We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

6,900
Open access books available

186,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Paediatric Brainstem Cancers — Where We Have Been; Where We Are; Where We Are Going

Adrianna Ranger, Navjot Chaudhary and
Jonathan Lau

Additional information is available at the end of the chapter

1. Introduction

In North America and Europe, cancer involving the central nervous system (CNS) ranks second as the most common malignancy seen in infancy through adolescence, second only to leukaemia [1-7]. Consistent with this are figures on cancer-related mortality. In the year 2004, for example, there were 566 confirmed cases of leukemia-related death among children in the United States, followed by 555 CNS cancer-related deaths; these numbers accounted for 25.5% and 25.0% of the total number of cancer deaths in individuals less than 20 years old, respectively [4].

In general, survival from cancer has improved dramatically over the past forty years, presumably due to a combination of improved treatments and earlier detection. This is especially true in the paediatric population, among whom the overall long-term survival rate across all cancers has risen from under 50% to roughly 70% [4;8;9]. Even with brain cancer, the prognosis in children has improved, such that long-term survival is now achieved in more than half of patients [10]. This being said, the neoplasm originates in the brainstem in roughly 10-20% of children with CNS cancer [7;11-13], accounting for 150 to 300 new cases per year in the U.S. [11;13] and thus rendering it more common in children and adolescents than in adults [14;15]. And in this subset of children, the prognosis generally is considered extremely bleak, akin to that of glioblastoma multiforme [1;4;14;16-19].

Despite a continued poor prognosis, much has changed over the past several decades — like how paediatric brainstem tumours are diagnosed and classified, if and when surgery is considered, approaches to surgery, the use of adjunct therapies like radiation and chemotherapy, and the evolution of several new therapeutic options. Once lumped together as a single

entity that was considered inoperable and, hence, completely incurable, recent developments in imaging and surgical techniques have led to the classification of several different types of brainstem tumour; and, for some of these, surgical resection is considered the treatment of choice [16;18;20].

This chapter reviews the historical progression of understanding of paediatric brainstem tumours, including evolving beliefs regarding their classification, diagnosis, management, prognosis and prognosticators, dating from the 1970s to current times. It then describes current diagnostic and management protocols for these tumours, ending with a glance forwards towards potentially promising treatments and technologies and how they might, hopefully within the near future, favourably alter outcomes in these patients, both in terms of their survival and quality of life.

2. Where we have been

2.1. Definitions, diagnosis and classification

The brainstem has been defined as extending from the midbrain (tectal plate) to the medullary cervical junction [7]. Brain stem tumours are, by definition, tumours that involve the brainstem. However, they include tumours not just in the brainstem *per se*, but also in the upper cervical spine [16]. In the paediatric population, posterior fossa tumours significantly outnumber those that are supratentorial [10;21;22], and brainstem tumours account for roughly 25% of all tumours found within the posterior fossa [16;23]. The vast majority of these are primary lesions, since just 3 to 5% of all brain metastases are found in the brainstem [24]. The most common paediatric posterior fossa tumours are cerebellar astrocytomas, medulloblastomas, ependy-momas and brainstem gliomas [25].

Traditionally, the term *brainstem glioma* has been used to incorporate all brainstem tumours, largely because biopsies often were not performed and the majority of brainstem tumours in childhood are, in fact, of glial cell origin [26;27]. However, other histological forms of tumours do exist, though they comprise but a small percentage of brainstem tumours, and generally tend to be exophytic, growing either external to the brainstem or on its surface. Even among such exophytic tumours, gliomas form the clear majority. In their series of 75 paediatric patients with exophytic tumours seen between 1970 and 1990, Pierre-Kahn et al. [28] noted 69 glial tumours (92% of the total), of which 58 were astrocytomas and 11 oligodendrogliomas. The remaining six non-glial tumours were two ependymomas; two primitive neuroectodermal tumours (PNET); one ganglioglioma; and one of unknown histology [28]. In a much more recent review of non-glial brainstem tumours, other brainstem lesions noted to occur anecdo-tally included medulloblastomas invading the brainstem, cavernomas, lymphomas, haeman-gioblastomas, and other ganglionic and mixed tumors [29]. Nonetheless, many continue to use the term *brainstem glioma* generically, given that the vast majority of brainstem tumours are glial cell based.

Up until the development of advanced imaging techniques — like computed tomography (CT) and, to an even greater extent, magnetic resonance imaging (MRI) — brainstem tumours

tended to be lumped together as a single clinical entity and considered uniformly inoperable [30]. Since they were presumed gliomas and surgery was deemed contraindicated, there was no call even to biopsy them, except in certain instances in which the diagnosis was in doubt. For example, in 1969, Matson wrote: "brainstem gliomas must be classified as malignant tumors since their location in itself renders them inoperable" [21]. And as late as 1984, Tomita et al. [31] wrote: "Since biopsy specimens often misrepresent the true pathology... surgery undertaken to obtain precise histological verification of brain stem gliomas is futile." Instead, these latter authors recommended computed tomography (CT) with high-resolution metriza-mide CT cisternography to distinguish surgically resectable extra-axial tumors adjacent to the brain stem from non-resectable intrinsic brain stem gliomas. Such sentiments — that tumours only were worth a biopsy if they were either completely exterior to brainstem tissue or, at worst, on the surface — were echoed by others [32]. Consequently, early classification of brainstem tumours often subdivided lesions into those that were exclusively or primarily intra-axial, and those that were exclusively or primarily extra-axial. Meanwhile, brainstem tumours were collectively contrasted against those involving the midbrain or thalamus, both of which exhibited considerably superior prognoses [33].

This being said, there were early reports of certain patients with brainstem tumours who survived long-term. For example, in 1971, Lassiter et al. reported on 37 patients with presumed brainstem gliomas (22 of them children), among whom there were four children with large, surgically-drained neoplastic cysts who achieved long-term survival: two of these children died 7½ and 13 years later, and two still were alive 8½ and 9 years post diagnosis, one of them going on to graduate from college and the other with residual hemiparesis and mental retardation [34]. In 1975, Hara et al. reviewed the cases of 24 brainstem gliomas, and found that the median survival was 9 months, except for one patient who survived beyond 4½ years and another who lived for 14 years and 10 months before succumbing to the disease [35]. Similar isolated cases of long-term survival with brainstem gliomas, especially cystic lesions, were reported as far back as 1937 and 1940 through the mid nineteen seventies and early eighties [36-42]. And, contrary to conventional wisdom, even then, some neurosurgeons were routinely performing biopsies and surgery on select patients with brainstem gliomas [27;40;41;43-46].

In the nineteen sixties and early nineteen seventies, angiography and pneumoencephalograms were largely used to identify brain and brainstem tumours [47-50]. These imaging modalities were replaced in the mid nineteen seventies as computed tomography (CT) emerged as the imaging tool of choice for the detection and diagnosis of both supra-and infra-tentorial lesions, including brainstem tumours [51-54]. By this point, some surgeons were starting to distinguish outcomes between different subsets of patient who were able to undergo either partial or radical resection of brainstem cancers [27;40;41;43-45]. The first to propose what he termed a staging system for brainstem gliomas was Epstein, in 1985, who first categorized tumours as intrinsic, exophytic and disseminated; and then subcategorized intrinsic (actual brainstem) tumours as either diffuse, focal or cervico-medullary [43]. In 1986 and again in 1988, Epstein et al. published series of paediatric patients undergoing surgery for brainstem cancer, again classifying patients as focal, diffuse or cervico-medullary; in the latter report, they added a

category for cystic lesions [27;44]. What these authors noted was uniformly dismal outcomes in children with diffuse lesions, but often favourable outcomes in those patients with any one of the three other classifications. In the 1988 report, co-authored by Wisoff [27], among 66 children with intrinsic brainstem gliomas diagnosed between 1980 and 1986 who underwent radical surgical resection and either CT, MRI or both pre-operatively, 27 (41%) were found to have diffuse tumors, all of whom died within 12 to 18 months of surgery with malignant neoplasms that had not benefitted from surgery. However, five of nine children with cystic tumors, three of five with focal tumors, and twenty of twenty-four with cervicomedullary tumors were discovered to have a histopathologically low-grade lesion, and these 28 children all remained alive between one and six years post-operatively. The authors proposed criteria combining clinical and neuroradiological findings to predict which patients with brainstem tumors were likely to benefit from radical surgical intervention [27].

Since that time, several additional and very different classification systems have been proposed for brainstem tumours, including those by Stroink et al., Barkovich et al., Albright, Fischbein et al., Choux et al., Fisher et al., Mehta et al. and, most recently, Ramos et al. [45;55-61]. (See Table 1) The system proposed by Stroink et al., published in 1987, was born out of a study of 16 children (9 girls, 7 boys; age range 1½-12 years) with dorsally exophytic transependymal benign brainstem gliomas diagnosed between 1962 and 1985 at Sick Kids Hospital in Toronto, Canada [45]. Of these, 13 were low-grade (grade I-II) astrocytomas, one a grade III astrocytoma, and two gangliogliomas. All 16 patients underwent subtotal resection of their tumours, and seven had post-operative radiation therapy. One died 18 months after surgery, but the remaining 15 remained alive an average of eight years post-operatively (median=7 years; range=8 months to 23 years). Based upon these results, Stroink et al. proposed dorsal exophytic gliomas (Type I) as a distinct clinical entity, to differentiate them from hypo-dense, non-enhancing intrinsic tumours (Type IIa); hyper-dense, contrast-enhancing exophytic intrinsic tumours (Type IIb); focal, enhancing cystic intrinsic tumours (Type III); and focal iso-dense and contrast-enhancing intrinsic tumours (Type IV) [45].

