



Analysis of safe entry zones into the brainstem

Yang Yang¹ · Bas van Niftrik¹ · Xiangke Ma¹ · Julia Velz¹ · Sophie Wang¹ · Luca Regli¹ · Oliver Bozinov¹

Received: 28 September 2018 / Revised: 9 December 2018 / Accepted: 21 January 2019 / Published online: 6 February 2019
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

Abstract

Intra-axial brainstem surgeries are challenging. Many experience-based “safe entry zones (SEZs)” into brainstem lesions have been proposed in the existing literature. The evidence for each one seems limited. English-language publications were retrieved using PubMed/MEDLINE. Studies that focused only on cadaveric anatomy were also included, but the clinical case number was treated as zero. The clinical evidence level was defined as “case report” when the surgical case number was ≤ 5 , “limited evidence” when there were more than 5 but less than 25 cases, and “credible evidence” when a publication presented more than 25 cases. Twenty-five out of 32 publications were included, and 21 different SEZs were found for the brainstem: six SEZs were located in the midbrain, 9 SEZs in the pons, and 6 SEZs in the medulla. Case report evidence was found for 10 SEZs, and limited evidence for 7 SEZs. Four SEZs were determined to be backed by credible evidence. The proposed SEZs came from initial cadaveric anatomy studies, followed by some published clinical experience. Only a few SEZs have elevated clinical evidence. The choice of the right approach into the brainstem remains a challenge in each case.

Keywords Brainstem lesions · Surgical safe entry zone · Evidence level

Introduction

The brainstem contains a dense concentration of nuclei and fibers that make it difficult to operate in this area. Historically, surgical eradication of intrinsic brainstem lesions, like focal gliomas, cavernous malformations, etc., has been controversial. In 1939, Bailey et al. [6] described this topic as “a pessimistic chapter” in the history of neurosurgery. For a long time and with few exceptions, the natural history of these lesions meant a steady progression to death. However, CT scanning and MRIs, along with the development of diverse treatments such as cyst aspiration, partial resection, and radiotherapy, prolonged survivals [9, 35]. In 1971, Lassiter et al. were among the first to advocate surgical intervention for brainstem lesions [29]. After that point, favorable outcomes were reported with radical removals of intrinsic brainstem gliomas [4, 13]. In the last two decades, improvements in neuroimaging, microsurgical techniques, and electrophysiological monitoring and mapping, in combination with more detailed

knowledge of regional and functional anatomy, have made this region more accessible for direct surgery.

However, intrinsic brainstem lesions remain difficult to treat with surgical interventions because of their relatively high morbidity and mortality rates. Recent studies show an overall morbidity rate of 20–50% for new or worsened neurological deficits after brainstem tumor surgery [16, 18]. Mortality rates are rarely published, but are assumed to be elevated. Some brainstem cavernoma series demonstrated mortality rates of 2–10% [2, 30, 33, 40].

Multiple safe entry zones (SEZs) and surgical approaches have been proposed as means of optimizing the resection of brainstem lesions, particularly deep-seated, and minimizing the manipulation and disruption of any eloquent parenchyma. However, many of the SEZs come from anatomical research and sporadic case reports, which means the evidence supporting them is limited. This study aims to summarize all the published anatomic brainstem SEZs and to establish an evidence level for each of them.

✉ Oliver Bozinov
Oliver.Bozinov@usz.ch

¹ Department of Neurosurgery, University Hospital of Zurich, Frauenklinikstrasse 10, 8091 Zurich, Switzerland

Materials and methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram was used as

guidance for this study [31]. English-language publications were retrieved through PubMed/MEDLINE searches, using the subject terms “brainstem (safe) entry zone/point,” “brainstem treatment zone/point,” and “brainstem surgery (cavernous malformation, tumor/gliomas, hemorrhage) zone/point.” All references in these publications were checked for SEZs if they were not shown in the initial search. Studies that only focused on cadaveric anatomy were also included in this study, but their clinical case number was treated as zero. Clinical studies without detailed descriptions of the selected entry zones were excluded. We looked for SEZs in the midbrain, pons, and medulla oblongata. All sides (anterior to posterior) were included.

We preferred the Oxford Centre for Evidence-Based Medicine scale, (<https://www.cebm.net/index.aspx?o=5653>), but only levels 4 and 5 fit our results. Therefore, we defined specific evidence levels for the SEZs. The smallest evidence level, used when the surgical case number was ≤ 5 , was “case reports.” “Limited evidence” was used when the number of cases was more than 5 and less than 25, and “credible evidence” was used when there were more than 25 cases. Clinical cases for each entry zone were also checked to find out how many neurosurgical centers used that zone.

Results

A total of 25 publications were included, and 21 separate SEZs were found for the brainstem (Figs. 1, 2, 3, and 4). Six SEZs were located in the midbrain, 9 SEZs in the pons, and 6 SEZs in the medulla (Figs. 2, 3, and 4). Case report evidence was found for 10 SEZs, limited evidence for 7 SEZs, and credible evidence for 4 SEZs (Fig. 5a). Most of them were used in less than two neurosurgical centers (Fig. 5b, all references are in Tables 1, 2, and 3).

Midbrain

From the dorsal to the ventral site of the midbrain, the proposed SEZs are as follows (Table 1):

1. Supracollicular/infracollicular (SC/IC) zones—credible evidence
The SC/IC SEZs, proposed in 2000, are described as horizontal strips lying just above or below the quadrigeminal tubercles, namely, the superior colliculus and inferior colliculus (Fig. 4). Further authors reported 47 clinical cases that were operated on through the SC/IC SEZs without mortality.
2. Intercollicular region (ICR)—case reports
Although it contains sparse fibers, the median intercollicular approach was still proposed as a SEZ.

