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Clinical, Anatomo-Radiological and Dosimetric Features Influencing Pain Outcome After Gamma Knife Treatment of Trigeminal Neuralgia

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1. Introduction

Gamma Knife radiosurgery has become nowadays a well validated and accepted option for the treatment of trigeminal neuralgia and numerous publications support its role in the management of this disease. The results achieved with this technique in terms of pain outcome are quite similar to other ablative treatments such as radiofrequency thermo-coagulation, balloon micro-compression or glycerol gangliolysis, nevertheless, complications seem to be less frequent (López 2004a).

In contrast to the mentioned treatments, radiosurgery does not mitigate pain immediately, existing a "latency period" for pain relief of about 2 to 6 weeks. Initially, favorable results (Barrow Neurological institute I -IIIb) are obtained in more than 80% of the cases, then, because of recurrences over time, at 3 to 5 years after the treatment, the percentage of patient which maintains this outcome is near 50%. (Kondziolka, 2010; Longhi, 2007; lópez, 2004a; 2004b; Pollock, 2002; Regís, 2009; Sheehan, 2005; Verheul, 2010).

From the evidence based medicine point of view, either for radiosurgery as well as for all other medical and surgical treatment options for trigeminal neuralgia, there is lacking of comparative randomized prospective trials and the majority of publications correspond to observational data, categorized in Class III studies, then, in general the level of evidence is poor (Cruccu, 2008; López, 2004b; Zakrzewska, 2007).

The aim of the present chapter consists in a systematic review of the literature searching and categorizing information about the prognostic factors involved in pain improvement after Gamma knife radiosurgery for trigeminal neuralgia.

A search in Pub med was done crossing the key words: Gamma Knife, and Trigeminal Neuralgia. Secondarily, other key words were introduced: Radiosurgery, Multiple sclerosis, Atypical, Secondary, postherpethic, anatomy, Neurovascular compression, contact or conflict, Nerve Atrophy, Target, root entry zone, Proximal, Retrogasserian and Distal. For the purposes of this study 67 Manuscripts published between 1997 and 2011 were selected.

Because of the relative low level of existing evidence, more than to state definitive conclusions about the influence on pain outcome of the different variables studied, each variable was arranged in one of 5 powered categories according to the number of publications and the agreement of their findings.

1. **Consistent agreement:** there are clear coincidental conclusions among the publications, without controversial findings. In this category is highly possible that the conclusion is right.
2. **Reasonable agreement:** there are more coincidental conclusions among the publications, but with some controversial findings. In this category is quite possible that the conclusion is right.
3. **Some agreement with a trend:** there are less coincidental conclusions among the publications, more controversial findings but a trend is observed. In this category the conclusion could be right but more information is recommended.
4. **Scarce information with a trend:** A trend is observed, but because the small quantity of data more information is recommended for definitive conclusions.
5. **Scarce information with no clear trend or controversial findings:** In these cases more information is absolutely needed for having any conclusion.

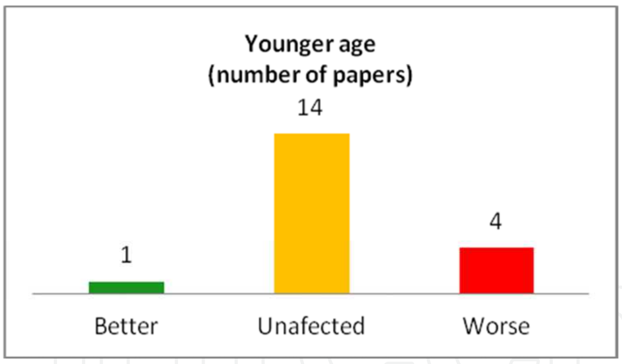
Two plots for each variable were built showing the influence on pain control. The first plot represents the number of publications (papers) supporting the prognostic value of the variable and the second plot shows the number of patients enrolled in such studies: better (variable is a positive prognostic factor), unaffected (variable is not a prognostic factor) and worse (variable is a negative prognostic factor).

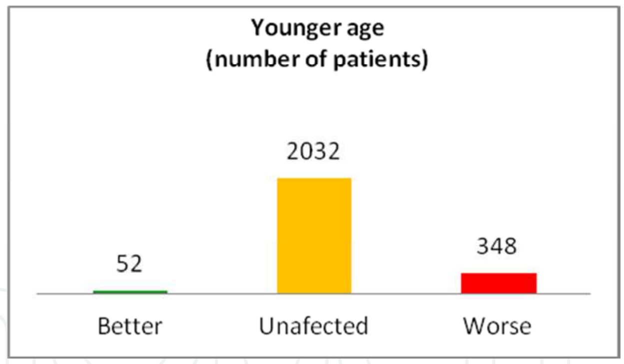
The variables studied were categorized in 3 types:

1. Clinical
2. Anatomo-radiological
3. Dosimetric.

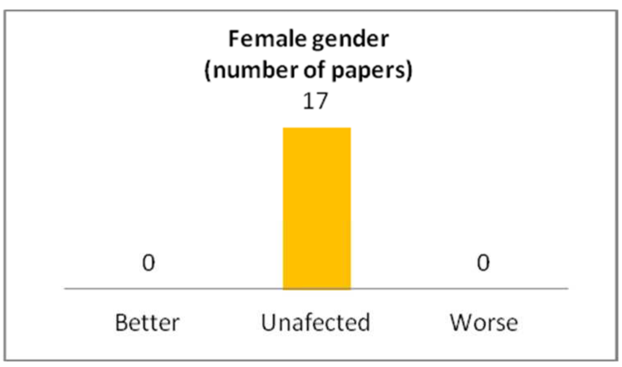
2.1 Clinical variables

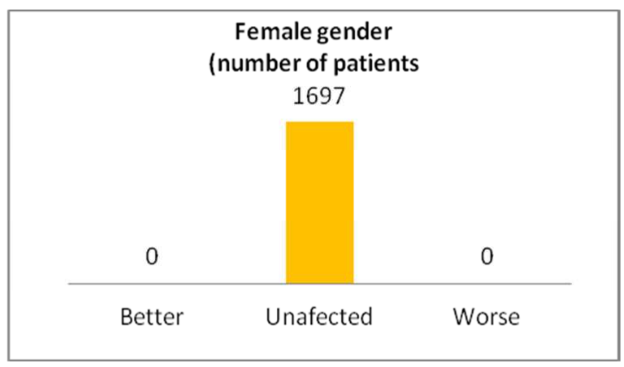
2.1.1 Age: Pan (Pan, 2010) communicated that younger patients obtained better result in terms of pain outcome. Han (Han, 2009), Sheehan (Sheehan, 2005), Regis (Regís, 2006) and Towk (Tawk, 2005) conversely described worse results in younger patients. In spite of these controversial results, the majority of authors have not found significant influence of the patient age in pain control (Aubuchon, 2010; Azar, 2009; Brisman, 2004; Dellaretti, 2008; Hayashi, 2009; Kondziolka, 2010; Little, 2008; Longhi, 2007; Massager, 2007a; Park, 2011; Petit, 2003; Riesenburger, 2010; Rogers, 2000; Young, 1998). **It seems that age is not a prognostic factor with "reasonable agreement".**



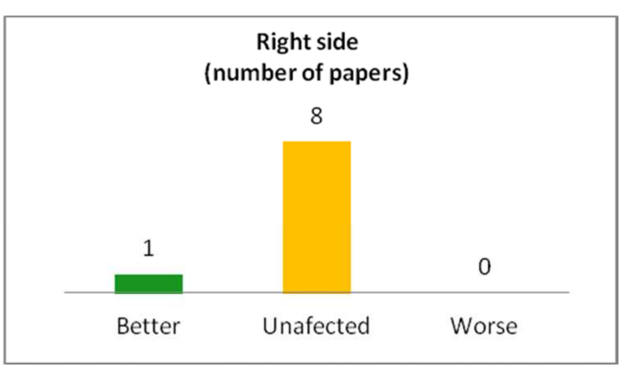


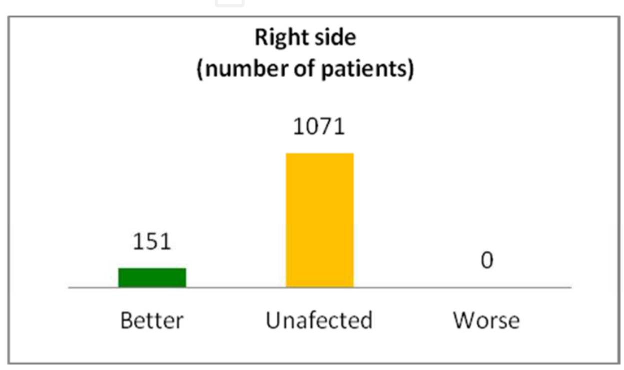
2.1.2 Gender: In spite of female gender seems to be slightly more frequent in the series (Brisman , 2004; Kondziolka, 2010; Longhi , 2007; Pollock, 2002;), concerning pain outcome it has been systematically communicated that this variable has not prognostic significance (Aubuchon, 2010; Azar, 2009; Brisman , 2004; Dellaretti, 2008; ; Hayashi, 2009; Kimball, 2010; Longhi, 2007; Massager 2007a Park, 2011; Riesenburger, 2010; ; Rogers, 2000; Sheehan, 2005; Tawk, 2005; Young, 1998): **There was found "Consistent agreement" indicating that gender is not a prognostic variable for pain control.**