Author(s)	Year Published	Imaging	Classification System
Epstein [43]	1985	CT, MRI	Intrinsic - diffuse; focal, cervicomedullary
			Exophytic - anterolateral; posterolateral
			Disseminated - positive cytology; positive myelography
Epstein et al. [44]	1986	CT, MRI	Diffuse
			Focal
			Cervicomedullary
Epstein et al. [27]	1988	CT, MRI	Diffuse
			Focal
			Cervicomedullary
			Cystic

Author(s)	Year Published	Imaging	Classification System
Stroink et al. [45]	1987	CT with contrast	Type I: dorsal exophytic glioma
			Type II intrinsic brainstem tumour
			* IIa - hypodense with no contrast enhancement
			IIb - hyperdense with contrast enhancement, exophytic
			Type III: focal cystic tumour with contrast enhancement
			Type IV: focal isodense tumour with contrast enhancement
Barkovich et al. [55]	1990	MRI	Tumours characterized by -
			(1) Location - midbrain, pons, medulla
			(2) Focality - focal or diffuse
			(3) Direction & extent of tumour growth
			(4) Degree of brainstem enlargement
			(5) Presence/absence of exophytic growth
			(6) Presence/absence of haemorrhage or necrosis
			(7) Evidence of hydrocephalus
Albright [58]	1996	MRI	Focal - midbrain; pons; medulla
			Diffuse
Fischbein et al. [56]	1996	MRI	Midbrain - diffuse; focal; tectal
			Pons - diffuse; focal
			Medulla - diffuse; focal; dorsal and exophytic
Choux et al. [57]	2000	MRI	Type I - diffuse
			Type II - intrinsic and focal
			Type III - intrinsic and exophytic
			Type IV - cervicomedullary
Fisher et al. [59]	2000	MRI	Pilocytic astrocytomas
			Fibrillary astrocytomas
			Other tumors
Mehta et al. [60]	2009	MRI	Intrinsic tumours - expanding; diffuse infiltrative; purely ventral
			Extrinsic tumours
Ramos et al. [61]	2013	MRI	Diffuse intrinsic/diffusely infiltrative
			Posterior exophytic/cervicomedullary gliomas; other focal tumours
			Dorsal exophytic tumours
			Cervicomedullary tumours
			Focal tectal tumours

Table 1. Classification Systems for Brain Stem Tumours-1985 to Present

It was in the mid to late nineteen-eighties that magnetic resonance imaging (MRI) started to replace CT as the imaging modality of choice for the diagnosis and classification of brainstem tumours [62]. As such, it was based upon MRI studies that Barkovich et al. proposed their criteria for brainstem tumours in 1990 [55]. Their criteria were derived from the results of retrospectively-reviewed MRI studies for 87 paediatric patients with brainstem gliomas. T2-weighted images were deemed most appropriate for use, given that they were the most accurate at demonstrating the extent of tumour. In this much more elaborate classification scheme, tumours were characterized in terms of (1) their location of origin, into midbrain, pons and medulla; (2) their degree of 'focality' (whether diffuse of focal); (3) the direction and extent of tumour growth; (4) the degree of brainstem enlargement; (5) the degree of exophytic growth; (6) the presence or absence of cysts, necrosis or hemorrhage; and (7) the presence or absence of hydrocephalus. This classification scheme was never scientifically validated to determine its ability to predict outcomes, however, and failed to achieve widespread acceptance. Likely reasons for this failure were how cumbersome the system was, and the lack of any firm guidelines as to its use.

As such, subsequent classification schemes have been much simpler, starting with those proposed by Albright, in 1996, who returned to the very simple categorization of lesions as being either focal (further distinguished by location, into midbrain, pons or medulla) or diffuse [58]; and Fischbein et al., also in 1996, who again categorized lesions as focal or diffuse, but categorized both forms of lesion by location — again into midbrain, pons or medulla [56]. Harkening back to the four-category system initially proposed by Epstein in 1985 [43], Freeman et al., in 1998, and Choux et al., in 2000, adopted the four relatively straight-forward categories largely in use today: diffuse intrinsic; focal intrinsic; focal exophytic, and cervicomedullary [18;57]. In 2009, Mehta et al. proposed a modified sub-categorization of intrinsic tumours, into expanding, diffuse infiltrative, and pure ventral varieties, achieving good surgical results and reasonable survival with the first of the three subtypes [60]. Then, most recently, Ramos et al. adopted yet another classification system that included 'diffuse intrinsic and diffusely infiltrative' as a single category, followed by four additional categories of various focal lesions [61]. The authors' conclusion was that "brainstem tumors are a heterogeneous group of tumors." Clearly then, in terms of how brainstem tumours are now perceived, there has been a 180 degree reversal from early statements [21;30;31] about their homogeneity and the inappropriateness of biopsies for brainstem tumours. The questions remain, however: Who warrants such biopsies? And how could biopsies and surgery influence outcomes?

2.2. Outcome predictors and indications for surgery

Early universal pessimism regarding the fate of children with brainstem tumours has also clearly changed in recent years, with reports of better than 90% five-and ten-year survival rates in children with certain types of tumour [23;63]. The primary objective of all the classification schemes proposed to date has been to identify which patients warrant surgical treatment and how aggressive such treatment should be. Contrary to early years, when all brainstem tumours were considered inoperable [21;30;31], for the past thirty years neurosurgeons have been operating to either de-bulk or completely excise lesions when doing so was felt to be of clinical

benefit, potentially positively influencing quality of life and/or survival. As stated earlier, that a subset of patients existed for whom long-term survival was possible has been suspected for almost eighty years [36;37]. Once again, it was Epstein et al. who first identified diffuse lesions as being the most rapidly fatal, and focal and cystic lesions as being more amenable to treatment and long-term survival [27;43;44]. Since then, other prognostic factors have been identified that can influence the decision to operate (See Table 2).

Factor	Studies	Year Published	Imaging	Comments
Focal (vs. diffuse intrinsic) tumour	Sandri et al. [77]	2006	MRI	87.4% 4-year vs. 12.3% 2-year survival
	Mauffrey [20]	2006	MRI	90% vs. 22% 2-year survival
	Fried et al.	2012	MRI	89% vs. 3% 5-year survival
Cystic appearance	Lassiter et al. [34]	1971	not identified	All 4 children with cystic lesions
Prolonged pre-diagnosis symptoms	Fisher et al. [59]	2000	MRI	Cox regression→ survival ↓w/ symptoms > 6 mo (p = .004)
	Shuper et al. [17]	1998	MRI	Mean survival 19.5 vs. 12.9 mo with >1 mo symptoms
Other than pons location	Fisher et al. [59]	2000	MRI	Cox regression→ survival ↓w/ pons involvement (p=.0002)
No presenting eye symptoms/eye palsies	Fisher et al. [59]	2000	MRI	Cox regression→survival ↓w/ abducens palsy (p<.0001)
	Shuper et al. [17]	1998	MRI	Mean survival 17.5 vs. 12.3 mo with no eye symptoms
Basilar artery engulfment	Fisher et al. [59]	2000	MRI	Cox regression→survival ↓w/ basilar artery engulfed (p=.006)
Tectal location	Poussaint et al. [65]	1998	MRI	All 32 children with tectal tumours alive
				after a mean 5 years follow-up
Non-enhancing on gadolinium MRI	Poussaint et al. [65]	1998	MRI	Gadolinium enhancement of tectal lesions
				increased odds of disease progression x15
Contrast enhancement on MRI	Dellaretti et al. [64]	2012	MRI	Mean survival with contrast enhancing lesions = 21.7 mo.;
				with non-enhancing lesions 54.2 months (p < .001)
Maximum diameter < 0.5 cm	Poussaint et al. [65]	1998	MRI	Each 1 cm increase in maximum diameter
				increased odds of disease progression x5
Neurofibromatosis type 1	Fried et al. [72]	2012	MRI	All 7 children with NF-1 had non-focal
				lesions & long-term survival
	Other papers			Numerous isolated anecdotal reports in other papers

Table 2. Factors Predicting Favourable Outcomes in Paediatric Brainstem Tumour Patients

One of the earliest attempts to empirically look at prognostic factors beyond imaging results was published by Fisher et al. in 2000 [59]. They reported on the results of a study of 77 patients, 21-years old or younger, seen between 1980 and 1997. In this study, they sought to identify characteristics statistically associated with poor survival. The factors that they identified were (a) symptom duration less than six months before diagnosis (p=0.004); (b) abducens palsy at presentation (p < 0.0001); (c) a pontine location (p=0.0002); and (d) engulfment of the basilar artery (p=0.006). Twenty of their patients were found to have pilocytic astrocytomas, which were associated with a very favorable 5-year overall survival rate of 95%, as well as with location outside the ventral pons (p=0.001) and dorsal exophytic growth (p=0.013). Another histological type they could predict based upon clinic-radiographic findings was fibrillary astrocytoma, of which they had 14 cases. These lesions were associated with symptoms < 6 months (p=0. 006), abducens palsy (p < 0.001), engulfment of the basilar artery (p=0.002), and a one-year survival rate of just 23% (p < 0.0001). Shuper et al. also found, in their analysis of 24 children operated upon between 1981 and 1997, that a shorter duration of symptoms (< 4 weeks) and visual symptoms at presentation were associated with shorter survival and lower survival rates [17]. Meanwhile, Dellaretti et al. found that contrast-enhancing lesions on MRI were associated with a significantly shorter mean duration of survival versus non-enhancing lesions (21.7 vs. 55.2 months, p < 0.001); however, on Cox proportional hazards regression analysis, tumour grade was the only significant predictor of survival, suggesting that contrast enhancement in that sample was an indicator of higher tumour grade [64].

Poussaint et al. specifically sought to determine which clinical and imaging findings best correlated with outcomes in children with tumours involving the midbrain tectum, via a retrospective review of the medical records and imaging studies of 32 children (16 boys and 16 girls; mean age, 8 years) with tectal tumours [65]. Of this number, eight children had undergone CT, 11 MRI, and 13 both CT and MRI studies. Over a mean follow-up period of five years (range, 3.6 months to 17 years), all patients experienced hydrocephalus, for which all but one required cerebrospinal fluid (CSF) diversion. The tectum was the centre of the tumour in all cases; and the majority of the tumours appeared iso-dense on CT scans, iso-intense on T1-weighted MR images, and hyper-intense on T2-weighted images. Twenty patients required no further treatment. In this group, the mean maximum tumour diameter was 1.8 cm, and enhancement occurred in only two cases (10%). At follow-up, 18 tumours were the same size as at baseline, one was larger due to cyst formation in the setting of stable symptoms, and one was smaller. The remaining 12 patients required further treatment (excision and/or radiotherapy) because of disease progression, indicated either by increased tumour size or by worsening symptoms. In this group, the mean maximum tumour diameter was 2.5 cm and contrast enhancement occurred in nine (75%). Further follow-up in this group showed decreased tumour size in eight and stable residual tumor in three. The authors then used regression analysis to calculate and compare the likelihood of a patient requiring further treatment with various-size enhancing versus non-enhancing tumours and identified two trends: larger tumours were more likely to require further treatment; and the same was true for enhancing lesions. Combining these two factors was especially predictive. For example, whereas 31% of lesions with a maximum diameter of 0.5 cm required further treatment, same-sized non-enhancing lesions warranted such treatment less than one percent of the time.