This approach requires a vertical incision in the quadrigeminal tubercles (Fig. 2). One study reported that it may result in less morbidity than the SC/IC zones, but this SEZ was only used in one case.

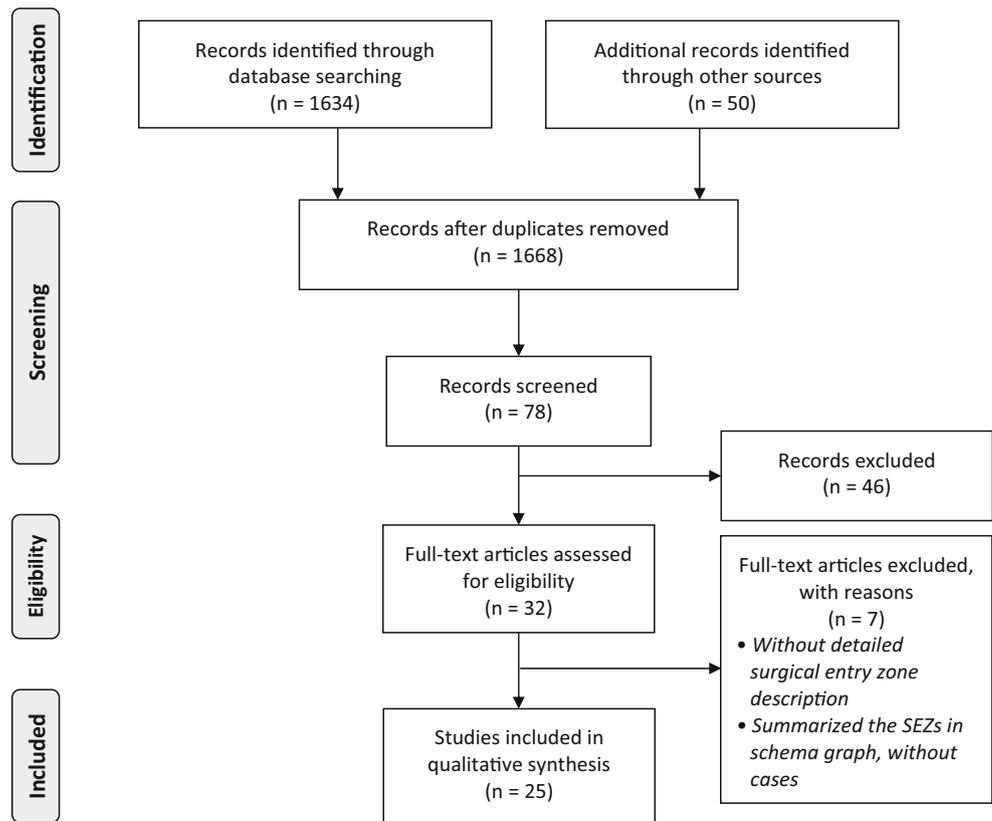
3. Lateral mesencephalic sulcus (LMS)—limited evidence
Lesions located laterally in the midbrain can be approached through the LMS (Fig. 3). It runs between the substantia nigra anterolaterally and the medial lemniscus posteriorly. The average length of the entry zone, extending from the medial geniculate body to the pontomesencephalic sulcus, is 9.6 mm (the acceptable range is from 7.4 to 13.3 mm), with an average depth of 8.0 mm (the acceptable range is from 4.9 to 11.7 mm). Thirteen clinical cases involving operations through the LMS were reported.
4. Inferior brachial triangle (IBT)—case reports
The IBT is bordered caudally by the trochlear nerve fibers inside the midbrain, laterally by the spinothalamic tract, and rostrally by the caudal margin of the brachium of the superior colliculus (Fig. 2). There were four reported clinical cases in which it was used as an access point.
5. Anterior mesencephalic (AM) zone—limited evidence
Also known as the *periolomotor zone*, this was firstly described as a “fairly safe” entry space in 1995. In previous studies, it was defined superiorly by the posterior cerebral artery, inferiorly by the superior cerebellar artery, and laterally by the pyramidal tract (Fig. 3). There were a total of 13 detailed reports of clinical cases involving operations via the AM zone.
6. Interpeduncular fossa (IPF) zone—case reports
The interpeduncular fossa extends laterally to the oculomotor nerves. It is suggested as an alternative way of AM entry point for lesions located ventrally and midline to the oculomotor nerve nucleus (Fig. 2). This SEZ is newly reported after two clinical case applications, as well as some cadaveric anatomy cases.

Pons

The proposed SEZs from the dorsal to the ventral site are as follows (Table 2):

1. Superior fovea (SFo) zone—case reports
The SFo entry zone is just at the level of the facial colliculus, located in the inferior half of the superior fovea triangle, lateral to the facial colliculus (Fig. 2). There was one reported clinical case involving this entry zone.
2. Suprafacial (SF) zone—credible evidence

Fig. 1 PRISMA flow diagram summarizing the search and selection of the articles



The superfacial and infrafacial triangle zones were first proposed in 1993, in a study that only considered one case. A total of 58 clinical cases have been reported since (Fig. 4).

3. Infrafacial (IF) zone—credible evidence

Multiple studies showed that following the first report in 1993, a total of 33 clinical cases were treated through the IF zone (Fig. 4).

4. Median sulcus (MS) zone—case reports

The MS zone is described as an entry point just above facial colliculi in the floor of the fourth ventricle without crossing fibers at this level (Fig. 2). Only two published cases involving entry through this zone were found.