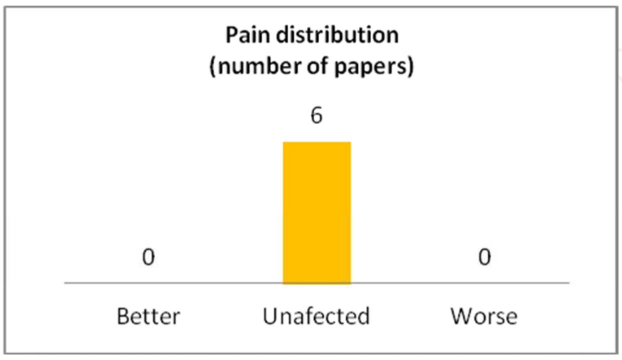


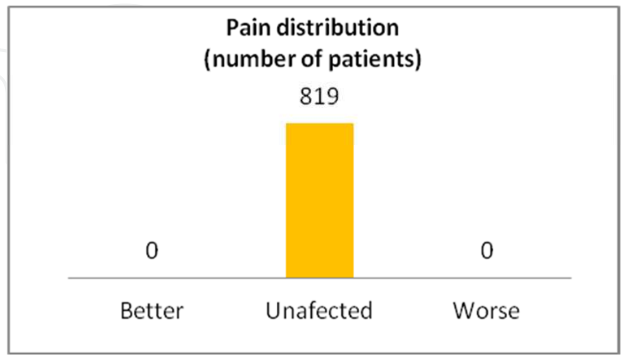
2.1.3 Side: Right side seems to be slightly more frequent (Aubuchon, 2010; Cheuk, 2004; Dhople, 2009; Huang, 2008; Kimball, 2010; Kondziolka, 2010; Pan, 2010; Park, 2011; Pollock, 2001 ; Regís, 2006; Shaya, 2004; Tawk, 2005), Most authors coincide that the side of the neuralgia has not a prognostic factor (Brisman, 2004; Hayashi, 2009; Kimball, 2010; Little, 2008; Massager , 2007a; ; Park, 2011; Riesenburger, 2010; Tawk, 2005). Sheehan (Sheehan, 2005) on the other hand, found better results in patients with right side neuralgia. **It seems that the side of the trigeminal neuralgia has not influence on pain outcome with "reasonable agreement" of findings.**



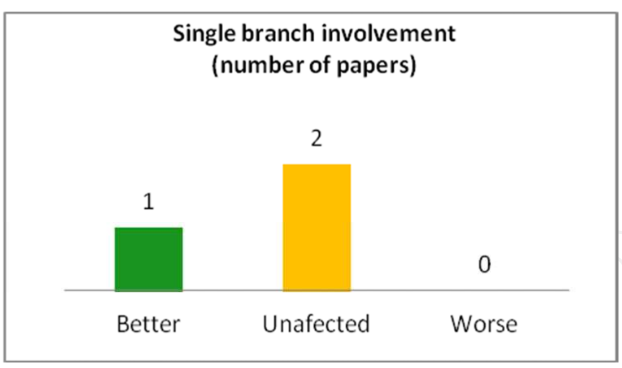


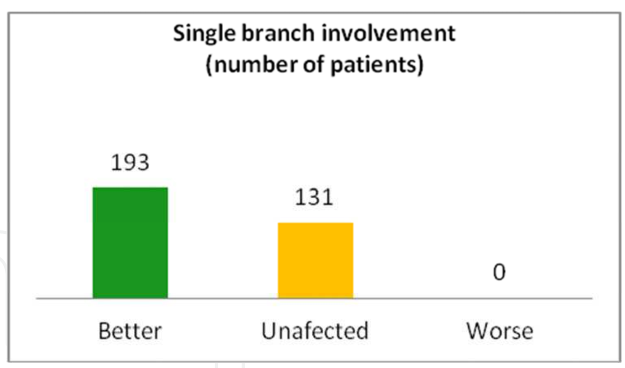
2.1.4 Pain distribution: All revised papers conclude that pain distribution does not affect the clinical outcome of trigeminal neuralgia after Gamma Knife treatment (Abuchon, 2010; Hayashi, 2009; Jawahar, 2005; Little, 2008; Massager, 2007a; Sheehan, 2005). **For this variable a "Consistent agreement" was observed**.



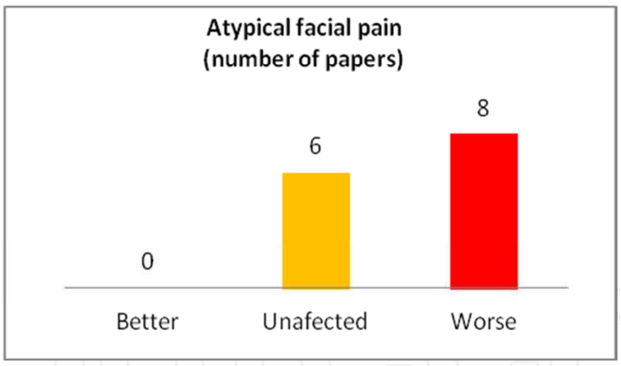


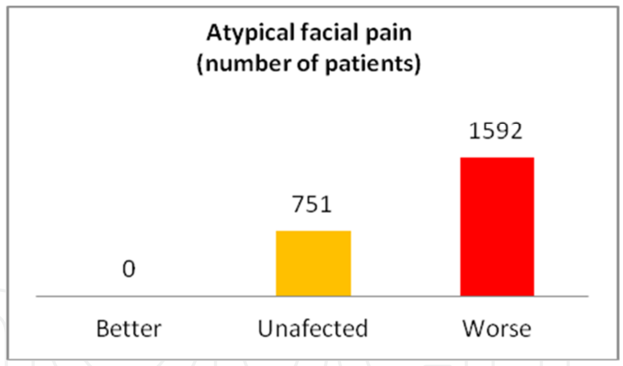
2.1.5 Single branch involvement: Kano, **(Kano, 2010)**, found a significant favorable pain outcome in patients with a single branch compromise, nevertheless other two publications mentioned no influence on pain outcome of a single branch compromise (Massager, 2007a; Tawk, 2005). No publication was found mentioning worse results when a unique branch is affected. **"Scarce information with a trend" suggests that single branch involved could be a positive prognostic variable.**



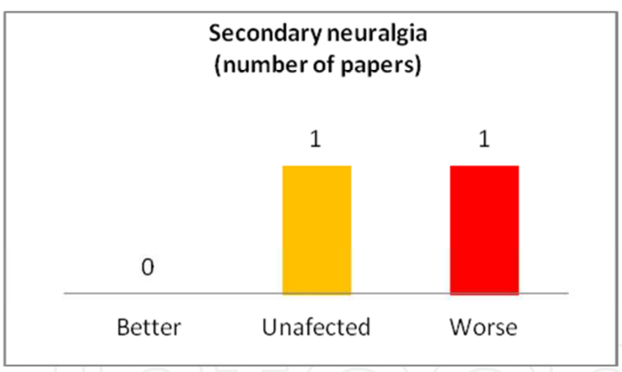


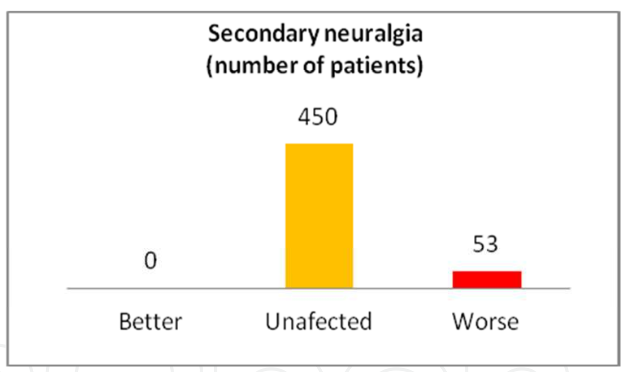
2.1.6 Atypical neuralgia: More reports found worse pain outcome in patients with atypical neuralgia (Brisman, 2004; Dhople, 2007; Kano,2010; Longhi, 2007; Maesawa, 2001; Rogers, 2000; Varheul, 2010; Young, 1998). Other authors did not found influence of atypical neuralgia on pain improvement (Aubuchon, 2010; Petit, 2003; Pollock, 2002; Regís, 2009; Sheehan, 2005). No publications informing better results in patients with atypical facial pain were found. **"Some agreement with a trend" indicates that atypical facial pain could responds worse to Gamma Knife treatment.**