Corresponding percentages for lesions of maximum diameter 1.0, 1.5, 2.0, 2.5, 3.0, 3.5 and 4.0 cm were 48 and 1%, 67 and 3%, 80 and 6%, 90 and 11%, 95 and 21%, 97 and 36%, and 98 and 54%. By the time a lesion reached 4.5 cm in maximum diameter, virtually all (99 and 70%) required further treatment, irrespective of whether they did or did not enhance. Overall, the odds of surgical or radiation treatment were almost five times greater for each 1 cm increase in maximum tumor diameter (odds ratio, 4.9; 95% confidence interval, 1.3-19.3; p=0.015); and 15 times greater when the tumor enhanced versus when it did not (15.0; 2.2-106.5; p < 0.003). The investigators thereby concluded that, though paediatric tectal tumors exhibit somewhat variable behavior, patients generally do well, and that larger tumours, and especially those that that enhance with contrast on MRI, are highly likely to be more aggressive [65]. Whether size and contrast-based enhancement on MRI or CT predict the need for treatment or ultimate outcomes with other non-diffuse intrinsic or exophytic brainstem tumours has not yet been demonstrated.

Another factor long believed to place individuals at increased risk of brainstem and other CNS malignancies, but also to confer a relatively favorable prognosis, is the presence of type 1 neurofibromatosis (NF-1), though this belief is largely based upon anecdotal reports [66-72]. In the large study of 223 children with brainstem tumours reported by Fried et al., however, there were seven children with concomitant NF-1; and all had low-grade brainstem tumours [72]; the statistical likelihood that this occurred merely by chance, assuming a fifty-fifty split of low-to high-grade lesions (which is roughly what they observed across the sample), is less than one percent.

Overall in NF-1 patients, brainstem gliomas comprise a heterogeneous group of lesions, consisting of three main subtypes: (1) diffuse brainstem enlargement; (2) focal enhancing nodules with or without cystic areas; and (3) peri-aqueductal gliomas. All of these subtypes, including diffuse brainstem enlargement, generally exhibit a very indolent course and do not require treatment, though MRI monitoring is indicated until their indolent course is confirmed. Some lesions even regress on their own [73]. The diffuse brainstem enlargement is somewhat similar in appearance to the unidentified bright objects (UBOs) that are the most commonly observed CNS lesions on MRI in patients with NF-1 [74]. Like UBOs, they exhibit abnormal signals on T1-weighted images. The major differences are that, as opposed to UBOs, there usually is a mass effect, and these lesions also tend to be considerably larger than most UBOs. What the diffuse enlargement represents remains controversial. Many presume them to be gliomas, but they exhibit a much more indolent course than brainstem gliomas seen outside of NF-1, such that adjuvant treatment is only required in the minority of patients whose lesions progress. However, ongoing monitoring is required to detect the few who do progress, before neurological deficits ensue, which often are irreversible. Rarely, these gliomas progress to more malignant forms of astrocytoma, including glioblastoma [73;75].

The focal enhancing nodules seen in the brainstem of NF-1 patients, which may occur with or without cystic areas, generally are thought to represent pilocytic astrocytomas, given their imaging characteristics. Like pilocytic astrocytomas elsewhere, they generally are indolent; but their course is unpredictable and the brainstem so susceptible to major deficits, relative to the cerebral hemispheres, that ongoing monitoring is required. Small, focal intrinsic lesions

may enlarge and then regress spontaneously. Exophytic tumours often are more aggressive and require treatment.

Periaqueductal gliomas occur adjacent to the aqueduct of Sylvius between the 3rd and 4th ventricles in the midbrain. They typically manifest with late-onset aqueductal stenosis, leading to hydrocephalus. Presumably, they represent low-grade gliomas or glial hamartomas, and typically are indolent. However, because of their location, CSF shunting often is necessary. But, as with the other two forms of brainstem tumour seen in NF-1 patients, resection usually is unnecessary [73;75].

Table 3 summarizes currently published research on tumour characteristics that predict a favourable outcome. What is most evident is the dearth of confirmatory studies. These findings aside, the brainstem tumour characteristic that is unquestionably the one most likely to dissuade surgeons from operating is evidence that the tumour is intrinsic and diffuse, due both to the known high risks of surgery and to the lack of evidence suggesting any benefit, in terms of either quality of life or survival time [16-18;20]. The corollary to this is that, contrary to thirty years ago when most surgeons preferred to leave all brainstem tumours alone, focal, exophytic and cystic tumours are increasingly being accessed and resected, often with good results [16-18;20;23;60].

	Year	Study	Study subjects	5-year survival	
Author(s)	Published	Type	N =	N =	% =
Lesniak et al. [76]	2003	Retrospective	57	26	45.6%
Sandri et al. [77]	2006	Retrospective	17	15	88.2%
Mauffrey [20]	2006	Retrospective	14	8	57.1%
Teo et al. [63]	208	Retrospective	34	27	79.4%
Fried et al. [72]	2012	Retrospective	108	96	88.9%
Klimo et al. [23]	2013	Retrospective	52	51	98.1%
OVERALL			**282**	**223**	**79.1%**

Table 3. Survival in Paediatric Patients with Non-Diffuse Intrinsic Brainstem Tumours

2.3. Treatment and outcomes

In 1984, Tomita [31] wrote that "radiation therapy is the choice of treatment, should CT indicate clear evidence of intrinsic brain stem tumor... posterior fossa craniotomy should be undertaken only for aspiration of cystic intrinsic stem tumors, resection of extra-axial juxtastem tumors and, although rare, in instances when CT is unable to definitively distinguish extra-axial from intra-axial mass for verification of lesion location." Clearly, sentiments have changed; but has the increase in surgical interventions altered outcomes?

In 1998, Shuper et al. published the results of their study of 24 children with brainstem tumours operated upon between 1981 and 1997 [17]. The main question they asked was: are we

improving outcomes? A tissue diagnosis was achieved in only six of the children. Although the investigators did not perform inferential statistical analysis, average survival in five patients seen before 1990 was 8.6 months, versus 19.4 months in the five patients seen in 1990 through 1994, and 20.0 months in those seen in 1995 and 1996. Moreover, raw data were provided, allowing the current author to perform a statistical comparison of months of survival pre (8.6) versus post (19.7) January 1st 1990. This difference, despite the low numbers, is significant (t=2.379, df 13, p=0.03). However, these patients generally were offered radiation +/-chemotherapy, and not surgery. In addition, other biases might have erroneously generated these results, like alterations in referral patterns or the earlier recognition of tumours as a result of major technological advances in imaging.

More recently, several authors have reported survival rates in paediatric patients treated surgically for non-diffuse tumours (Table 3). In 2003, Lesniak et al. [76] retrospectively reviewed the charts of all pediatric patients admitted to Johns Hopkins University Hospital with a diagnosis of a brainstem tumor between January 1985 and December 2000: 89 patients met the inclusion criteria, among whom 57 (64.0%) underwent surgical resection, while 32 (36%) were treated with radiation and/or chemotherapy. Of the surgical candidates, 57 (100%) had an accompanying MRI scan significant for an enhancing lesion in the midbrain, pons or the medulla. The pathology was consistent with juvenile pilocytic astrocytoma in 30 patients (52.6%) and glioblastoma multiforme in 12 patients (21.1%). The remaining cases consisted of ten patients (17.5%) with fibrillary astrocytomas, three (5.3%) with gangliogliomas, one (1.8%) with an oligodendroglioma and one (1.8%) with a primitive neuroectodermal tumor. Total surgical resection was attained in 29 patients, near total resection (>90%) in eight, subtotal resection (50-90%) in 15, and partial resection (<50%) in five. The progression-free survival of all patients, which included the twelve with glioblastomas, was 71.9% at 3 years and 45.6% at 5 years. Excluding the 12 patients with known glioblastomas, all of whom died prior to three years, these survival rates rise to 83 and 53%, comparable to rates observed in a subsequent study by Sandri et al. [77].

In 2006, Sandri et al. [77] published their series of 31 children admitted to their institution from 1995 to 2003, 14 of whom were classified on MRI as having diffuse and 17 as having focal brainstem tumours. Patients with diffuse lesions were treated with locoregional radiotherapy (1.8 Gy/day for 54 Gy) and weekly vincristine for radiosensitization (1.5 mg/sm for six total doses). Meanwhile, patients with focal tumours underwent surgical resection, with adjunct chemotherapy and/or radiotherapy considered on a case-by-case basis. Among the 14 with diffuse tumours, ten experienced a partial response, three exhibited stabilization of their disease, and one progressed. General and/or neurological symptoms improved in more than 80% of these patients. However, the median time from diagnosis to progression and from diagnosis to death were just 8 (range of 3-13) and 13 (range of 4-25) months, respectively, with a 2-year overall survival rate of just 12.3%. Conversely, among the 17 children with focal lesions, gross total removal was achieved in 4/17 cases, subtotal removal in 7/17, and partial removal in 6/17. There was one surgery-related death. Eight out of 17 patients had adjuvant chemo-and/or radiotherapy after progression, among whom six remained free of neurological symptoms and two died secondary to tumor progression. The 4-year overall and disease-free

survival rates were 87.4 (SE 8.4) and 58.8% (SE 11.9), respectively, with the extent of resection identified as the best predictor of survival (p=0.012) [77].