5. Area acustica (AA) zone—case reports

The area acustica was first described as a relatively safe entry zone into the dorsal brainstem in 2000 (Fig. 2). However, the authors did not provide any detail about clinical cases that used this entry zone.

Fig. 2 Case reports (clinical case numbers ≤ 5). ICR intercollicular region, IBT inferior brachial triangle, IPF interpeduncular fossa zone, MS median sulcus (above facial colliculi), SFo superior fovea triangle, AA acoustic area, FP floccular peduncle, PIS posterior intermediate sulcus, LM lateral medullary zone, ALS anterolateral (preolivary) sulcus zone, PLS posterior lateral (postolivary) sulcus zone, also called the retro-olivary entry zone

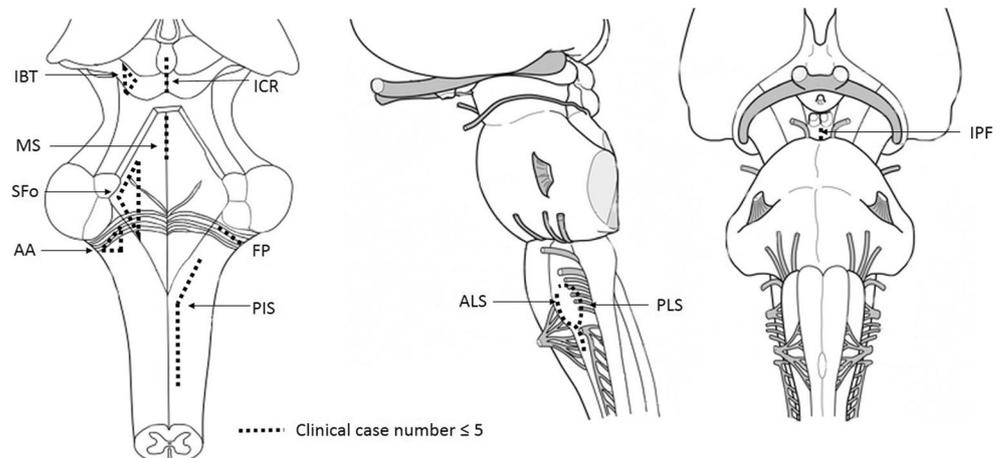
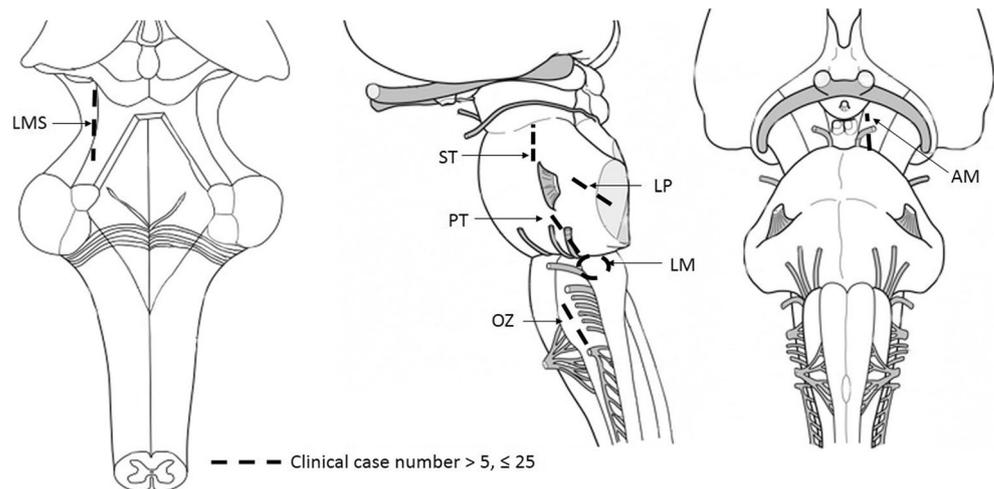


Fig. 3 Limited evidence (clinical case numbers $> 5, \leq 25$). LMS lateral mesencephalic sulcus, AM anterior mesencephalic (periculomotor) zone, ST supratrigeminal zone, LP lateral pontine (middle cerebellar peduncle) zone, PT peritrigeminal zone, OZ olivary zone



6. Floccular peduncle (FP)—case reports

The floccular peduncle was identified first in 2017, in a study that examined 10 cadaveric heads, but no clinical case published (Fig. 2).

7. Supratrigeminal (ST) zone—limited evidence

The supratrigeminal zone is located just above the root of the trigeminal nerve (CN V) on the middle cerebellar peduncle (Fig. 3). Six clinical cases using this entry zone were reported.

8. Peritrigeminal (PT) zone—limited evidence

The peritrigeminal entry point is bordered superiorly by the CN V and inferiorly by the facial and vestibulocochlear nerve

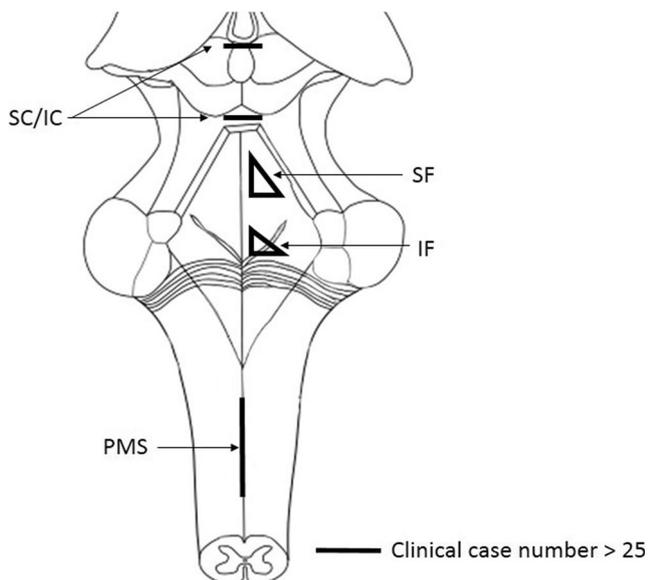


Fig. 4 Credible evidence (clinical case numbers > 25). SC/IC supracollicular/infracollicular, SF superafacial triangle zone, IF infrafacial triangle zone, PMS posterior median sulcus

(CNs VII and VIII) complex (Fig. 3). There were 19 clinical cases in which this entry zone was used, and the results were described in detail.