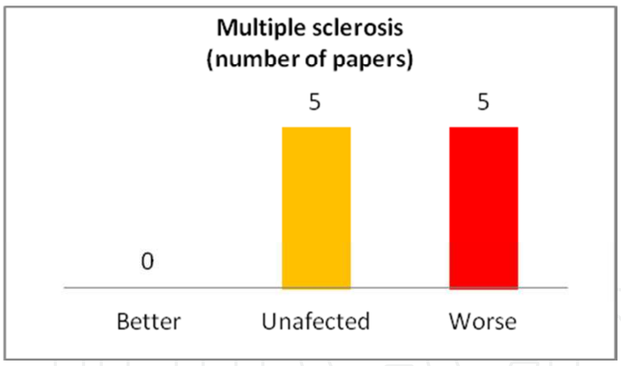


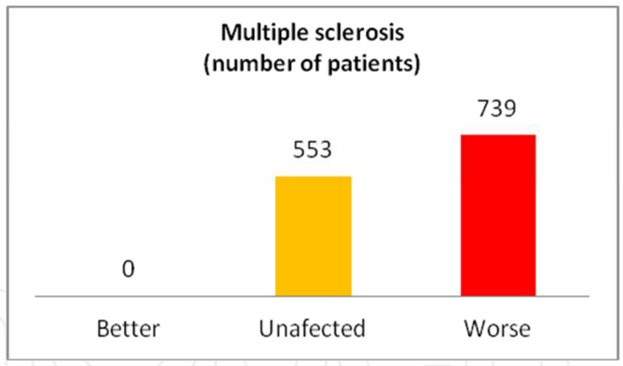
2.1.7 Secondary neuralgia: Young (Young, 1997) reported 88% of pain relief in 9 patient treated targeting the tumor, Regis (Regis 2001), obtained pain cessation in 79.5% of 46 patients targeting the tumor, in 3 cases the target was the nerve and in 4 the target was the tumor with the nerve together. Pollock (Pollock, 2000) treated 23 patients (16 meningiomas and 8 malignant tumors). After treatment 50% of patients were initially pain free and 46% experience significant pain improvement. Chang (Chang, 1999) in a series of 27 patients (mainly meningiomas and schwannomas) targeting the tumor found 40% of pain improvement and a slower response. If the analysis is done in those series that compare classic trigeminal neuralgia and secondary neuralgia (Chang, 2000), worse results in patients with secondary trigeminal neuralgia were found. Verheul (Verheul, 2010) on the other hand, did not found differences in clinical results between secondary and classic trigeminal pain. **"Scarce information with a trend" could suggest that secondary trigeminal neuralgia could be a negative prognostic variable.**



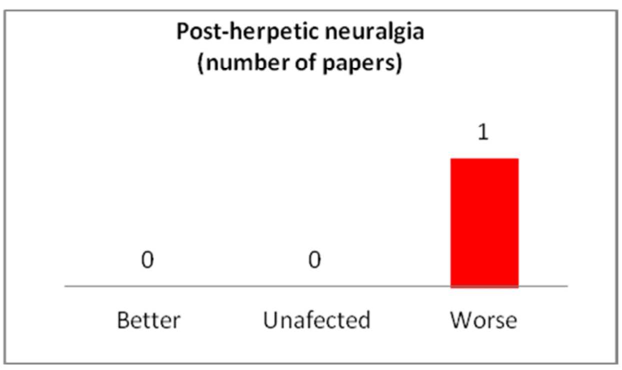


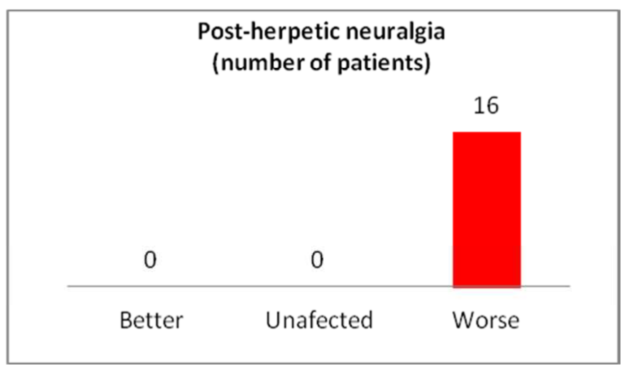
2.1.8 Association with Multiple sclerosis: When specific publications for multiple sclerosis were analized, some authors (Huang, 2002; Rogers, 2002; Zorro, 2009) communicated quite similar results of Gamma Knife radiosurgery in patients harboring trigeminal neuralgia secondary to multiple sclerosis. If the analysis is done in those series that compare classic trigeminal neuralgia and neuralgia associated to multiple sclerosis, some authors reported worse results in cases of multiple sclerosis (Brisman 2000a; Cheng, 2005; Morbidini-gaffney, 2006; Verheul, 2010; Young, 1998). Other manuscripts did not report significant differences in pain control between classic trigeminal neuralgia and neuralgia secondary to multiple sclerosis (Cheuk, 2004; Petit, 2003; Regís, 2009; Riesenburger, 2010; ; Rogers, 2000). No communication exists informing better results when multiple sclerosis is present. **With "Some agreement with a trend" It seems that trigeminal neuralgia secondary to multiple sclerosis could respond worse to Gamma Knife treatment.**



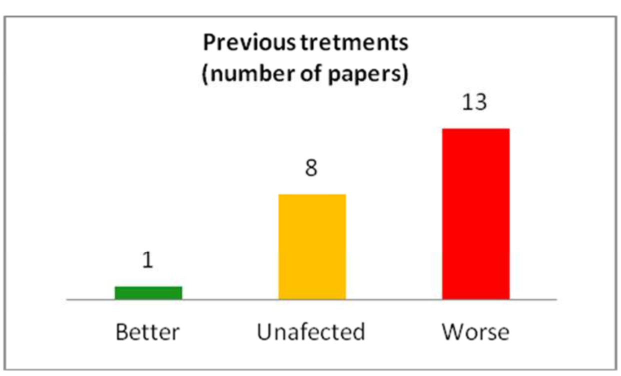


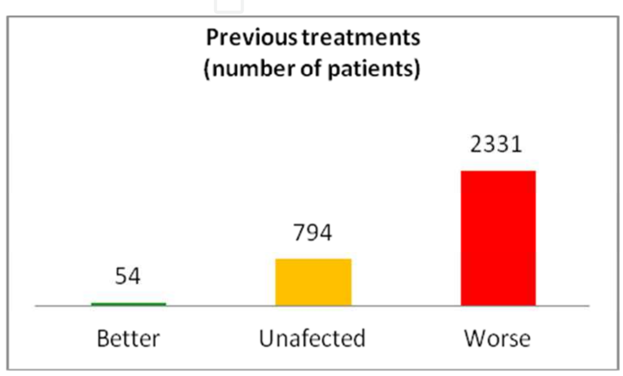
2.1.9 Postherpetic neuralgia: There was found only one study concerning Gamma Knife treatment for post herpetic neuralgia. Urgosík (Urgosík, 2000) It comprised 16 patients and the favorable pain response was 44%, results quite inferior to those communicated in the literature for classic trigeminal neuralgia. **"Scarce information with a trend" suggests that post herpetic trigeminal neuralgia could not respond well to Gamma Knife treatment.**