Also in 2006, Mauffrey reported on his retrospectively reviewed series of 27 paediatric patients admitted to hospital in Turin, Italy with a diagnosis of brainstem glioma [20]. Thirteen patients had a diffuse pontine tumour on MRI scan, while fourteen had other brainstem gliomas. Those in the first group had a shorter mean duration of symptoms prior to diagnosis (2.6 vs. 10.6 months), never demonstrated gadolinium enhancement of their tumour on MRI (vs. 78.6% in the other group), and were much more likely to have symptoms or findings indicating cranial nerve involvement (77.0 vs. 28.5%). None of the 13 with diffuse gliomas underwent radical surgery, whereas it was the treatment of choice in the remaining 14. Two-year survival rates were 25% and 90%, respectively, and 60% of the latter remained alive at five years [20].

In 2008, Teo and Siu [63] reported on their results with 34 consecutive patients between 3 and 16 years of age who underwent endoscope-assisted microsurgery for focal brainstem gliomas with the intent of radial resection between 1999 and 2005. More than 90% tumour resection was achieved in 31patients, while >50% was attained in the remainder. There was no peri-operative mortality and the average follow-up was 46 months. Twenty-three patients (74%) harboured low-grade and 11 (26%) high-grade gliomas. Kaplan-Meier survival analysis revealed marked differences in the 5-year survival rates between the two groups (100% vs. 33%). Multivariate analysis demonstrated that the degree of tumour resection was not associated with poor outcome at 6 months.

Two papers published over the past couple of years are those by Fried et al. [72], based at The Hospital for Sick Children in Toronto Canada, and Klimo et al., based at George Washington University in Washington, DC [23]. The latter study, like all those described previously, was relatively small, with just 52 patients (32 boys), all with radiographically-confirmed, low-grade focal brainstem gliomas seen from 1986 to 2010. The median duration of follow-up was 10.0 years, and the median age at diagnosis 6.5 years (range 1-17 years). Tumors were located in the midbrain (n=22, 42%), pons (n=15, 29%), and medulla (n=15, 29%). Surgical extirpation was the primary treatment in 25 patients (48%). Five-and 10-year event-free survival and overall survival rates were 59% and 98%, and 52% and 90%, respectively. Surprisingly, children with intrinsic tumors trended towards slightly higher event-free survival at 5 years than those with exophytic tumors (p=0.054), but not at 10 years (p=0.147). No other variables were predictive of event-free survival [23].

The retrospective study by Fried et al. is by far the largest to date, assessing a total of 223 children with brainstem tumours (12% of all CNS tumours seen) followed at The Hospital for Sick Children in Toronto over the preceding 25 years [72]. Ninety-five of these tumours were diffuse and an additional 17 were high-grade astrocytomas (grade III or IV). The investigators made several novel observations. First, whereas 75% of tumors involving the pons were high-grade, 98% of tumours lacking pontine involvement were low-grade (p = 0.0001). Second, residual tumour after surgery, even when visualized, did not adversely alter either progression-free survival or overall survival. And, among those requiring further treatment, 5-year progression-free and overall survival were comparable between those receiving chemotherapy (53 and 93%) and those administered radiotherapy (66 and 83%) (p = 0.26 and 0.30, respective-

ly). Among those with focal lesions, five-year progression-free survival (PFS) and overall survival (OS) were 57% and 89%.

Combining the results of these last seven studies (Table 3), in which children with non-focal brainstem tumours were identified and treated, either surgically or non-surgically, there were 282 such children, of whom 223 (79.1%) survived long-term (beyond 4 years and most beyond 5 years). In the largest study, which had 108 such children [72], 90% remained alive 10 years post diagnosis. Several comments are warranted. First, every one of the above-mentioned studies had significant methodological issues, not the least being that they all were retrospective. Moreover, because patients were selected for surgery, it is not possible to rule out the possibility that the characteristics that made them surgical candidates in the first place (e.g., a focal vs. diffuse tumour) were responsible for their survival, rather than the surgery itself. Nonetheless, what is clear is that long-term survival among children with non-diffuse tumours clearly is not at all uncommon. In fact, it seems likely for four out of five such children, making it the rule and not the exception, which is radically distant from both the beliefs and outcomes of thirty and forty years ago, and considerably improved from survival rates in at least one older study in which those with non-diffuse tumours were identified but not offered surgery [78]. Fried et al. concluded that children with non-diffuse brainstem tumours do well even with conservative management; but their conservative management appears to have consisted of surgical resection in most cases, with adjuvant chemotherapy or radiation considered more aggressive [72]. Ideally, from a purely methodological standpoint, future studies would randomize surgery-eligible patients to surgery versus non-surgery groups. Practically, however, this author considers it unlikely that most parents would consent to allow their children to be randomly assigned to one group or the other when surgery offers at least the potential of cure.

The good news, then, irrespective of methodological questions regarding the true effectiveness of surgery, is that children with several types of brainstem tumour appear to do well. The bad news is that the majority of brainstem tumours in children continue to be either diffuse intrinsic lesions or high-grade astrocytomas [72], and the prognosis for either remains dismal, with only about 10% of children alive two years after diagnosis [79;80]. One major challenge currently facing researchers and clinicians is to identify non-surgical ways to better target these otherwise poorly responsive tumours.

3. Where we are and where we are going

Clearly, the past forty years have brought about substantial changes in the way brainstem tumours are both perceived and managed. No longer is the term 'brainstem glioma' used to lump all brainstem lesions together as homogenous, untreatable and ultimately fatal. Now, either three or four heterogeneous classes of tumour are described, and all but one is considered to be an indication for aggressive, often surgical treatment. Some investigators sub-classify lesions further, related to their anatomical location (e.g., midbrain, pons, medulla). In essence, though, irrespective of the number of tumour types proposed, all categorization systems ultimately separate diffuse intrinsic lesions from all others.

Current diagnosis largely depends on the use of patient histories and physical findings, especially paying attention to the duration of symptoms prior to diagnosis and the type(s) of neurological deficits identified (e.g., ocular palsies), followed by magnetic resonance imaging, both with and without contrast. Lesions that are intrinsic and diffuse, and lesions that involve the pons are generally considered to be a contraindication to surgery, though many clinicians are now biopsying them to determine if they are high-or low-grade to estimate course and likely survival time [81]. Conversely, lesions that are focal, cystic, and extraphytic are usually considered treatable, with surgery to remove as much of the tumour as possible often considered the treatment of choice. Table 4, utilizing the most recently proposed classification system of Ramos et al. [61], summarizes current general practices. Following the 2013 publication of guidelines promoting the biopsy of diffuse intrinsic brainstem lesions to aid in the development of targeted therapies [82], stereotactic biopsies must now be at least considered standard of care for these patients. Radiation therapy, sometimes combined with chemotherapy, appears to induce brief clinical remissions in patients with diffuse tumours for whom surgery is not indicated, and may prolong survival slightly [83]. With other tumours, surgery often plays the major role; though some patients merely require monitoring and others respond well to radiation or conservative measures like CSF shunting alone.

Tumour type	Typical location	Usual histology	Biopsy	Surgery	Radiation	Chemotherapy	2-year survival
Diffuse Intrinsic or	Pons	grade III-IV gliomas	Yes	No	Yes	+/-	10%
Diffusely Infiltrative		fibrillary astrocytomas					
Focal	Medulla	pilocystic astrocytomas	Yes	Complete resection	+/-	+/-	≥ 90%
	Brainstem	gangliocytomas		often possible			
Dorsal Exophytic	Mostly in 4th	pilocystic astrocytomas	Yes	Usually only partial	+/-	+/-	≥ 90%
	ventricle	other low-grade glioma		resection is possible			
Cervicomedullary	Epicentre either	pilocystic astrocytomas	Yes	Complete resection	+/-	+/-	~ 100%
	in medulla or	gangliocytomas		possible in ~75% of pts			
	cervical spine						
Focal Tectal	Tectum	low-grade gliomas	Yes	Shunt placement	Yes	Usually not	~ 100%
				Resection often			
				unnecessary			

Table 4. Current Management of Paediatric Brainstem Tumours

There remains no consensus, however, as to how to best categorize lesions; and the lion's share of brainstem tumours continue to be considered untreatable and to have a dismal prognosis. Consequently, three major challenges that remain are (1) coming to some consensus as to classifying lesions, so as to best predict their course, likely response to treatment and, hence, when and how best to treat them; (2) developing more effective non-surgical treatments to treat the intrinsic diffuse tumours for which all current treatments, including surgery, have been ineffective and the prognosis remains abysmal; and (3) optimizing quality of life in these children and their families, irrespective of long-term prognosis. With a view to these three main objectives, we now briefly explore current and future directions in the detection, diagnosis and classification of brainstem tumours, and in their non-operative and operative management.

3.1. Enhanced diagnostics and classification

In few fields have there been as many and as dramatic advances as in the field of diagnostic imaging, and this appears to be having a significant impact upon how brain and brainstem tumours are now detected and diagnosed. Increasing recognition that not all brainstem tumours are a diverse collection of pathological entities with distinct courses and responses to treatment, has led to attempts to distinguish between them using advanced imaging. Typically, for example, diffuse intrinsic fibrillary astrocytomas appear hypo-intense on T1-weighted images, while heterogeneously hyper-intense on T2-weighted images; they also exhibit indistinct margins that reflect the tumour's highly infiltrative nature [61]. Beyond distinctions made using different MR sequences, various contrasts are now being used to try to detect lesions that otherwise might be missed [84] and to delineate low-from high-grade lesions [19; 45;56;64;76]. For example, dorsal exophytic tumours often are low-grade pilocytic astrocytomas that, like high-grade fibrillary astrocytomas, may be hypo-intense on T1-weighted images and hyper-intense on T2-weighted images; however, they classically appear well-demarcated. Moreover, after gadolinium infusion, a cystic component often is identified, as only the solid portion of the tumour is enhanced, revealing a hypo-intense centre [61;85;86]. More recent advances in MR scanning — like MR spectroscopy, MR perfusion, and diffusion tensor imaging (DTI) — are also being utilized to further establish the histopathologic diagnosis of brainstem lesions [18;61]. An additional advantage of these newer MR technologies is that they are better at monitoring for disease recurrence or progression after treatment, since radiation-induced necrosis may be mistaken for tumour re-growth with traditional MRI [87-90]. In addition, functional scans — like functional MRI (fMRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT) — are emerging as additional imaging tools to identify and characterize lesions in the brain, brainstem and spinal cord [19;91-95]. Further development of these tools may aid in further delineating the various brainstem tumours, even obviating the need for tissue in those patients for whom biopsies pose undue risk.