9. Lateral pontine (LP) zone—limited evidence

The lateral pontine zone, also known as *middle cerebellar peduncle zone*, is described as a safe corridor on the junction between the cerebellum and the pons (Fig. 3). There were a total of 10 reported clinical cases in which it was used as a SEZ.

Medulla

The existing safe entry zones (SEZs) from the dorsal to the ventral site are as follows (Table 3):

1. Posterior median sulcus (PMS)—credible evidence

The PMS lies below the obex. It is restricted laterally by the gracile fasciculus, which covers the gracile nucleus (Fig. 4). In 2015, there were 45 reported clinical cases involving this entry zone, and 3 deaths. Two other studies reported each one case using the PMS approach in 2002 and 2010.

2. Posterior intermediate sulcus (PIS)—case reports

The PIS entry zone is located between the gracile and cuneate fasciculi (Fig. 2). One clinical case involving this entry zone was reported in 1991.

3. Lateral medullary (LM) zone—limited evidence

The LM zone, also known as the *inferior cerebellar peduncle zone*, is located in the inferior cerebellar peduncle, inferior to the cochlear nuclei, and posterior to the origin of CNs IX and X (Fig. 2). A total of eight clinical cases involving the LM zone were reported in two studies in 2014. A further study reported 1 clinical case and 4 cadaveric anatomy dissections in 2017.

Fig. 5 a Evidence level classification, based on the clinical case number for each entry zone. Case reports, clinical case number ≤ 5 . Limited evidence, clinical case number $> 5, \leq 25$. Credible evidence, clinical case number > 25 . Abbreviations of SEZs are listed in Figs. 2, 3, and 4. **b** Clinical cases come from different neurosurgical centers. The vertical axis shows the number of neurosurgical centers, and the horizontal axis displays all published safe entry zones. Abbreviations of SEZs are listed in Figs. 2, 3, and 4