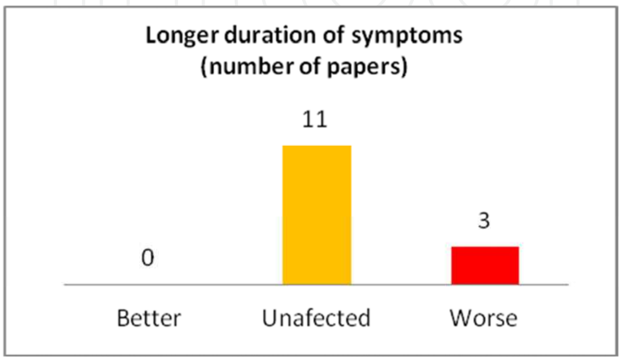


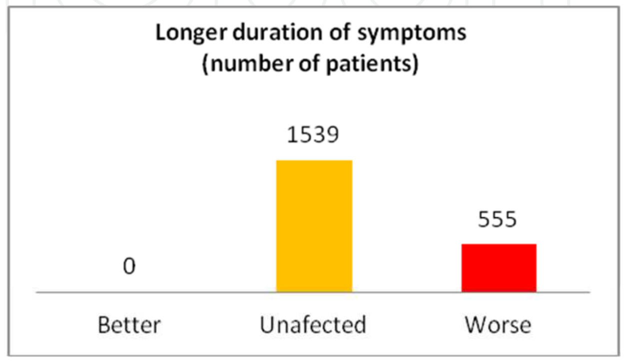
2.1.10 Previous treatments: The majority of studies found worse pain outcome in patients with the antecedent of previous treatments of the trigeminal neuralgia. (Brisman, 2000a; Dellanretti, 2008; Dhople, 2009; Kondziolka, 2010; Little, 2008; Longhi, 2007; Pan, 2010; Petit, 2003; Pollock, 2002; Regís, 2009; Tawk, 2005; Verheul, 2010; Young 1997), lesses number of articles found no influence of this variable (Dhople, 2009 ; Fountas, 2007; Hayashi, 2009; Massager, 2007a; Park, 2011; Reisenburger, 2010; Sheehan, 2005). Only one study showed better pain outcome in those patients previously treated (Rogers, 2000). **It seems that the antecedent of previous surgical treatments is a negative prognostic factor with "reasonable agreement".**



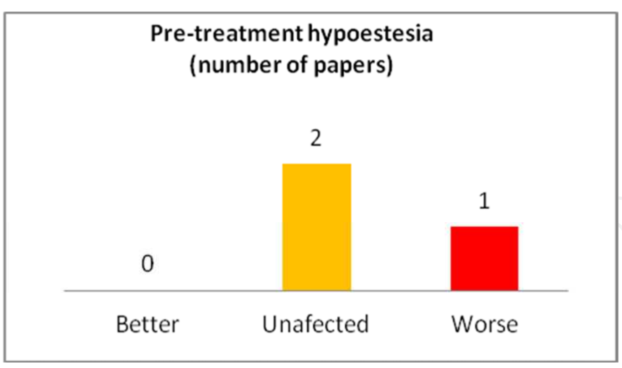


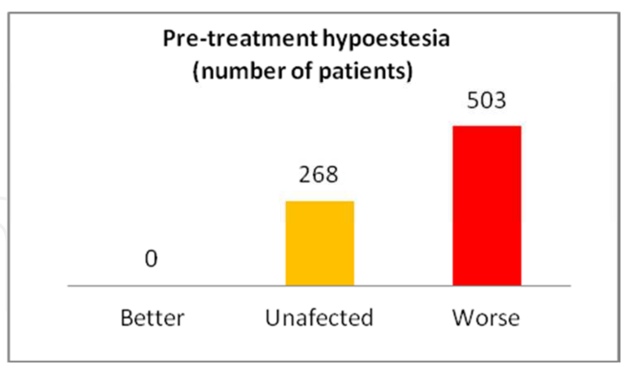
2.1.11 Longer duration of symtoms: Kondziolka (Kondziolk, 2010) found better results in patients with less than 3 years of disease. Pan (Pan, 2010) communicate better outcome in patients with less of 24 months of evolution and Petit (Petit, 2003) reported better pain control when the time of disease was less than 50 months. Other manuscripts did not confirm influence of this variable (Brisman, 2004; Dellaretti, 2008; Hayashi, 2009; Kano, 2010; Kimball, 2010; Little, 2008; Pollock, 2002; Reisenburger, 2010; Sheehan, 2005; Tawk, 2005; Young, 1998). No communication exist informing better results when the illness was present for a longer time. **A longer time of evolution of the trigeminal neuralgia could be a variable associated to a worse prognosis wit "Some agreement with a trend".**



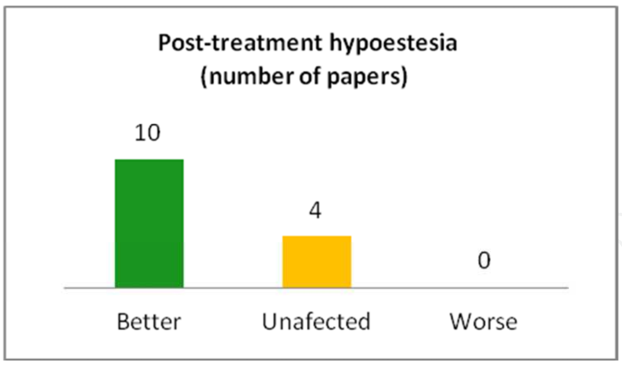


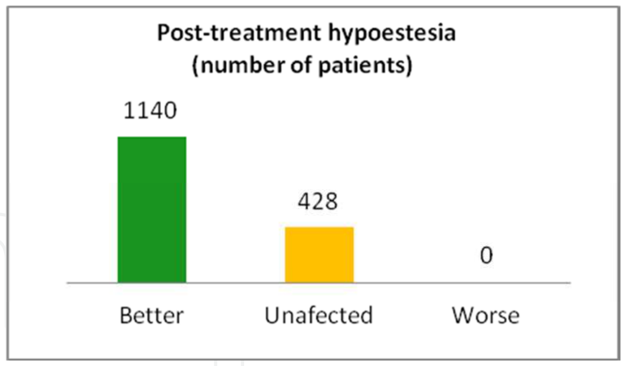
2.1.12 Pre-treatment sensory deficit: Kondziolka (Kondziolka, 2010) found better pain control in patients without previous sensory deficit; nevertheless this variable could be associated with other variable (no previous treatments). Pollock (Pollock 2002) and Sheehan (Sheehan, 2005) did not find this association. No communication was found informing better results in cases with pre-treatment sensory deficit. **"Scarce information with a trend" suggests that pre-treatment sensory deficit could be associated to a worse pain control.**



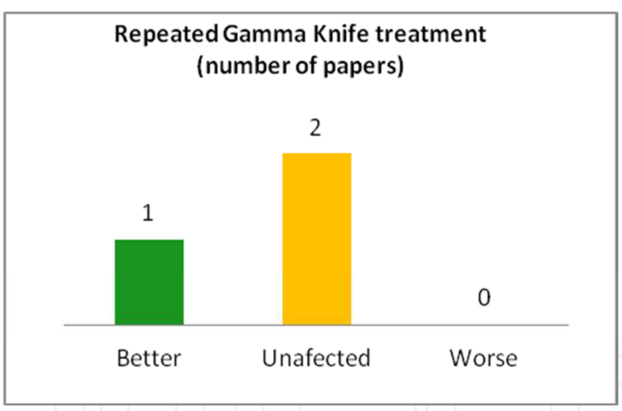


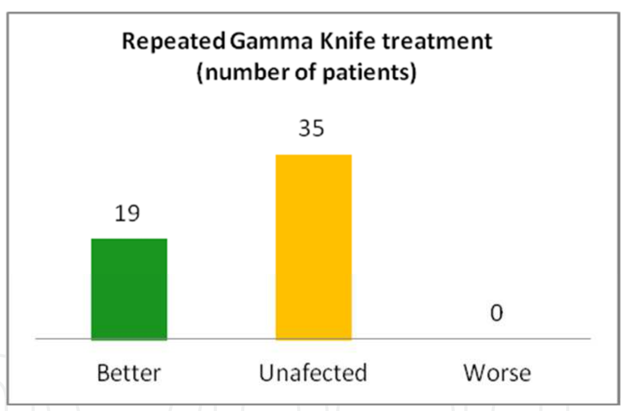
2.1.13 Post-treatment sensory deficit: Clear predominance was found concerning the association between post-treatment sensory deficit and better pain outcome (Aubuchon, 2010; Dellaretti, 2008; Huang, 2008; Kimball, 2010; Kondziolka, 2010; Massager 2007a; Matsuda, 2010; Pollock, 2002; Rogers, 2000; Tawk, 2005). Four authors reported no influence of this variable (Cheuk, 2004; Petit 2003; Reisenburger, 2010; Sheehan, 2005). No publications informing worse pain control in patients with post operative sensitive deficit was got. **Post Gamma knife sensory dysfunction is associated with better pain outcome with "reasonable agreement of findings".**