This being said, among the most major imaging advances related to brainstem tumours relates to stereotactic biopsies. A *stereotactic biopsy* utilizes a computer and images performed in at least two planes, first to localize a target lesion, like a tumour, in three-dimensional space; then

to determine its depth; and finally to guide the removal of tissue for pathological examination. Stereotactic biopsies rely on the underlying principle of *parallax*, a process that initially was used in astrology to estimate distances between stars [96]. *Parallax* is the concept of using multiple site lines to visualize the same object relative to objects of known position in front of and behind it. Since objects closer to the observer tend to move more than objects that are more distant when the point of observation changes, measuring the degree of movement of the target lesion relative to reference points, combined with recording the change in viewing angle, permits one to estimate the depth or "Z-dimension" of the target lesion [97]. Long used to aid in the biopsy of breast lesions [98], CT-guided stereotactic biopsies have been used for the diagnosis of brain lesions since the nineteen seventies [99;100], but not with brainstem lesions until more recently. Just this year, Cage et al. reported on their results specifically biopsying diffuse brainstem tumours; they also extensively reviewed the literature [81]. In their own series, nine children with pontine lesions were biopsied, with successful tissue collection achieved in all cases. Among these lesions, four were found to be low-grade (grade I or II) astrocytomas, and five high-grade (grade III or IV) gliomas, demonstrating heterogeneity even among diffuse pontine lesions. Moreover, only one patient experienced any post-operative complication – transient seizures and hydrocephalus. In their review of the literature, the same authors identified twenty case series besides their own, ranging in size from a single paediatric patient [101] to 52 children [102]. In this latter series, among 52 paediatric brainstem biopsies, only five patients experienced any post-operative morbidity, in four instances transient; and there were no deaths. Biopsy was felt to alter management in 18% of the cases. In another one of the larger series, Kondziolka and Lunsford reported on their use of CT-guided stereotactic biopsies in 40 consecutive patients seen over a 13-year interval [103]. Of this number, 20 patients had midbrain lesions (n=20), 18 pontine lesions, and two medullary lesions. Midline lesions were approached via a coronal, trans-thalamic trajectory; lateral brain stem lesions usually were approached via a trans-cerebellar route. A histologic diagnosis was achieved in 38 patients (95%), and no post-biopsy haemorrhages were noted on CT performed immediately after the procedure. Only one patient (2.5%) experienced a complication, which was transient diplopia. Altogether across the twenty-one papers Cage et al. reviewed, there were 294 documented brainstem biopsies in paediatric patients, among whom there were 16 cases of an intra-operative complication (5.4%); 42 cases of increased post-operative morbidity (14.3%) that was transient in the vast majority of cases; 29 inconclusive biopsies (9.9%); and two procedure-related deaths (0.7%) [102]. The authors concluded that brainstem biopsies are safer than widely perceived and that, when used judiciously, might be both safe and of advantage in terms of determining treatment. Stereotactic biopsies have been demonstrated to be superior to MRI alone in accurately diagnosing brainstem lesions [104].

3.2. Enhanced non-operative management

Many have argued against biopsying diffuse intrinsic brainstem lesions, since they cannot be surgically removed or even de-bulked without causing unacceptable neurological deficits because of their location and infiltrating nature, and given the lack of enduring response that the vast majority of patients demonstrate to traditional chemotherapy and radiation. But this pessimistic outlook may be changing, given emerging knowledge about potential therapeutic

targets and optimized ways to cross the blood-brain barrier. In fact, one key rationale behind obtaining tissue in patients with diffuse pontine lesions stems from recent work to further classify lesions based upon a number of identifiable genetic and molecular alterations that may render these tumors susceptible to targeted therapies [79-81].

Until the last couple of years, the biology of diffuse intrinsic brainstem tumours was entirely unknown. However, tissue analysis has now identified a number of identifiable genetic and molecular alterations — like amplification of receptor tyrosine kinases and cell-cycle regulatory genes, and alterations in membrane proteins and the Hedgehog (Hh) signaling pathway [79;105-109] — that could serve as therapeutic targets. Much of this research is being aided by the development of human glioma cell lines that can be studied in the lab [110]. One particular membrane protein that has garnered considerable recent interest is B7-H3 (also called CD276), a type I trans-membrane glycoprotein that is part of the B7-CD28 family [111]. This glycoprotein is known to interact with host defenses in certain cancers, being recognized by the monoclonal antibody 8H9 [112] that binds to a vast array of different tumours. Among primary brain tumors, for example, it bound to 15 of 17 glioblastomas, three of four mixed gliomas, and six of eight astrocytomas, among others; however, it did not bind to normal neurons or glial cells [113]. Moreover, extremely favourable results were observed in a study in which 21 children with recurrent stage IV neuroblastoma — like gliomas, a neuroectodermal tumor — were administered compartmental intra-thecal antibody-based radio-immunotherapy [114]. The therapy consisted of ^{131}I-monoclonal antibodies targeting B7-H3. Among the 21 children treated, 17 (81%) remained alive between seven and 74 months later (median 33 months), significantly longer than the expected, post-disease-recurrence median survival of six months. For all these reasons, the potential is there for B7-H3 to be a future therapeutic target for diffuse intrinsic brainstem gliomas. Considerable interest also has focussed on the epidermal growth factor receptor (EGFR), which has been the target of several chemotherapeutic drugs currently undergoing early phase trials, like gefitinib and erlotinib [115-117]. Another drug currently undergoing early phase testing is vandetanib, a tyrosine kinase inhibitor of both the EGFR and vascular endothelial growth factor receptor (VEGFR) [118]. To date, one-year survival rates have ranged from 38 to 56% [115-118], not significantly better than the median survival of 9 to 12 months reported elsewhere [79].

Promising results were observed when data were combined across four phase II trials [119] in which 18 mostly paediatric (age range 2 – 42 years, median=10) patients with brainstem gliomas were treated with anti-neoplaston A10 (A10I) and AS2-1 injections over a median of five months [120]. Fourteen of the 18 patients had diffuse intrinsic tumors; four were glioblastomas and 14 anaplastic gliomas. Prior to treatment, twelve patients had suffered a relapse and six had never received either radiation or chemotherapy. Contrary to the expected 2-year survival rate of roughly 10%, 39% remained alive at two years, and 22% at five years, including one patient with an anaplastic astrocytoma who remained alive for 17 years and another with a glioblastoma for more than five years. The only adverse event was a single case of reversible anaemia.

Another potential boon to the treatment of all CNS malignances may be the development of nanotherapeutic approaches, which include an entire new generation of novel targeted-

delivery devices — 'smart' nanoparticles — that facilitate the transfer of a variety of therapies, from drugs to thermotherapy, across the blood-brain barrier [121], a barrier that has traditionally hampered the delivery of most anti-neoplastic drugs. Stem cells that are themselves drawn to tumour cells are another potential vehicle that is being explored for the treatment of high-grade gliomas [122;123] and may have applications in the treatment of inoperable brainstem gliomas. Some investigators are also examining the potential to test the effectiveness of anti-neoplastic drugs *ex vivo* prior to patient administration via the use of *in vitro* assays [124]. In this way, drug regimens might be more appropriately taylorized to each patient, and *in vivo* drug effectiveness more accurately predicted prior to initiating therapy, thereby minimizing unnecessary toxicity and enhancing the likelihood of initial treatment response.

Finally, as mentioned earlier, advanced imaging techniques are now allowing for enhanced prospective monitoring of treatment response and the earlier detection of disease recurrence and progression [87;88]. Another previously-unexplored means by which to accomplish such monitoring might be via the analysis of various bodily fluids — like blood, urine and cerebrospinal fluid (CSF) — to identify and estimate levels of various CNS tumour markers, similar to how prostate-specific antigen (PSA) is being used to detect and monitor prostate cancer. For example, Saratsis et al. recently performed protein profiling by mass spectrometry of 76 specimens — including CSF, serum, urine, and normal and tumor brainstem tissue [125] — from 10 patients with diffuse intrinsic brainstem gliomas and four healthy controls. CSF proteomic analysis revealed selective up-regulation of both cyclophillin A (CypA) and dimethylarginase 1 (DDAH1) in patients relative to controls. Protein expression was validated further via Western blot analysis and immunohistochemical assays. Immunohistochemical staining exhibited selective up-regulation of secreted but not cytosolic CypA and DDAH1 in patients. The authors proposed that the detection of secreted CypA and DDAH1 in serum and urine could have clinical applications in the monitoring of treatment response and disease recurrence in patients with brainstem gliomas [125].

As such, although the prognosis for patients with inoperable brainstem gliomas remains bleak for the time being, beliefs regarding the potential for enhanced survival certainly are changing with the emergence of targeted therapies, better delivery systems, and enhanced imaging and other techniques to monitor disease regression and progression. But what will the neurosurgeon's role be in all this?

3.3. Emerging role of the neurosurgeon in the management of diffuse brainstem tumours

Nothing has changed in terms of neurosurgeons' reluctance to operate on diffuse intrinsic brainstem gliomas; nor does it seem likely to anytime soon, given the known aggressiveness of the vast majority of these tumours, their high degree of infiltration that would preclude anything more than partial resection, and the extreme risks of such surgery, given the anatomical compactness of vital structures and neural pathways. Consequently, the main change in current surgical practices relates to the stereotactic biopsy of these lesions, a practice that this year was formally recommended in a published, multi-disciplinary consensus statement concerning surgical approaches to low-and high-grade astrocytomas and diffuse intrinsic pontine gliomas in childhood [82].