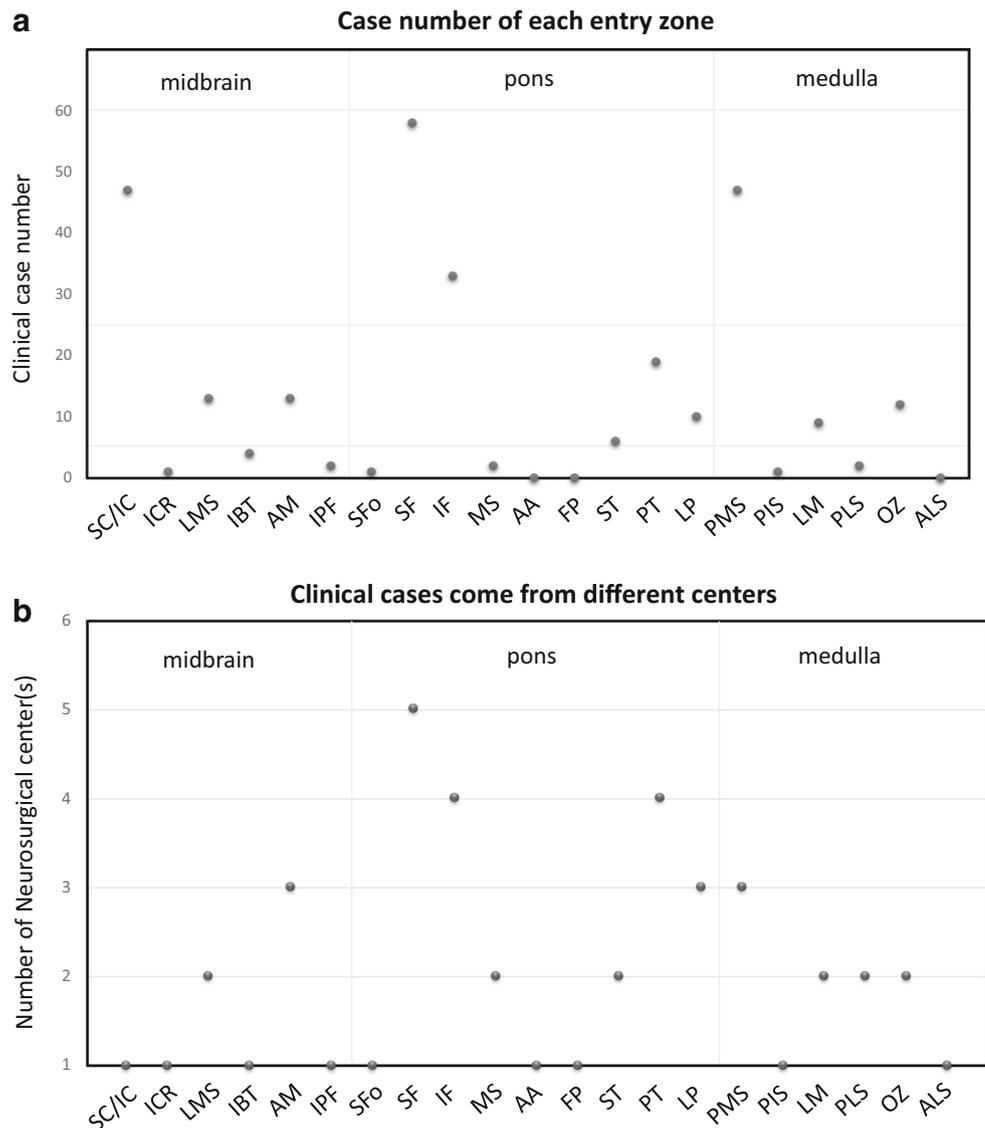


Table 1 Summary of each entry zone in the midbrain

Entry point	First author	Year	Case number
SC/IC	Cavalheiro S [16]	2015	47
ICR	Kalani MY [24]	2016	1
LMS	Cavalheiro S [16]	2015	1
	Kalani MY [24]	2016	12
IBT	Ishihara H [23]	2006	4
AM	Bricolo A [12]	1995	2
	Cavalheiro S [16]	2015	10
	Kalani MY [24]	2016	1
IPF	Kalani MY [26]	2018	2

Abbreviations of SEZs are listed in Figs. 2, 3, and 4

4. Posterior lateral sulcus (PLS) zone—case reports

The PLS entry zone, known as *postolivary sulci* or *retro-olivary sulcus*, is located laterally to the cuneate fasciculus. It could be an alternative to the PIS entry zone in cases where lateral access to lesions is required (Fig. 2). Although many studies mentioned it, only two clinical cases were reported in detail.

5. Olivary zone (OZ)—limited evidence

The olive is an oval prominence on the anterolateral surface of the medulla. It could be a safe entry point, with a depth ranging from 4.7 to 6.9 mm and a length of 13.5 mm (Fig. 3). There were a total of 12 reported clinical cases involving operations through the OZ entry zone.

6. Anterolateral sulcus (ALS) zone—case reports

The ALS entry zone, also known as the preolivary sulci zone, is defined as a short space between the rootlets of

Table 2 Summary of each entry zone in the pons

Entry point	First author	Year	Case number
SFo	Yagmurlu K [38]	2017	1
SF	Kyoshima K [28]	1993	1
	Strauss C [37]	1999	7
	Bertalanffy H [7]	2002	3
	Kumar R [27]	2004	2
	Cavalheiro S [16]	2015	45
IF	Kyoshima K [28]	1993	2
	Strauss C [37]	1999	13
	Bertalanffy H [7]	2002	2
MS	Cavalheiro S [16]	2015	16
	Bertalanffy H [7]	2002	1
	Kumar R [27]	2004	1
AA	Bricolo A [11]	2000	0
FP	Akiyama O [3]	2017	0
ST	Bertalanffy H [7]	2002	3
	Cavalheiro S [16]	2015	3
PT	Bertalanffy H [7]	2002	1
	Giliberto G [20]	2010	1
	Hauck EF [21]	2010	9
	Cavalheiro S [16]	2015	8
LP	Bertalanffy H [7]	2002	6
	Hebb MO [22]	2010	1
	Kalani MY [24]*	2016	2
	Kalani MY [25]*	2016	1

Abbreviations of SEZs are listed in Figs. 2, 3, and 4

*From the same center

CN XII and the C1 nerve rootlets (Fig. 2). This entry zone is preferred for exophytic lesions because of its superficial position and close compagination of the pyramidal tract.

Table 3 Summary of each entry zone in the medulla

Entry point	First author	Year	Case number
PMS	Bertalanffy H [7]	2002	1
	Giliberto G [20]	2010	1
	Cavalheiro S [16]	2015	45
PIS	Giliberto G [20]	2010	1
LM	Deshmukh VR [17]*	2014	4
	Bozkurt B [10]*	2017	1
	Abla AA [1]	2014	4
PLS	Bertalanffy H [7]	2002	1
	Giliberto G [20]	2010	1
OZ	Bertalanffy H [7]	2002	1
	Cavalheiro S [16]	2015	11
ALS	Yagmurlu K [39]	2014	0

Abbreviations of SEZ are listed in Figs. 2, 3, and 4

*From the same center

However, only 15 cadaveric heads were studied; there have been no relevant clinical cases reported.

Discussion

The direct surgical approach to brainstem lesions is discouraged by the fundamental fact that any manipulation, no matter how delicate, in the brainstem area will lead to high morbidity rates and significant mortality rate. A previous study indicates a mortality rate of up to 60% [13]. Safe entry zones are the regions in the brainstem surface where incisions could be done with acceptable outcomes, because of the sparse character of eloquent structures in these areas [26]. The concept of safe approaches into the brainstem for either tumor resection or biopsy emerged in the 1990s. In 1982, Baghai et al. [5] reported a safe approach from the ventrolateral portion of the pons, which was only used for biopsy. In 1993, Kyoshima et al. [28] reported two safe entry zones in the floor of the 4th ventricle. Then, in 1995, Bricolo and Turazzi introduced five relatively safe entry zones into the dorsal brainstem [12].

Twenty-one different SEZs for brainstem surgery have been identified before now (Figs. 2, 3, 4, and 5a and Tables 1, 2, and 3). According to “the Oxford Levels of Evidence 2” issued by the OCEBM Levels of Evidence Working Group, the existing evidence for those SEZs is limited, because none of the current studies have been confirmed by a randomized controlled trial or even a case-control study. In addition, the proposed entry zones are heterogeneous. Most of them are used in less than two neurosurgical centers and are not confirmed by a reasonable quantity of clinical cases. Only four entry zones (Fig. 4), namely, SC/IC in midbrain, SF and IF in pons, and PMS in medulla, were used in more than 25 clinical cases. They were therefore classified as having credible evidence, according to our sub-classification. Seven entry zones (Fig. 3), including the LMS, AM, ST, PT, LP, LM, and OZ, could be classified as being supported by limited evidence. The remaining 10 entry zones (Fig. 2), for which there was little published evidence, were regarded as case reports.