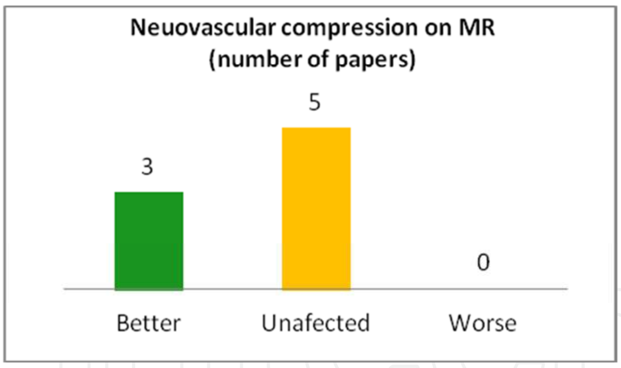
2.1.14 Repeated gamma Knife treatment: With regard a second treatment by Gamma Knife, two studies report no difference in term of pain control compared with the results obtained after a first Gamma Knife treatment (Huang, 2010; Verheul, 2010). Pollock (Pollock, 2005) found even better pain outcome after the second treatment. All these three studies report significant more trigeminal dysfunction after the second treatment. **"Scarce information with a trend" suggests that pain control after a second Gamma Knife treatment could be similar or better compared with the first treatment; nevertheless, it is associated to higher nerve toxicity.**

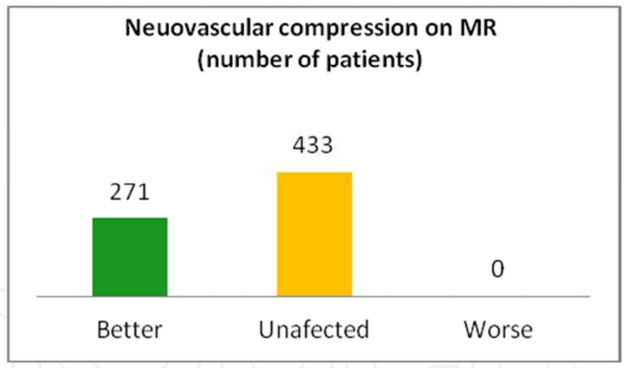




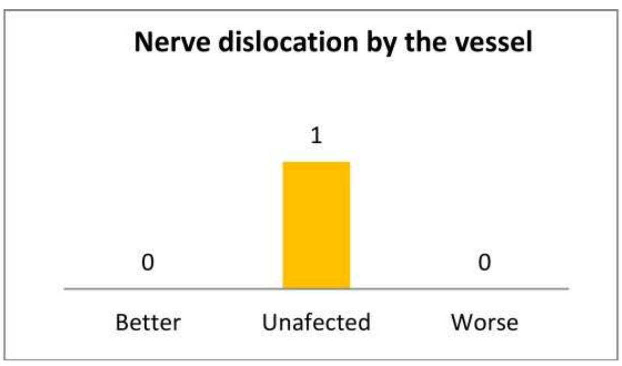
2.2 Anatomo-radiological variables

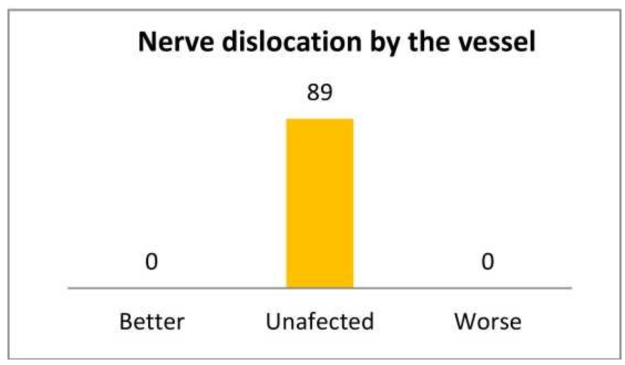
2.2.1 Neurovascular compression on magnetic resonance: Erbay (Erbay, 2006), Pan (Pan, 2010) and Brisman (Brisman ,2002a) report better pain control in those patients with neurovascular compression visualized on magnetic resonance. Other authors (Cheuk, 2004; Lorenzoni, 2008; Park, 2011; Shaya, 2004; Sheehan, 2010) did not find significant influence of this variable. No paper informing better outcome in patients without neurovascular compression in the magnetic resonance was found. Based in this, **"Some agreement with a trend" suggests that a neurovascular compression visualized on MR could be a neutral or good prognostic factor but not a negative factor.**



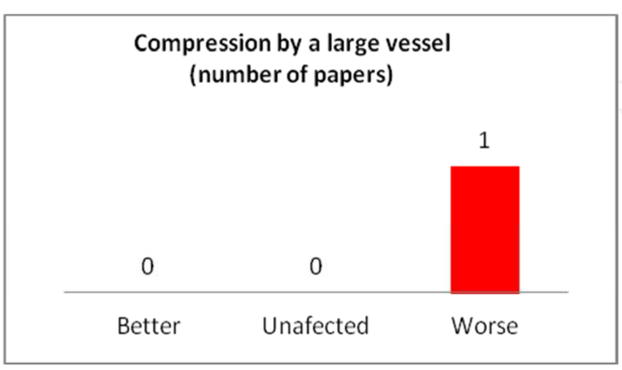


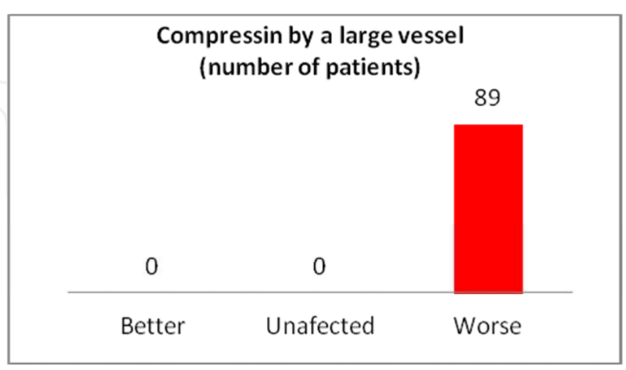
2.2.2 Nerve deformation or dislocation by the vessel: Lorenzoni et al (Lorenzoni 2008) found no influence of this factor on pain outcome. In spite of these findings, **"Scarce information with a trend" exists and this fact needs to be validated with further studies.**



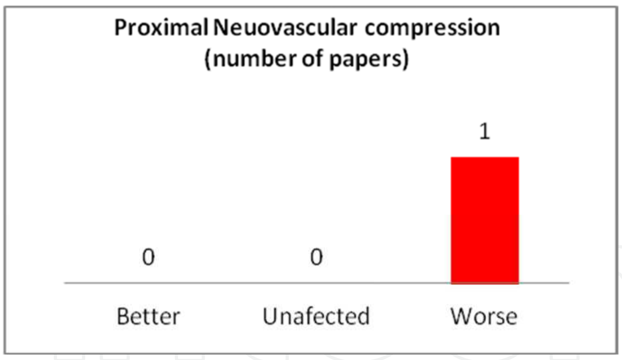


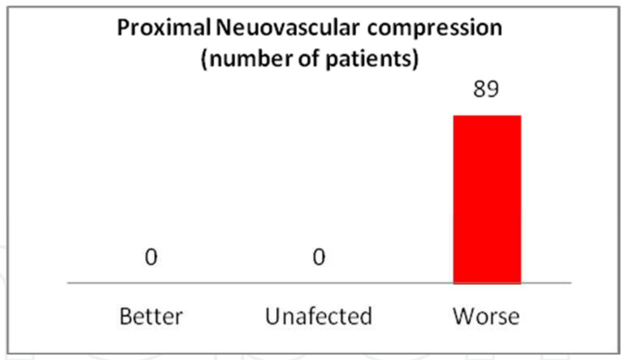
2.2.3 Large vessel involved in the neurovascular compression: Lorenzoni and co-workers (Lorenzoni, 2008) informed that a neurovascular compression by a large vessel such as a dolicoectatic basilar artery or a tortuous vertebral artery is a negative factor for pain mitigation. In spite of these findings, **"Scarce information with a trend" exists and these findings need to be validated with further studies.**