There also has been a clear swing in the route selected for brainstem biopsy access, at least in studies involving paediatric patients. For example, over the decade of the nineteen nineties, 82% of reported brainstem biopsies were accessed via a trans-frontal route, versus just 18% trans-cerebellar. Since the year 2000, however, these percentages have completely reversed, with 82% of reported biopsies trans-cerebellar and 18% trans-frontal. In the five studies published since 2006 in which paediatric patients were identified among those biopsied [81;126-129], every one of the ninety biopsies were performed through the cerebellum. Across these ninety biopsies, 77 of them in children, there was one intra-operative complication (1.1%), nine post-operative complications (10%), two inconclusive biopsies (2.2%) and no deaths. The reason(s) for this shift in surgical approach is not entirely clear. In 2012, Dellaretti et al. published the results of their study comparing the two approaches over twenty-three years of practice (1984-2007), and no significant differences were noted [130]; however, whether any children were included within the sample of 142 patients is not stated in the manuscript. Moreover, there was a clear preference for trans-frontal biopsies, which were performed in 123 of the patients versus just 19 via the cerebellum, and no explanation for this preference was offered.

Cage et al. described their trans-cerebellar surgical approach in nine children with diffuse intrinsic brainstem tumours as follows [81]: "Preoperatively, patients all completed an MRI with and without gadolinium intravenous contrast of the brain according to Brainlab (Brainlab AG, Germany) protocols to allow for intraoperative neuronavigation. Patients were positioned either supine (n=3) or in the lateral decubitus position (n=6) opposite the side of their lesion with neck flexion in the same direction. The head was then fixed using both a horseshoe head-holding device and further immobilized with Mayfield pin fixation. For all stereotactic procedures, the Brainlab neuronavigation system was used to plan the trajectory from the skull to target locations in the brainstem. The biopsy entry point was transcerebellar, either right (n=4) or left (n=5) for all patients. A side-cutting biopsy needle was then passed along the trajectory path. Between one and four samples were obtained from within the lesion.... Target selection was designed to minimize the trajectory through the brainstem. If there was an obvious area of enhancement suggesting a pathologically-aggressive area of the tumour, then this was chosen as the biopsy target. Otherwise, the target was usually just deep to the cerebellar peduncle. Care was taken to avoid the lateral edge of the fourth ventricle and the ventral corticospinal tracts." [81]

Otherwise, surgeons continue to operate successfully on patients with focal, exophytic and cystic brainstem tumours, with survival and quality of life enhanced even by subtotal resections, as well as by cyst drainage procedures and the insertion of shunts when necessary [61]. But here too, stereotactic biopsies play a significant role, as some apparent tumours are found to be focal areas of inflammation, infectious lesions, vascular anomalies, or some other pathology necessitating different treatment [29;131]. As such, neurosurgeons now appear to have a role to play in all paediatric patients with brainstem tumours, a far cry from forty years ago, when they seemed to have no role at all.

4. Conclusions

Over the past forty years, much has changed in the way in which brainstem tumours are treated in children. Though these lesions continue to be the most common cause of CNS cancer-related death in the paediatric population, the discovery of a brainstem tumour is no longer a death sentence. Formerly thought to be pathologically homogeneous and/or of no pathological interest since they were not surgically accessible, paediatric brainstem tumours are now understood to be highly heterogeneous; and knowing the pathology is now considered critical to management decisions. For the minority of children who have focal, exophytic or cystic lesions, long-term survival is now the rule, with 5-and 10-year survival rates often 90% or higher. For those children in the future who will develop diffuse brainstem lesions, mostly high-grade gliomas, emerging therapies are now providing multiple reasons to hope. Besides providing competent, compassionate care to each child and their families, what is critical, from the current neurosurgeon's standpoint, is to assist in the collection of tissue, either by biopsy while a child is alive, or at autopsy via respectful conversations with parents and other caregivers, so that future targeted therapies can be developed, tested and ultimately approved for widespread use.

Author details

Adrianna Ranger[*], Navjot Chaudhary and Jonathan Lau

London Health Sciences Center-Department of Clinical Neurological Sciences; Division of Neurosurgery, Western University, London, Ontario, Canada

References

[1] Ellison LF, De P, Mery LS, Grundy PE, Canadian Cancer Society's Steering Committee for Canadian Cancer Statistics.: Canadian cancer statistics at a glance: cancer in children. CMAJ 2009;180:422-424.

[2] Bunin GR, Feuer EJ, Witman PA, Meadows AT: Increasing incidence of childhood cancer: report of 20 years experience from the greater Delaware Valley Pediatric Tumor Registry. Paediatr Perinat Epidemiol 1996;10:319-338.

[3] Linet MS, Ries LA, Smith MA, Tarone RE, Devesa SS: Cancer surveillance series: recent trends in childhood cancer incidence and mortality in the United States. J Natl Cancer Inst 1999;91:1051-1058.

[4] Centers for Disease Control and Prevention (CDC): Trends in childhood cancer mortality--United States, 1990-2004. MMWR Morb Mortal Wkly Rep 2007;56:1257-1261.

[5]   Rendon-Macias ME, Ramos-Becerril C, Bernadez-Zapata I, Iglesias-Leboreiro J: [Cancer epidemiology in children and adolescents at private health care (1995-2004)] [Article in Spanish]. Rev Med Inst Mex Seguro Soc 2008;46:353-360.

[6]   Barr RD, Greenberg ML, Shaw AK, Mery L: The Canadian Childhood Cancer Surveillance and Control Program (CCCSCP): a status report. Pediatr Blood Cancer 2008;50:518-519.

[7]   Stiller C: Population based survival rates for childhood cancer in Britain 1980-1991. BMJ 1994;309:1612-1616.

[8]   La Vecchia C, Levi F, Lucchini F, Lagiou P, Trichopoulos D, Negri E: Trends in childhood cancer mortality as indicators of the quality of medical care in the developed world. Cancer 1998;83:2223-2227.

[9]   Chatenoud L, Bertuccio P, Bosetti C, Levi F, Negri E, La Vecchia C: Childhood cancer mortality in America, Asia, and Oceania, 1970 through 2007. Cancer 2010;116:5063-5074.

[10] Dolecek TA, Propp JM, Stroup NE, Kruchko C: CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005-2009. Neuro Oncol 2012;14:1-49.

[11] Allen J: Brain stem glioma. Neurol Neurosurg Update Series 1983;2-7.

[12] Fisher PG, Carson BS: Management of brainstem gliomas in children. Contemp Neurosurg 1996;18:1-7.

[13] Walker DA, Punt JA, Sokal M: Clinical management of brain stem glioma. Arch Dis Child 1999;80:558-564.

[14] Russell DS, Rubenstein LJ: Pathology of Tumours of the Nervous System, ed Fourth Edition. Baltimore, Wilkins & Williams, 1977.

[15] Tumor Types. National Brain Tumor Society.

[16] Recinos PF, Sciubba DM, Jallo GI: Brainstem tumors: where are we today? Pediatr Neurosurg 2007;43:192-201.

[17] Shuper-A, Kornriech L, Loven D, Michowitz S, Schwartz S, Cohen IJ: Diffuse brain stem gliomas. Are we improving outcome? Childs Nerv Syst 1998;14:578-581.

[18] Freeman CR, Farmer JP: Pediatric brain stem gliomas: a review. Int J Radiat Oncol Biol Phys 1998;40:265-271.

[19] Laigle-Donadey F, Doz F, Delattre JY: Brainstem gliomas in children and adults. Curr Opin Oncol 2008;20:662-667.

[20] Mauffrey C: Paediatric brainstem gliomas: prognostic factors and management. J Clin Neurosci 2006;13:431-437.

[21] Matson D: Tumors of the posterior fossa.; in Thomas C (ed): Neurosurgery of Infancy and Childhood. Springfield, MA, Charles C. Thomas Publishing, 1969, pp 469-477.

[22] Gold JA, Smith KRJr: Childhood brain tumors: a 15-year survey. South Med J 1975;68:1337-1344.

[23] Klimo PJr, Pai Panandiker AS, Thompson CJ, Boop FA, Qaddoumi I, Gajjar A, et al.: Management and outcome of focal low-grade brainstem tumors in pediatric patients: the St. Jude experience. J Neurosurg Pediatr 2013;11:274-281.

[24] Lamm AF, Elaimy AL, Lamoreaux WT, MacKay AR, Fairbanks RK, Demakas JJ, Cooke BS, Lee CM: A review of the clinical outcomes for patients diagnosed with brainstem metastasis and treated with stereotactic radiosurgery. ISRN Surg 2013 Apr 11;2013:652895 doi: 10 1155/2013/652895 Print 2013.

[25] Duffner PK: Diagnosis of brain tumors in children. Expert Rev Neurother 2007;7:875-885.

[26] Albright AL, Pollack IF: Brainstem Gliomas; in Winn HD (ed): Youman's Neurological Surgery, Volume 3. Philadelphia, PA, Saunders, 2004, pp 3663-3669.

[27] Epstein F, Wisoff JH: Intrinsic brainstem tumors in childhood: surgical indications. J Neurooncol 1988;6:309-317.

[28] Pierre-Kahn A, Hirsch JF, Vinchon M, Payan C, Sainte-Rose C, Lelouch-Tubiana A, Fermanian J, et al.: Surgical management of brain-stem tumors in children: results and statistical analysis of 75 cases. J Neurosurg 1993;79:845-852.

[29] Pinero-Gonzalez de la Pena P, Rodriguez-Romero R: Nonglial tumors of the brainstem. Semin Ultrasound CT MR 2013;34:113-122.

[30] Bailey P, Buchanan DN, Buoy PC: Intracranial Tumors of Infancy and Childhood. Chicago, University of Chicago Press, 1939.

[31] Tomita T, McLone DG, Naidich TP: Brain stem gliomas in childhood. Rational approach and treatment. J Neurooncol 1984;2:117-122.

[32] Golden GS, Ghatak NR, Hirano A, French JH: Malignant glioma of the brain-stem. A clinicopathological analysis of 13 cases. J Neurol Neurosurg Psychiatry 1972;35:732-738.

[33] Greenberger JS, Cassady JR, Levene MB: Radiation therapy of thalamic, midbrain and brain stem gliomas. Radiology 1977;1:2-463.

[34] Lassiter KR, Alexander EJr, Davis CHJr, Kelly DLJr: Surgical treatment of brain stem gliomas. J Neurosurg 1971;34:719-725.

[35] Hara M, Takeuchi K: A temporal study of survival of patients with pontine gliomas. J Neurol 1977;216:189-196.

[36] Eisenhardt L: Long post-operative survivals in cases of intracranial tumor. Proc Ass Res Nerv Ment Dis 1937;16:390-416.