The 2-point method

The “2-point method,” that is a line drawn through the first point at the center of a lesion, and another at the point where the lesion is closest to the pial surface, is a safe entry approach proposed by Spetzler’s team [14]. It aims to facilitate the resection of brainstem lesions while minimizing damage to the surrounding normal parenchyma. In a study of 100 consecutive patients with brainstem cavernous malformation, the 2-point method was used to determine the surgical approach [33]. A subsequent study of 260 brainstem cavernous malformation patients reported the use of a modified version of the

method. Here, one point is placed at the middle or most distal extent of the lesion, and the other is again at the most superficial point [2]. With this approach, anywhere on the pial surface could be an entry point if necessary, even though it may lie in some important brainstem tissue. Safe entry zones are proposed as advantageous compared to simply traversing the eloquent brain structure along a 2-point trajectory.

Controversies of SEZs

Some anatomical SEZs are very controversial. The corpora quadrigemina, that is the superior collicula and inferior collicula in the dorsal midbrain, was reported in Bricolo's book as a dangerous area for entry [12]. However, the intercollicular region, in the corpora quadrigemina area, was then described as a safe entry zone in the same publication [12]. In 2000, the supracollicular and infracollicular (SC/IC) were recommended as relatively safe entry zones compared to the intercollicular region [11]. Although more than 45 clinical cases were reported to involve the use of the SC/IC, two recent publications still have different opinions on this topic. Based on anatomical study, Parraga et al. [32] recommended the SC/IC as SEZs to access lesions at the quadrigeminal plate. Cavalcanti et al. [15], on the other hand, explained that because the intercollicular corridor contains very sparse fibers, it is the most appropriate area for lesions in the region. We found credible evidence in the literature for SC/IC, and only case reports evidence for the intercollicular region. In our opinion, the intercollicular approach is unfavorable.

Another disputed area, the medial longitudinal fascicles above the facial colliculi, was described as a dangerous area in the floor of the fourth ventricle in both of Bricolo's studies [11, 12]. Interestingly, these two studies also described the MS, above the facial colliculus and passing through the medial longitudinal fascicles, as a safe entry zone to enter into the dorsal pons [11, 12]. In addition, the superafacial (SF) and infrafacial (IF) zones in the floor of the fourth ventricle were first proposed by Kyoshima et al. [28], and supported by evidence from more than 30 clinical cases. However, Bertalanffy et al. [8] reported that mapping of the facial nerve response area within the rhomboid fossa showed an unexpectedly high variability in the size and position of that area when lesions were close to or present in it. This was caused by the marked distortion of the lesions. Even in patients with lesions far away from the facial colliculus, the response area was also heterogeneous. Thus, brainstem mapping for surgeries involving the rhomboid fossa was strongly recommended in place of just going through any "safe entry zone" [8].

Similarities

The SEZs are usually defined by anatomical landmarks. For example, the anterolateral sulcus zone and the PLS zone of the

medulla are well-documented areas lying pre- and post-olivary. Both of them are very near the olivary body, with a surgical space of approximately 2.5 mm in its anterodorsal axis, especially when the anatomical structures are distorted by any lesion in it [34]. SEZs in the supratrigeminal zone and lateral pontine zone are also quite similar. The anatomical areas are near the fifth nerve. Although the incisions in the brainstem are different from each other, both of them need to go through the transverse pontine fibers in order to access to lesions in this region [22, 36]. Therefore, there might not be an essential difference in clinical outcomes between these two entry zones.

Confirmation

The number of neurosurgical centers that reported clinical cases involving each entry zone is shown in Fig. 5 and Tables 1, 2, and 3. Among the four credible SEZs (SC/IC, SF, IF, and PMS) used in more than 25 clinical cases, the high case number of the SC/IC SEZ comes from only one neurosurgical center. Seven SEZs (LMS, AM, ST, PT, LP, LM, and OZ) that were classified as being supported by limited evidence were used in two or more neurosurgical centers. Most of the remaining 10 SEZs were used at a single center, with the exceptions of the MS and PLS, which were used in 2 different neurosurgical centers. These results indicate that most of the SEZs are not confirmed by multiple centers, which could limit the credibility and application of these entry zones.

Theoretically, in our opinion, lateral approaches for brainstem lesions may have less influence on the structures of the inner crossing fibers or the displaced and distorted nerve response area than direct access from a dorsal or ventral midline. Ferroli et al. [19] reported that these anterolateral pontine trajectories are particularly safe and well tolerated for resection of brainstem cavernoma, with favorable long-term outcomes. Thus, lateral approaches, such as the LMS and supratrigeminal (ST) zones, may be better choices for lesions in the brainstem. Strict midline approaches (like ICR) are not supported by large bodies of evidence, and seem to be abandoned lately. Only SC/IC seems to be used with credible evidence.