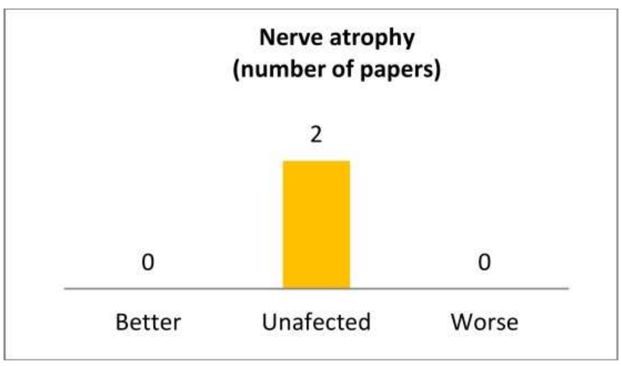


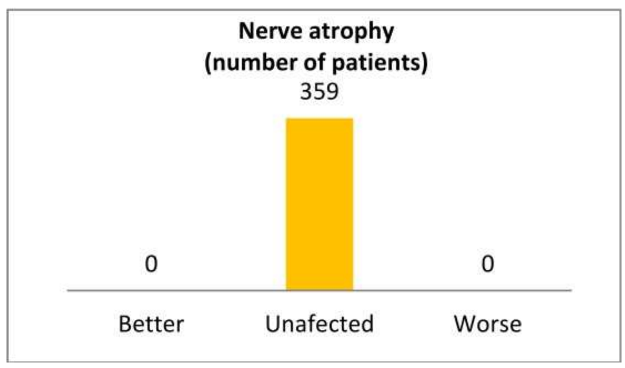
2.2.4 Proximal neurovascular compression: Lorenzoni et al (Lorenzoni, 2008; Lorenzoni, 2009) communicated that neurovascular compression can be located at any place along the trajectory of the trigeminal nerve. Proximal neurovascular compressions (less than 3 mm to the nerve emergency in the brainstem), was associated to a worse pain control (Lorenzoni 2008). **"Scarce information with a trend" exists and this fact needs further confirmation.**



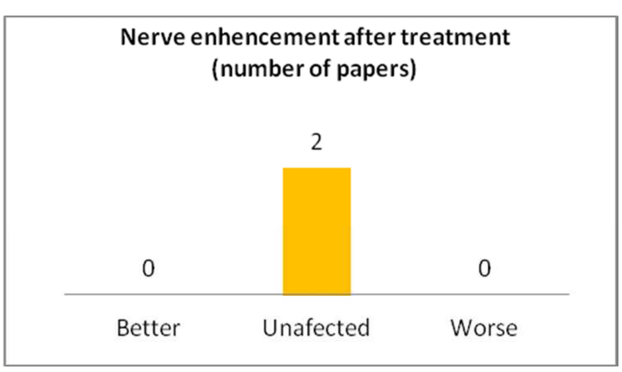


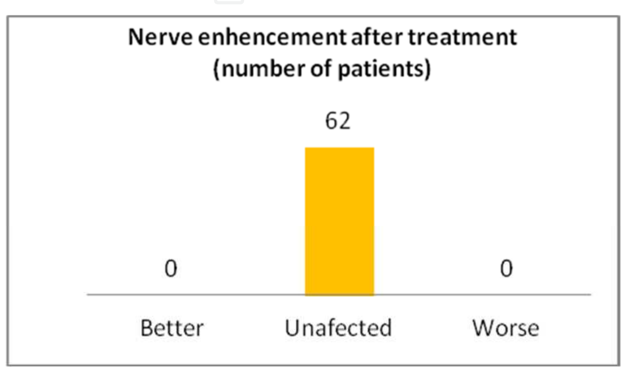
2.2.5 Nerve atrophy: Two articles (Hayashi, 2009; Lorenzoni, 2008) found no influence of this variable on pain response. **"Scarce information with a trend" suggests that nerve atrophy could not be a predictive factor; nevertheless, because of the little information available, more studies are desirable for a definitive conclusion.**



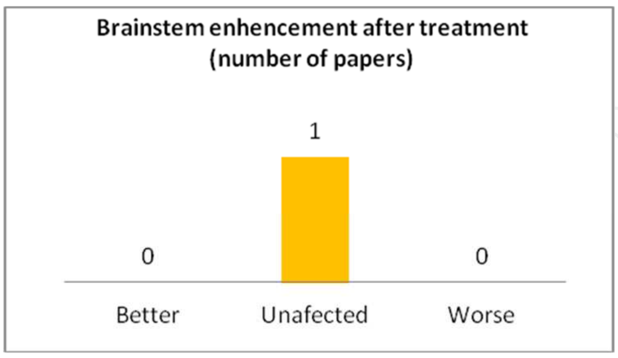


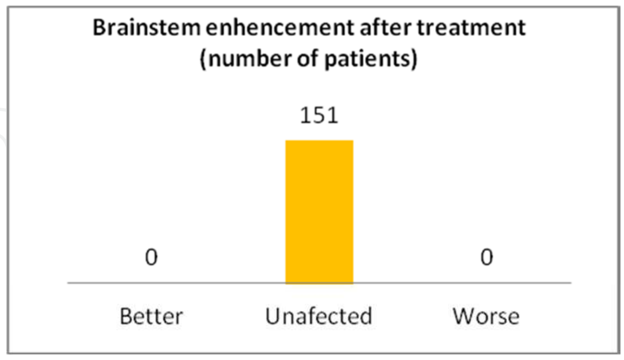
2.2.6 Nerve enhancement after treatment: In many cases, but not always, contrast enhancement of the trigeminal nerve is visualized on magnetic resonance some weeks or months after the Gamma Knife treatment. Fountas (Fountas, 2007), reports this phenomenon in 79% of the treated patients. This finding confirms the zone that received the irradiation. Alberico (Alberico, 2001) studied 15 patients and in 10 there was nerve enhancement. This finding was not related with pain response. Massager (Massager 2004) in a series of 47 patients did not find a prognostic value of this variable. Based on these two articles, it was considered that there is **"Scarce information with a trend" suggests that nerve contrast enhancement after treatment is not related to pain results.**





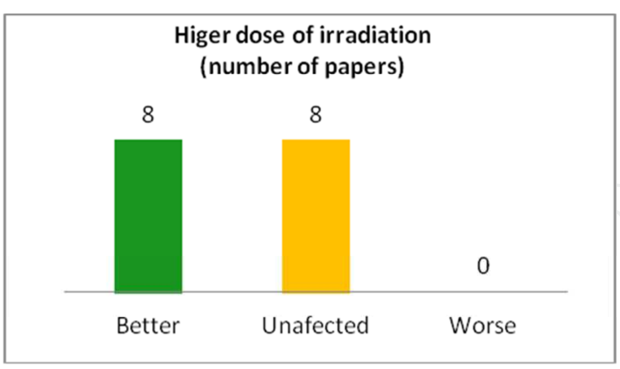
2.2.7 Brainstem enhancement after treatment: Sheehan (Sheehan, 2005) reported that brainstem contrast enhancement after treatment did not correlate with results of the Gamma Knife treatment. **"Scarce information with a trend" suggests that brainstem contrast enhancement after treatment is not related to pain control.**

