocrine adenoma/carcinoma (8246)	7 (6)	6 (5)	1 (14)
Chromophobe adenoma/carcinoma (8270)	17 (15)	15 (14)	2 (29)
Prolactinoma (8271)	1 (1)	1 (1)	0 (0)
Pituitary adenoma/carcinoma, NOS (8272)	47 (40)	46 (42)	1 (14)
Acidophil adenoma/carcinoma (8280)	7 (6)	5 (4)	2 (29)
Extent of disease[b]			
Localized, confined to gland of origin	14 (12)	14 (13)	0 (0)
Localized NOS	28 (24)	28 (25)	0 (0)
Invading adjacent connective tissue or organs	35 (30)	35 (32)	0 (0)
Further contiguous extension	2 (2)	2 (2)	0 (0)
Metastases	7 (6)	0 (0)	7 (100)
Unknown	31 (26)	31 (28)	0 (0)

[a] All tumors classified as adenoma or adenocarcinoma (M8140-M8389). Histologic sub-classifications within the larger grouping of adenoma/adenocarcinoma based on ICD-0-3 codes in the SEER database

[b] Only malignant tumors with documented metastases classified as pituitary carcinomas

Table 3

Frequency of treatment with radiation therapy and/or surgery in our study population

	Total (%)	Invasive adenoma (%)	Pituitary carcinoma (%)
Radiation therapy (RT)	*N*=117	*N*=110	*N*=7
External beam	34 (29)	33 (30)	1 (14)
None	79 (68)	73 (66)	6 (86)
Unknown	4 (3)	4 (4)	0 (0)
Surgery (1983+)[a]	*N*=97	*N*=91	*N*=6
Incisional, needle, or aspiration biopsy	2 (2)	2 (2)	0 (0)
Simple tumor resection (STR)	60 (62)	58 (64)	2 (33)
Gross tumor resection (GTR)	9 (9)	9 (10)	0 (0)
None	29 (30)	26 (29)	3 (50)
Unknown	17 (18)	15 (16)	2 (33)
Combination therapy[b]	*N*=90	*N*=83	*N*=7
STR alone	36 (40)	34 (41)	2 (29)
STR + RT	20 (22)	20 (24)	0 (0)
RT alone	3 (3)	2 (2)	1 (14)
No STR or RT	10 (11)	8 (10)	2 (29)
None of the above	21 (23)	19 (23)	2 (29)

[a] Surgical data available only from 1983–2008 (*N*=91 invasive adenomas, 6 carcinomas). Some patients received multiple surgical procedures. Description of surgical techniques in the “Methods” section

[b] Numbers included only those cases that met the inclusion and exclusion criteria for survival analysis (*N*=83 invasive adenomas, 7 carcinomas) listed in the “Methods” section

Table 4

Five-year overall survival in patients with invasive adenoma (*N*=83) stratified by pituitary adenoma histologic subclassification according to ICD-0-3 codes

	Overall survival (%)
Adenoma, NOS (8140)	86.6
Neuroendocrine adenoma (8246)	100
Chromophobe adenoma (8270)	71.2
Pituitary adenoma, NOS (8272)	69.7
Acidophil adenoma (8280)	80