Limitations

To our best knowledge, this is the first study attempting to classify the existing evidence for the entry zones into the brainstem. However, all current studies do show weak Oxford evidence for each entry zone and our attempt to categorize the zones using a more precise evidence scale has limitations. Bricolo et al., for example, reported around 175 clinical cases of brainstem surgery, but these cases are excluded from this study because of the lack of detailed descriptions of the selected entry zones and the number of times each SEZ

was used [11]. This is a significant body of cases that should be classified, but it was not possible for us to provide accurate classifications on the basis of the data presented. There were more publications that did not specify the approaches used in specific cases, which means data that was potentially important to our study could not be analyzed. Further, some surgical approaches in current use might not be reflected in published studies. Many centers use these approaches rarely, see some morbidity, or do not believe their results qualify for publication. Proper scientific analysis can only be performed on qualifying, published data. However, we agree that extrapolation of the number of cases reported in the literature cannot be correlated with the safety of an approach.

Conclusions

Many of the entry zones described as safe approaches into the brainstem came from anatomical studies, retrospective case reports, or limited clinical experience. Four existing entry zones, the supracollicular and infracollicular, the superafacial triangle zone, the infrafacial triangle zone, and the posterior median sulcus are backed by a greater degree of clinical experience, as demonstrated in the current literature.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Not required.

Informed consent Not required.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

- Abla AA, Benet A, Lawton MT (2014) The far lateral transpontomedullary sulcus approach to pontine cavernous malformations: technical report and surgical results. *Neurosurgery* 10(Suppl 3):472–480. <https://doi.org/10.1227/NEU.000000000000389>
- Abla AA, Lekovic GP, Turner JD, de Oliveira JG, Porter R, Spetzler RF (2011) Advances in the treatment and outcome of brainstem cavernous malformation surgery: a single-center case series of 300 surgically treated patients. *Neurosurgery* 68:403–414; discussion 414–405. <https://doi.org/10.1227/NEU.0b013e3181ff9cde>
- Akiyama O, Matsushima K, Nunez M, Matsuo S, Kondo A, Arai H, Rhoton AL Jr, Matsushima T (2017) Microsurgical anatomy and approaches around the lateral recess with special reference to entry into the pons. *J Neurosurg* 129:1–12. <https://doi.org/10.3171/2017.5.JNS17251>
- Albright AL, Scلابassi RJ (1985) Cavitron ultrasonic surgical aspirator and visual evoked potential monitoring for chiasmal gliomas in children. Report of two cases. *J Neurosurg* 63:138–140. <https://doi.org/10.3171/jns.1985.63.1.0138>
- Baghai P, Vries JK, Bechtel PC (1982) Retromastoid approach for biopsy of brain stem tumors. *Neurosurgery* 10:574–579. <https://doi.org/10.1227/00006123-198205000-00005>
- Bailey P, Buchanan DN, PC B (1939) *Intracranial tumors of infancy and childhood*. University of Chicago Press
- Bertalanffy H, Benes L, Miyazawa T, Alberti O, Siegel AM, Sure U (2002) Cerebral cavernomas in the adult. Review of the literature and analysis of 72 surgically treated patients. *Neurosurg Rev* 25:1–53. <https://doi.org/10.1007/s101430100179>
- Bertalanffy H, Tissira N, Krayenbuhl N, Bozinov O, Samthein J (2011) Inter- and inpatient variability of facial nerve response areas in the floor of the fourth ventricle. *Neurosurgery* 68:23–31; discussion 31. <https://doi.org/10.1227/NEU.0b013e31820781fb>
- Bodensteiner J, Bell WE, Hart MN (1977) 13-year survival of a child with an untreated brainstem glioma. *J Pediatr* 90:842–843. [https://doi.org/10.1016/S0022-3476\(77\)81270-5](https://doi.org/10.1016/S0022-3476(77)81270-5)
- Bozkurt B, Kalani MYS, Yagmurlu K, Belykh E, Preul MC, Nakaji P, Spetzler RF (2017) Low retrosigmoid infratonsillar approach to lateral medullary lesions. *World Neurosurg* 111:311–316. <https://doi.org/10.1016/j.wneu.2017.12.064>
- Bricolo A (2000) Surgical management of intrinsic brain stem gliomas. *Oper Tech Neurosurg* 3:137–154. <https://doi.org/10.1053/oy.2000.6559>
- Bricolo A, Turazzi S (1995) Surgery for gliomas and other mass lesions of the brainstem. *Adv Tech Stand Neurosurg* 22:261–341. https://doi.org/10.1007/978-3-7091-6898-1_5
- Bricolo A, Turazzi S, Cristofori L, Talacchi A (1991) Direct surgery for brainstem tumours. *Acta Neurochir Suppl* 53:148–158
- Brown AP, Thompson BG, RF S (1996) The two-point method: evaluating brain stem lesions. *BNI* 12:20–24
- Cavalcanti DD, Preul MC, Kalani MY, Spetzler RF (2016) Microsurgical anatomy of safe entry zones to the brainstem. *J Neurosurg* 124:1359–1376. <https://doi.org/10.3171/2015.4.JNS141945>
- Cavalheiro S, Yagmurlu K, da Costa MD, Nicacio JM, Rodrigues TP, Chaddad-Neto F, Rhoton AL (2015) Surgical approaches for brainstem tumors in pediatric patients. *Childs Nerv Syst* 31:1815–1840. <https://doi.org/10.1007/s00381-015-2799-y>
- Deshmukh VR, Rangel-Castilla L, Spetzler RF (2014) Lateral inferior cerebellar peduncle approach to dorsolateral medullary cavernous malformation. *J Neurosurg* 121:723–729. <https://doi.org/10.3171/2014.5.JNS132276>
- Elhammady MS, Teo C (2013) Surgical management of adult intrinsic brainstem tumors. *Neurosurgery* 60(Suppl 1):131–138. <https://doi.org/10.1227/01.neu.0000417806.84351.f0>
- Ferrolli P, Sinisi M, Franzini A, Giombini S, Solero CL, Broggi G (2005) Brainstem cavernomas: long-term results of microsurgical resection in 52 patients. *Neurosurgery* 56:1203–1214. <https://doi.org/10.1227/01.neu.0000159644.04757.45>
- Giliberto G, Lanzino DJ, Diehn FE, Factor D, Flemming KD, Lanzino G (2010) Brainstem cavernous malformations: anatomical, clinical, and surgical considerations. *Neurosurg Focus* 29:E9. <https://doi.org/10.3171/2010.6.FOCUS10133>
- Hauck EF, Barnett SL, White JA, Samson D (2010) The presigmoid approach to anterolateral pontine cavernomas. *Clinical article*. *J Neurosurg* 113:701–708. <https://doi.org/10.3171/2010.1.JNS08413>
- Hebb MO, Spetzler RF (2010) Lateral transpeduncular approach to intrinsic lesions of the rostral pons. *Neurosurgery* 66:26–29; discussion 29. <https://doi.org/10.1227/01.NEU.0000350865.85697.18>
- Ishihara H, Bjeljac M, Straumann D, Kaku Y, Roth P, Yonekawa Y (2006) The role of intraoperative monitoring of oculomotor and trochlear nuclei—safe entry zone to tegmental lesions. *Minim*