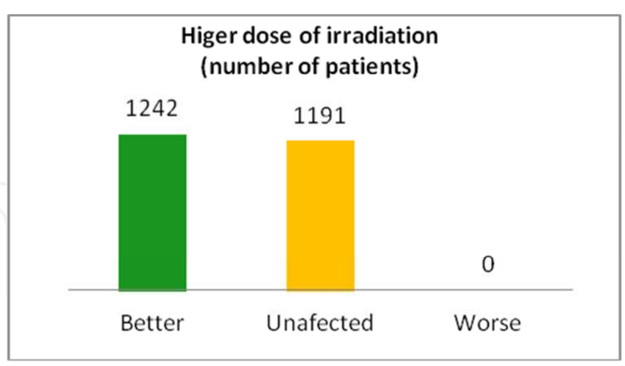




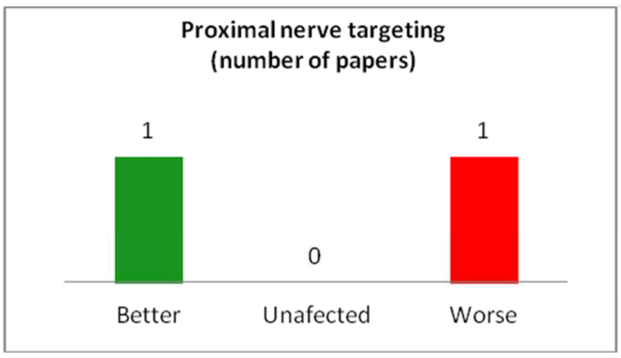
2.3 Dosimetric variables

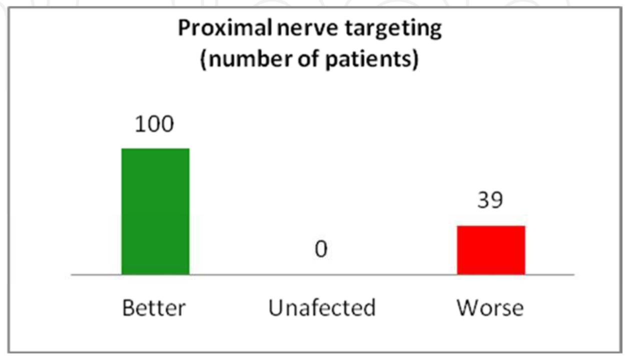
2.3.1 Maximal dose administered to the nerve: For the analysis of the maximal dose delivered (in the range of 70 to 90 Gray), Many authors (Alpert, 2005; Kim, 2010; Longhi, 2007; Massager, 2007b; Morbidini-Gaffnay, 2006; Regis, 2009; Park, 2011; Shaya, 2004), communicate that using a maximal prescribed dose in the range of 80 to 90 Gray the patients response is better compared with treatment with a lower dose. On the other hand, other authors communicated that maximal dose of irradiation is not a prognostic factor (Aubuchon, 2010; Azar, 2009; Brisman, 2004; Dellaretti, 2008; Hayashi, 2009; Kondziolka, 2010; Little, 2008; Longhi, 2007; Park, 2011; Petit, 2003; Riesenburger, 2010; Rogers, 2000; Young, 1998;). Conversely, no study has shown better results using a lower dose. Concerning this fact, **"Some agreement with a trend" suggests that the use of a higher dose of irradiation (in the range of 80 to 90 Gray) achieve better results.**



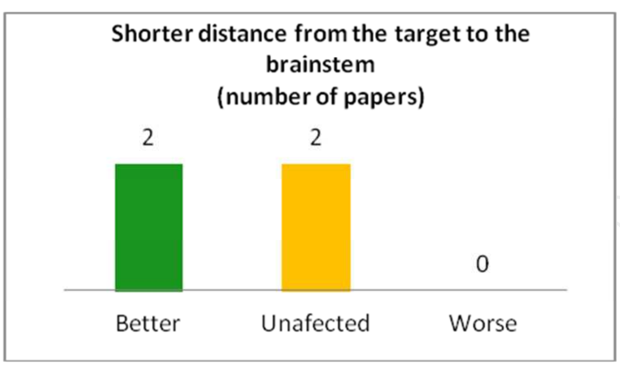


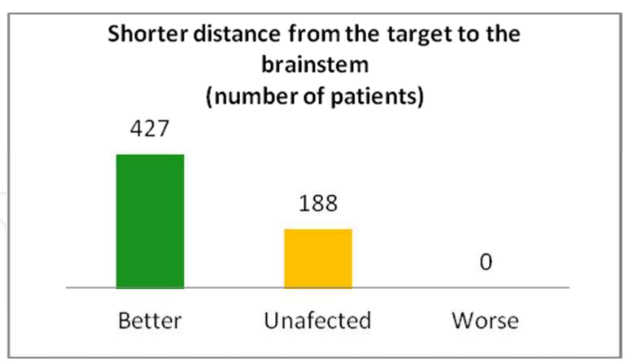
2.3.2 Proximal nerve targeting: Two zones in the trigeminal nerve has been described as targets for radiosurgical treatment of trigeminal neuralgia, a proximal target located at the root entry zone and a distal one located at the retrogaserian portion of the nerve. It seems that clinical results are quite similar using either the proximal target (Brisman 2004; Cheuk, 2004; Dhople, 2007; Han, 2009; Huang, 2008; Kim, 2010; Kondziolka, 2010; Little, 2008; Longhi, 2007; 2005 Matsuda, 2010; Nicol, 2000; Pan, 2010; Park, 2011; Pollock, 2002; Rogers, 2000 Tawk; Verheul, 2010; Young, 1998) as well as the distal one (Dellaretti, 2008; Hayashi 2009; Massager, 2007a; Regis, 2009). Matsuda (Matsuda 2008) in a series of 100 patients reports better pain control and lesser morbidity in patients treated with a proximal compared with those treated with a distal target. Conversely, Park (Park 2010) in a series of 39 patients found that a distal target was associated to more rapid response, better pain control and lower nerve morbidity. With the data available in the literature there are not clear differences in terms of clinical results between the two targets, then, considering any of these two targets as prognostic variable **"scarce information with no clear trend or controversial findings" exist.**



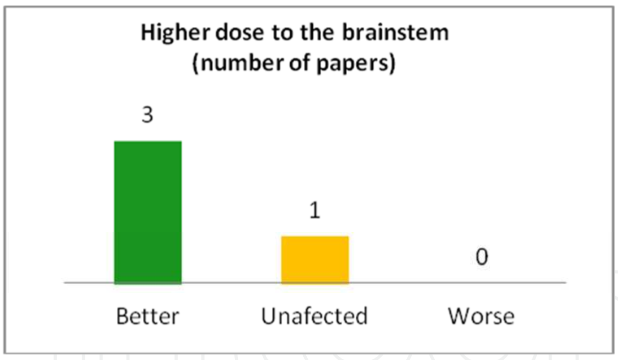


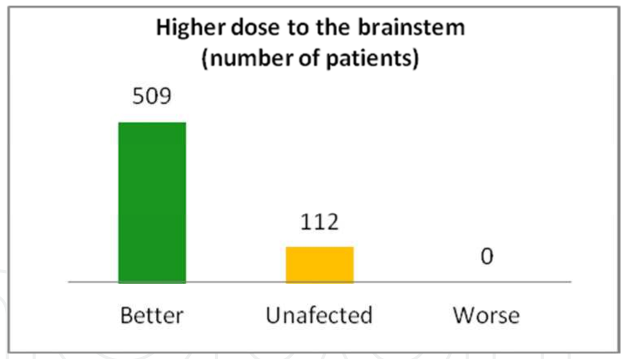
2.3.3 Shorter distance from the isocenter to the brainstem: Regís (Regís, 2009) and massager (Massager 2007a) using distal retrogaserian targeting report better pain control when the distance between the isocenter and the brainstem is less. Sheehan (Sheehan, 2005) and Aubuchon (Aubuchon, 2010) found no influence. No article showing worse outcome when a smaller distance from the isocenter to the brainstem was identified. This variable could be linked with the next variable analyzed (higher dose of irradiation received by the brainstem) **"Scarce information with a trend" suggests that a shorter distance from the isocenter to the brainstem is a good prognostic variable.**



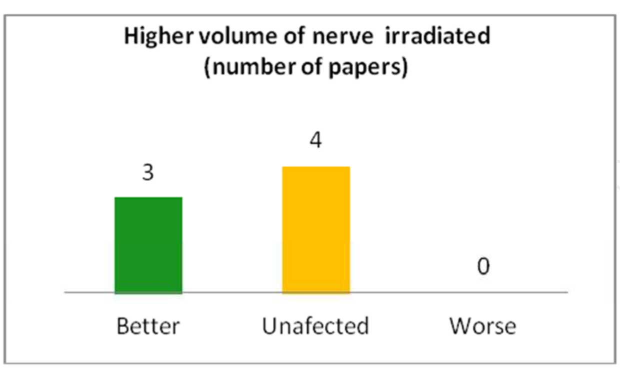


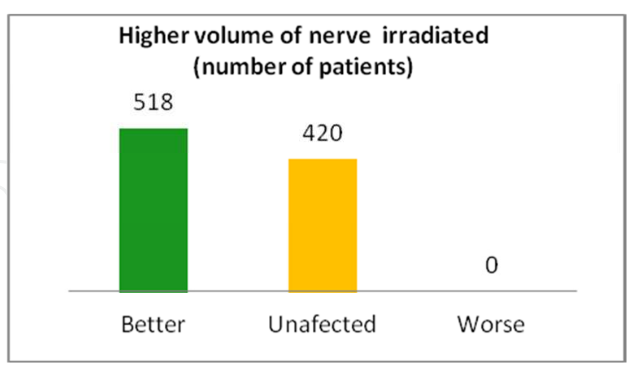
2.3.4 Higher dose received by the brainstem: A higer dose of irradiation received by the brainstem was associated to better results in 3 papers (Brisman, 2000b; Massager, 2007a; Regís 2009). Cheuk (Cheuk, 2004) in a series of 112 patients did not find this correlation. No manuscript showing worse results when a lower dose is received by the brainstem was recognized. As it was previously mentioned, this variable could be linked to the precedent variable (Shorter distance from the isocenter to the brainstem). **There is "reasonable agreement" suggesting better results when the brainstem receives a higher dose of irradiation.**