[37] Patton WB, Craig WM: Glioma of the pons: report of a case. Proc Staff Meet Mayo Clin 1940;15:506-508.

[38] Pool JL: Gliomas in the region of the brain stem. J Neurosurg 1968;29:164-167.

[39] Gilday DL, Ash J: Accuracy of brain scanning in pediatric craniocerebral neoplasms. Radiology 1975;117:93-97.

[40] Alvisi C, Cerisoli M, Maccheroni ME: Long-term results of surgically treated brain-stem gliomas. Acta Neurochir (Wien) 1985;76:12-17.

[41] Hoffman HJ, Becker L, Craven MA: A clinically and pathologically distinct group of benign brain stem gliomas. Neurosurgery 1980;7:243-248.

[42] Renier WO, Gabreels FJ: Evaluation of diagnosis and non-surgical therapy in 24 children with a pontine tumour. Neuropediatrics 1980;11:262-273.

[43] Epstein F: A staging system for brain stem gliomas. Cancer 1985;56:1806.

[44] Epstein F, McCleary EL: Intrinsic brain-stem tumors of childhood: surgical indications. J Neurosurg 1986;64:11-15.

[45] Stroink AR, Hoffman AJ, Hendrick EB, Humphreys RP, Davidson G: Transependymal benign dorsally exophytic brain stem gliomas in childhood: diagnosis and treatment recommendations. Neurosurgery 1987;20:439-444.

[46] Reigel DH, Scarff TB, Woodford JE: Biopsy of pediatric brain stem tumors. Childs Brain 1979;5:329-340.

[47] Strange P, Wohlert L: Primary brain stem tumours. Acta Neurochir (Wien) 2013;62:219-232.

[48] James AEJr: The efficacy of the brain scan in diagnosis of brainstem gliomas. Radiology 1975;116:117-120.

[49] Seeger JF, Gabrielsen TO: Angiography of eccentric brain stem tumors. Radiology 1972;105:343-351.

[50] Brnini FP, Calabro A, Corrado A, De Rosa G, Elefante R, Fucci G, et al.: [Radiological diagnosis of tumours of brain stem (author's transl)] [Article in Italian]. Radiol Med 1977;63:497-526.

[51] Baker HIJr, Howser OW: Computed tomography in the diagnosis of posterior fossa lesions. Radiol Clin North Am 1976;14:129-147.

[52] Gado M, Huete I, Mikhael M: Computerized tomography of infratentorial tumors. Semin Roentgenol 1977;12:109-120.

[53] Kazner E, Meese W, Kretzschmar K: The role of computed tomography in the diagnosis of brain tumors in infants and children. Neuroradiology 1978;16:10-12.

[54] Thomson JL: Computerised axial tomography in posterior fossa lesions. Clin Radiol 1978;29:233-250.

[55] Barkovich AJ, Krischer J, Kun LE, Packer R, Zimmerman RA, Freeman CR, et al.: Brain stem gliomas: a classification system based on magnetic resonance imaging. Pediatr Neurosurg 1990;16:73-83.

[56] Fischbein NJ, Prados MD, Wara W, Russo C, Edwards MS, Barkovich AJ: Radiologic classification of brain stem tumors: correlation of magnetic resonance imaging appearance with clinical outcome. Pediatr Neurosurg 1996;24:9-23.

[57] Choux M, Lena G, Do L: Brainstem tumors; in Choux M, Di Rocco C, Hockley A (eds): Pediatric Neurosurgery. New York, NY, Churchill Livingstone, 2000, pp 471-491.

[58] Albright AL: Brain stem gliomas; in J Y (ed): Neurological Surgery. Philadelphia, PA, Saunders, 1996, pp 2603-2611.

[59] Fisher PG, Breiter SN, Carson BS, Wharam MD, Williams JA, Weingart JD, et al.: A clinicopathologic reappraisal of brain stem tumor classification. Identification of pilocystic astrocytoma and fibrillary astrocytoma as distinct entities. Cancer 2000;89:1569-1576.

[60] Mehta VS, Chandra PS, Singh PK, Garg A, Rath GK: Surgical considerations for 'intrinsic' brainstem gliomas: proposal of a modification in classification. Neurol India 2009;57:274-281.

[61] Ramos A, Hilario A, Lagares A, Savador E, Perez-Nunez A, Sepulveda J: Brainstem gliomas. Semin Ultrasound CT MR 2013;34:104-112.

[62] Fasano VA, Urciuoli R, Ponzio RM, Lanotte MM: The effects of new technologies on the surgical management of brainstem tumors. Surg Neurol 1986;25:219-226.

[63] Teo C, Siu TL: Radical resection of focal brainstem gliomas: is it worth doing? Childs Nerv Syst 2008;24:1307-1314.

[64] Dellaretti M, Reyns N, Touzet G, Dubois F, Gusmao S, Pereira JL, Blond S: Diffuse brainstem glioma: prognostic factors. J Neurosurg 2012;117:810-814.

[65] Poussaint TY, Kowal JR, Barnes PD, Zurakowski D, Anthony DC, Goumnerova L, Tarbell NJ: Tectal tumors of childhood: clinical and imaging follow-up. AJNR Am J Neuroradiol 1998;19:977-983.

[66] Milstein JM, Geyer JR, Berger MS, Bleyer WA: Favorable prognosis for brainstem gliomas in neurofibromatosis. J Neurooncol 1989;7:367-371.

[67] Cohen ME, Duffner PK, Heffner RR, Lacey DJ, Brecher M: Prognostic factors in brainstem gliomas. Neurology 1986;36:602-605.

[68] Blatt J, Jaffe R, Deutsch M, Adkins JC: Neurofibromatosis and childhood tumors. Cancer 1986;57:1225-1229.

[69] Ilgren EB, Kinnier-Wilson LM, Stiller CA: Gliomas in neurofibromatosis: a series of 89 cases with evidence for enhanced malignancy in associated cerebellar astrocytomas. Pathol Annu 1985;20:331-358.

[70] Pascual-Castroviejo I, Pascual-Pascual SI, Viano J, Carceller F, Gutierrez-Molina M, Morales C, Frutos-Martinez R: Posterior fossa tumors in children with neurofibromatosis type 1 (NF1). Childs Nerv Syst 2010;26:1599-1603.

[71] Albers AC, Guttman DH: Gliomas in patients with neurofibromatosis type 1. Expert Rev Neurother 2009;9:535-539.

[72] Fried I, Hawkins C, Scheinemann K, Tsangaris E, Hesselson L, Bartels U, et al.: Favorable outcome with conservative treatment for children with low grade brainstem tumors. Pediatr Blood Cancer 2012;58:556-560.

[73] Hottinger AF, Khakoo Y: Neuro-oncology of Neurofibromatosis Type 1. Curr Treat Options Neurol 2009;11:306-314.

[74] Lopes Ferraz Filho JR, Munis MP, Soares Souza A, Sanches RA, Goloni-Bertollo EM, Pavarino-Bertelli EC: Unidentified bright objects on brain MRI in children as a diagnostic criterion for neurofibromatosis type 1. Pediatr Radiol 2008;38:305-310.

[75] Leonard JR, Perry A, Rubin JB, et al.: The role of surgical biopsy in the diagnosis of glioma in individuals with neurofibromatosis-1. Neurology 2006;67:1509-1512.

[76] Lesniak MS, Klem JM, Weingart J, Carson BSSr: Surgical outcome following resection of contrast-enhanced pediatric brainstem gliomas. Pediatr Neurosurg 2003;39:314-322.

[77] Sandri A, Sardi N, Genitori L, Giordano F, Peretta P, Basso ME, et al.: Diffuse and focal brain stem tumors in childhood: prognostic factors and surgical outcome. Experience in a single institution. Childs Nerv Syst 2006;22:1127-1135.

[78] Tokurika Y, Handa H, Yamashita J, Okumura T, Paine JT: Brainstem glioma: an analysis of 85 cases. Acta Neurochir (Wien) 1986;79:67-73.

[79] Jansen MH, van Vuurden DG, Vandertop WP, Kaspers GJ: Diffuse intrinsic pontine gliomas: a systematic update on clinical trials and biology. Cancer Treat Rev 2012;38:27-35.

[80] Hargrave D, Bartels U, Bouffet E: Diffuse brainstem glioma in children: critical review of clinical trials. Lancet Oncol 2006;7:241-248.

[81] Cage TA, Samagh SP, Mueller S, Nocolaides T, Haas-Kogan D, Prados M, et al.: Feasibility, safety, and indications for surgical biopsy of intrinsic brainstem tumors in children. Childs Nerv Syst 2013;29:1313-1319.

[82] Walker DA, Liu J, Kieran M, Jabado N, Picton S, Packer R, St.Rose C, CPN Paris 2011 Conference Consensus Group: A multi-disciplinary consensus statement concerning surgical approaches to low-grade, high-grade astrocytomas and diffuse intrinsic pontine gliomas in childhood (CPN Paris 2011) using the Delphi method. Neuro Oncol 2013;15:462-468.

[83] Wagner S, Warmuth-Metz M, Emser A, Gnekow AK, Strater R, Rutkowski S, et al.: Treatment options in childhood pontine gliomas. J Neurooncol 2006;79:281-287.

[84] Mann SD, Danesh BJ, Kamm MA: Intractable vomiting due to a brainstem lesion in the absence of neurological signs or raised intracranial pressure. Gut 1998;42:875-877.

[85] Guillamo JS, Doz F, Delattre JY: Brain stem gliomas. Curr Opin Neurol 2001;711.

[86] Jallo GI, Biser-Rohrbaugh A, Freed D: Brainstem gliomas. Childs Nerv Syst 2004;20:143-153.

[87] Laprie A, Pirzkall A, Haas-Kogan DA, Cha S, Banerjee A, Le TP, et al.: Longitudinal multivoxel MR spectroscopy study of pediatric diffuse brainstem gliomas treated with radiotherapy. Int J Radiat Oncol Biol Phys 2005;62:20-31.

[88] Barajas RF, Chang JS, Sneed PK, Segal MR, McDermott MW, Cha S: Distinguishing recurrent intra-axial metastatic tumor from radiation necrosis following gamma knife radiosurgery using dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging. AJNR Am J Neuroradiol 2009;30:367-372.