- Invasive Neurosurg: MIN 49:168–172. <https://doi.org/10.1055/s-2006-944239>
24. Kalani MY, Yagmurlu K, Martirosyan NL, Cavalcanti DD, Spetzler RF (2016) Approach selection for intrinsic brainstem pathologies. *J Neurosurg* 125:1596–1607. <https://doi.org/10.3171/2016.6.JNS161043>
 25. Kalani MY, Yagmurlu K, Martirosyan NL, Spetzler RF (2016) The retrosigmoid petrosal fissure transpeduncular approach to central pontine lesions. *World Neurosurg* 87:235–241. <https://doi.org/10.1016/j.wneu.2015.11.025>
 26. Kalani MYS, Yagmurlu K, Spetzler RF (2018) The interpeduncular fossa approach for resection of ventromedial midbrain lesions. *J Neurosurg* 128:834–839. <https://doi.org/10.3171/2016.9.JNS161680>
 27. Kumar R, Vinita S (2004) Tuberculous brain stem abscesses in children. *J Pediatr Neurol* 2:101–106
 28. Kyoshima K, Kobayashi S, Gibo H, Kuroyanagi T (1993) A study of safe entry zones via the floor of the fourth ventricle for brainstem lesions. Report of three cases. *J Neurosurg* 78:987–993. <https://doi.org/10.3171/jns.1993.78.6.0987>
 29. Lassiter KR, Alexander E Jr, Davis CH Jr, Kelly DL Jr (1971) Surgical treatment of brain stem gliomas. *J Neurosurg* 34:719–725. <https://doi.org/10.3171/jns.1971.34.6.0719>
 30. Menon G, Gopalakrishnan CV, Rao BR, Nair S, Sudhir J, Sharma M (2011) A single institution series of cavernomas of the brainstem. *J Clin Neuromuscul Dis* 18:1210–1214. <https://doi.org/10.1016/j.jocn.2011.01.022>
 31. Moher D (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 151:264. <https://doi.org/10.7326/0003-4819-151-4-200908180-00135>
 32. Parraga RG, Possatti LL, Alves RV, Ribas GC, Ture U, de Oliveira E (2016) Microsurgical anatomy and internal architecture of the brainstem in 3D images: surgical considerations. *J Neurosurg* 124:1377–1395. <https://doi.org/10.3171/2015.4.JNS132778>
 33. Porter RW, Detwiler PW, Spetzler RF, Lawton MT, Baskin JJ, Derksen PT, Zabramski JM (1999) Cavernous malformations of the brainstem: experience with 100 patients. *J Neurosurg* 90:50–58. <https://doi.org/10.3171/jns.1999.90.1.0050>
 34. Recalde RJ, Figueiredo EG, de Oliveira E (2008) Microsurgical anatomy of the safe entry zones on the anterolateral brainstem related to surgical approaches to cavernous malformations. *Neurosurgery* 62:9–15; discussion 15–17. <https://doi.org/10.1227/01.neu.0000317368.69523.40>
 35. Schain RJ, Wilson G (1971) Brainstem encephalitis with radiographic evidence of medullary enlargement. *Neurology* 21:537–537. <https://doi.org/10.1212/wnl.21.5.537>
 36. Spetzler RF, Kalani MY, Nakaji P, Yagmurlu K (2017) Color atlas of brainstem. *Surgery*:85–102
 37. Strauss C, Romstock J, Fahlbusch R (1999) Pericolicular approaches to the rhomboid fossa. Part II. Neurophysiological basis. *J Neurosurg* 91:768–775. <https://doi.org/10.3171/jns.1999.91.5.0768>
 38. Yagmurlu K, Kalani MYS, Preul MC, Spetzler RF (2017) The superior fovea triangle approach: a novel safe entry zone to the brainstem. *J Neurosurg* 127:1134–1138. <https://doi.org/10.3171/2016.8.JNS16947>
 39. Yagmurlu K, Rhoton AL Jr, Tanriover N, Bennett JA (2014) Three-dimensional microsurgical anatomy and the safe entry zones of the brainstem. *Neurosurgery* 10(Suppl 4):602–619; discussion 619–620. <https://doi.org/10.1227/NEU.0000000000000466>
 40. Zaidi HA, Mooney MA, Levitt MR, Dru AB (2017) Impact of timing of intervention among 397 consecutively treated brainstem cavernous malformations. *Neurosurgery* 81:620–626. <https://doi.org/10.1093/neuros/nyw139>