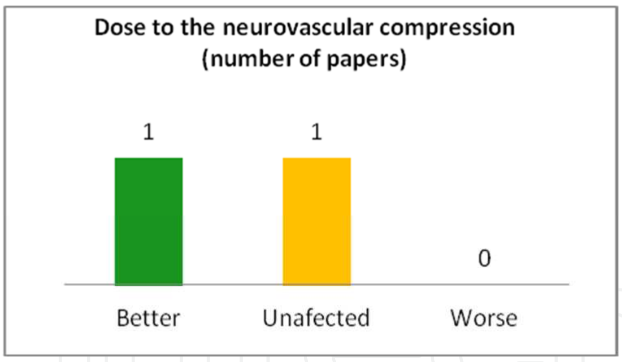


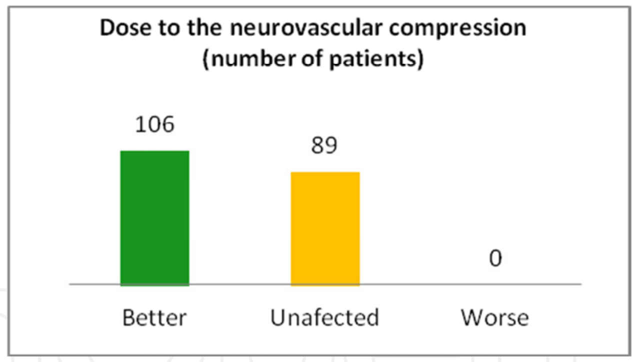
2.3.5 Higher volume of nerve irradiated (multiple isocenters or plugging): This topic is related to the concept of "integral dose", in other words, the quantity of energy received by the nerve in a determined volume. A higher integral dose can be augmented either using of two isocenters or using of plugs. Morbidini-Gaffney (Morbidini-Gaffney, 2006) and Alpert (Alpert, 2005) found better pain control using two isocenters, Conversely Flickinger (Flickinger 2001) in a randomized prospective study found no differences using one or two isocenters and Fountas (Fountas, 2007) reports no differences using one, 2 or 3 isocenters. Nevertheless, nerve dysfunction was more important in the group of patients treated with multiple isocenters. With regard the length of nerve irradiated Sheehan (Sheehan, 2005) and Delarenti (Dellaretti, 2008) reported that this variable did not correlate with pain control. Massager (Massager, 2006; Massager, 2007b), found a larger volume of nerve irradiated and a higher integral dose received by the trigeminal nerve when plugs are used. In these cases better pain outcome but higher nerve toxicity was achieved. The author recommends avoiding the use of plugs in patients treated with a maximal dose of 90 Gray. **"Some agreement with a trend" suggests that a larger irradiated volume of the nerve could correlate with better pain control but associated with more nerve dysfunction.**



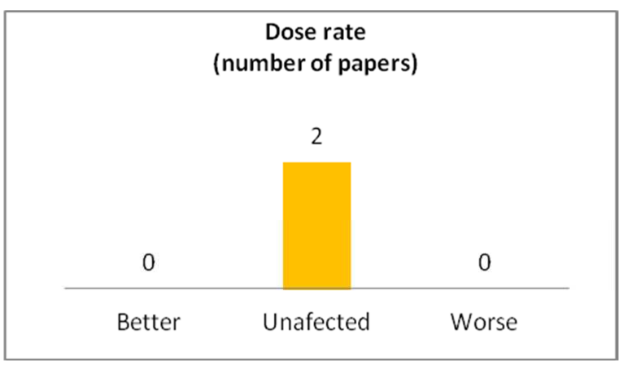


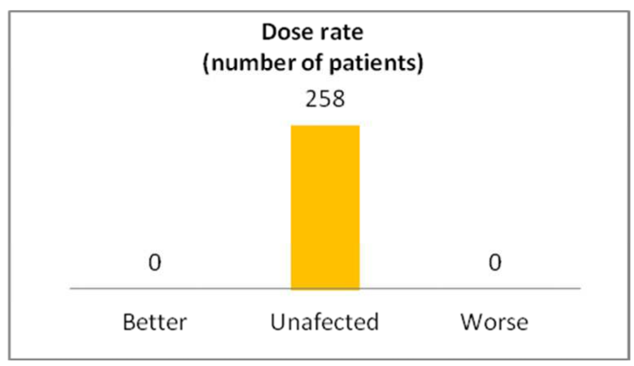
2.3.6 Dose received by the nerve at the level of neurovascular compression: Lorenzoni (Lorenzoni, 2008) found no correlation between the dose of irradiation received by the nerve at the level of the neurovascular compression visualized on magnetic resonance imaging, Sheehan (Sheehan, 2010) by the contrary communicate that pain relief correlated with a higher dose to the point of contact between the impinging vessel and the nerve. With regard to this variable **"scarce information with no clear trend or controversial findings" exist.**





2.3.7 Dose rate: Along the time the cobalt sources decay and the irradiation of the Gamma unit is progressively less, then, for to obtain the same physical dose of irradiation a longer time of treatment is needed. A concern may exist because a longer time of irradiation can allow more tissue reparation with a theoretically less biologic effect. Despite this theory, Arai (Arai, 2010) and Massager (Massager, 2007a) concluded that Gamma Knife dose rate do not affect outcomes (pain control or morbidity). Concerning this variable there is **"Scarce information with a trend".**





3. Conclusions

3.1 There is consistent agreement for the following variables

1. Gender is not a prognostic factor
2. Pain distribution is not a prognostic factor

3.2 There is reasonable agreement for the following variables

1. Age is not a prognostic factor
2. Side is not a prognostic factor
3. Previous treatments is a negative prognostic factor
4. Post-treatment hypoesthesia is a positive prognostic factor

3.3 There is some agreement with a trend for the following variables

1. Atypical facial pain is a negative prognostic factor
2. Multiple sclerosis is a negative prognostic factor
3. A longer duration of the symptoms is a negative prognostic factor

4. A neurovascular compression visualized on MR is a positive prognostic factor
5. A higher dose of irradiation is a positive prognostic factor
6. A higher volume of nerve irradiated is a positive prognostic factor

3.4 There is scarce information with some trend for the following variables

1. A single branch involved is a positive prognostic factor
2. Secondary trigeminal neuralgia is a negative prognostic factor
3. Post-herpetic neuralgia is a negative prognostic factor
4. Pre-treatment hypoesthesia is a negative prognostic factor
5. Repeated Gamma knife treatment is not prognostic for pain control but associated ith more nerve dysfunction
6. Nerve deformation or dislocation by the vessel is not a prognostic factor
7. Compression by a large vessel (basilar or vertebral artery) is a negative prognostic factor
8. Proximal neurovascular compression is a negative prognostic factor
9. Nerve atrophy has not prognostic value
10. Nerve enhancement after treatment is not a prognostic factor
11. Brainstem enhancement after treatment is not a prognostic factor
12. Shorter distance between the target and the brainstem is a positive prognostic variable
13. Dose rate is not a prognostic factor

3.5 There is scarce information with no clear trend or controversial findings for the following variables

1. Proximal or distal targeting
2. Dose of irradiation received by the nerve at the neurovascular compression

When many papers are analyzed it is frequent to find some differences or even controversial findings in the results and conclusions, then, an overview of a constellation of manuscript could be necessary to have a more solid idea about the multiple variables concerned with Gamma Knife treatment of Trigeminal Neuralgia. A paper is a brick in the knowledge wall and it could be better to look the whole wall instead of focusing the attention in just one brick.

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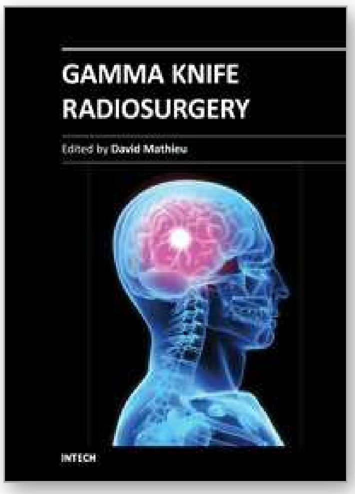

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