[89] Thakur SB, Karimi S, Dunkel IJ, Koutcher JA, Huang W: Longitudinal MR spectroscopic imaging of pediatric diffuse pontine tumors to assess tumor aggression and progression. AJNR Am J Neuroradiol 2006;27:806-809.

[90] Porto L, Hattingen E, Pilatus U, Kieslich M, Yan B, Schwabe D, et al.: Proton magnetic resonance spectroscopy in childhood brainstem lesions. Childs Nerv Syst 2007;23:305-314.

[91] Kovacs A, Toth L, Glavak C, Liposits G, Hadjiev J, Antal G, Emri M, et al.: Integrating functional MRI information into conventional 3D radiotherapy planning of CNS tumors. Is it worth it? J Neurooncol 2011;105:629-637.

[92] Pirotte B, Acerbi F, Lubansu A, Goldman S, Brotchi J, Leviver M: PET imaging in the surgical management of pediatric brain tumors. Childs Nerv Syst 2007;23:739-751.

[93] Leitch JK, Figley CR, Stroman PW: Applying functional MRI to the spinal cord and brainstem. Magn Reson Imaging 2010;28.

[94] Nadvi SS, Ebrahim FS, Corr P: The value of 201thallium-SPECT imaging in childhood brainstem gliomas. Pediatr Radiol 1998;28:575-579.

[95] Oriuchi N, Tamura M, Shibazaki T, Ohye C, Watanabe N, Tateno M, Tomiyoshi K, et al.: Clinical evaluation of thallium-201 SPECT in supratentorial gliomas: relationship to histologic grade, prognosis and proliferative activities. J Nucl Med 1993;34:2085-2089.

[96] Adams WS: Investigations in Stellar Spectroscopy: III. Application of a Spectroscopic Method of Determining Stellar Distances to Stars of Measured Parallax. Proc Natl Acad Sci U S A 1916;2:152-157.

[97] Carr JJ, Hemler PF, Halford PW, Freimanis RI, Choplin RH, Chen MY: Stereotactic localization of breast lesions: how it works and methods to improve accuracy. Radiographics 2001;21:463-473.

[98] Becker W: Stereotactic localization of breast lesions. Radiology 1979;133:238-240.

[99] Lewander R, Bergstrom M, Boethius J, Collins VP, Edner G, Greitz T, Willems J: Stereotactic computer tomography for biopsy of gliomas. Acta Radiol Diagn (Stockh) 1978;19:867-888.

[100] Boethius J, Collins VP, Edner G, Lewander R, Zajicek J: Stereotactic biopsies and computer tomography in gliomas. Acta Neurochir (Wien) 1978;40:223-232.

[101] Coffey RJ, Lunsford LD: Stereotactic surgery for mass lesions of the midbrain and pons. Neurosurgery 1985;17:12-18.

[102] Rajshekhar V, Chandy MJ: Computerized tomography-guided stereotactic surgery for brainstem masses: a risk-benefit analysis in 71 patients. J Neurosurg 1995;82:976-981.

[103] Kondziolka D, Lunsford LD: Results and expectations with image-integrated brainstem stereotactic biopsy. Surg Neurol 1995;43:558-562.

[104] Rachinger W, Grau S, Holtmannspotter M, Herms J, Tonn JC, Kreth FW: Serial stereotactic biopsy of brainstem lesions in adults improves diagnostic accuracy compared with MRI only. J Neurol Neurosurg Psychiatry 2009;80:1134-1139.

[105] Paugh BS, Qu C, Jones C, Liu Z, Adamowicz-Brice M, Zhang J, et al.: Integrated molecular genetic profiling of pediatric high-grade gliomas reveals key differences with the adult disease. J Clin Oncol 2010;28:3061-3068.

[106] Paugh BS, Broniscer A, Qu C, Miller CP, Zhang J, Tatevossian RG, et al.: Genome-wide analyses identify recurrent amplifications of receptor tyrosine kinases and cell-cycle regulatory genes in diffuse intrinsic pontine glioma. J Clin Oncol 2011;29:3999-4006.

[107] Monje M, Mitra SS, Freret ME, Raveh TB, Kim J, Masek M, et al.: Hedgehog-responsive candidate cell of origin for diffuse intrinsic pontine glioma. Proc Natl Acad Sci U S A 2011;108:4453-4458.

[108] Zhou Z, Luther N, Ibrahim GM, Hawkins C, Vibhakar R, Handler MH, Souweidane MM: B7-H3, a potential therapeutic target, is expressed in diffuse intrinsic pontine glioma. J Neurooncol 2013;111:257-264.

[109] Puget S, Philippe C, Bax DA, Job B, Varlet P, Junier MP, et al.: Mesenchymal transition and PDGFRA amplification/mutation are key distinct oncogenic events in pediatric diffuse intrinsic pontine gliomas. PLoS One 2012;7:e30313.

[110] Hashizume R, Smirnov I, Liu S, Phillips JJ, Hyer J, McKnight TR, et al.: Characterization of a diffuse intrinsic pontine glioma cell line: implications for future investigations and treatment. J Neurooncol 2012;110:305-313.

[111] Chapoval AI, Ni J, Lau JS, Wilcox RA, Flies DB, Liu D, et al.: B7-H3: a costimulatory molecule for T cell activation and IFN-gamma production. Nat Immunol 2001;2:269-274.

[112] Xu H, Cheung IY, Guo HF, Cheung NK: MicroRNA miR-29 modulates expression of immunoinhibitory molecule B7-H3: potential implications for immune based therapy of human solid tumors. Cancer Res 2009;69:6275-6281.

[113] Modak S, Kramer K, Gultekin SH, Guo HF, Cheung NK: Monoclonal antibody 8H9 targets a novel cell surface antigen expressed by a wide spectrum of human solid tumors. Cancer Res 2001;61:4048-4054.

[114] Kramer K, Kushner BH, Modak S, Pandit-Taskar N, Smith-Jones P, Zanzonico P, et al.: Compartmental intrathecal radioimmunotherapy: results for treatment for metastatic CNS neuroblastoma. J Neurooncol 2010;97:409-418.

[115] Geoerger B, Hargrave D, Thomas F, Ndiaye A, Frappaz D, Andreiuolo F, et al.: Innovative Therapies for Children with Cancer pediatric phase I study of erlotinib in brainstem glioma and relapsing/refractory brain tumors. Neuro Oncol 2011;13:109-118.

[116] Geyer JR, Stewart CF, Kocak M, Broniscer A, Phillips P, Douglas JG, et al.: A phase I and biology study of gefitinib and radiation in children with newly diagnosed brain stem gliomas or supratentorial malignant gliomas. Eur J Cancer 2010;46:3287-3293.

[117] Pollack IF, Stewart CF, Kocak M, Poussaint TY, Broniscer A, Banerjee A, et al.: A phase II study of gefitinib and irradiation in children with newly diagnosed brainstem gliomas: a report from the Pediatric Brain Tumor Consortium. Neuro Oncol 2011;13:290-297.

[118] Broniscer A, Baker JN, Tagen M, Onar-Thomas A, Gilbertson RJ, Davidoff AM, et al.: Phase I study of vandetanib during and after radiotherapy in children with diffuse intrinsic pontine glioma. J Clin Oncol 2010;28:4762-4768.

[119] Burzynski SR: The present state of antineoplaston research (1). Integr Cancer Ther 2004;3:47-58.

[120] Burzynski SR, Janicki TJ, Weaver RA, Burzynski B: Targeted therapy with antineoplastons A10 and AS2-1 of high-grade, recurrent, and progressive brainstem glioma. Integr Cancer Ther 2006;5:40-47.

[121] Del Burgo LS, Hernandez RM, Orive G, Pedraz JL: Nanotherapeutic approaches for brain cancer management. Nanomedicine 2013 Oct 14 pii: S1549-9634(13)00555-8 doi: 10 1016/j nano 2013 10 001 [Epub ahead of print] 2013.

[122] Binello E, Germano IM: Stem cells as therapeutic vehicles for the treatment of high-grade gliomas. Neuro Oncol 2012;14:256-265.

[123] Kosztowski T, Zaida HA, Quinones-Hinojosa A: Applications of neural and mesenchymal stem cells in the treatment of gliomas. Expert Rev Anticancer Ther 2009;9:597-612.

[124] Costello PC, MacDonald D, McDonald R, Hammond R, Sloby V, Faubert B, Megyesi J: Determination of human brain tumour therapy response using an ex vivo invasion assay provides a potential step toward individualized treatment. J Clin Oncol 2006;24:18S.

[125] Saratsis AM, Yadavilli S, Magge S, Rood BR, Perez J, Hill DA, et al.: Insights into pediatric diffuse intrinsic pontine glioma through proteomic analysis of cerebrospinal fluid. Neuro Oncol 2012;14:547-560.

[126] Perez-Gomez JL, Rodriguez-Alvarez CA, Marhx-Bracho A, Rueda-Franco F: Stereotactic biopsy for brainstem tumors in pediatric patients. Childs Nerv Syst 2010;26:29-34.

[127] Patel P, Balamurugan M: Transcerebellar stereotactic biopsy for brainstem lesions in children. J Pediatr Neurosci 2009;4:17-19.

[128] Sanai N, Wachorst SP, Gupta NM, McDermott MW: Transcerebellar stereotactic biopsy for lesions of the brainstem and peduncles under local anesthesia. Neurosurgery 2008;63:460-466.

[129] Roujeau T, Machado G, Garnett MR, Miquel C, Puget S, Geoerger B, et al.: Stereotactic biopsy of diffuse pontine lesions in children. J Neurosurg 2007;107:1-4.

[130] Dellaretti M, Reyns N, Touzet G, Dubois F, Gusmao S, Pereira JL, Blond S: Stereotactic biopsy for brainstem tumors: comparison of transcerebellar with transfrontal approach. Stereotact Funct Neurosurg 2012;90:79-83.

[131] Valdez-Gorcia J, Espinoza-Diaz DM, Paredes-Diaz E: Stereotactic biopsy of brain stem and posterior fossa lesions in children. Acta Neurochir (Wien) 1998;140:899-903.