Chapter 1

Scope and implications of MRI-negative refractory focal epilepsy

Elson L. So and Philippe Ryvlin

Definition of MRI-negative epilepsy

In the absence of a demonstrable epileptogenic lesion, epilepsy is often referred to as “nonlesional epilepsy.” In this book, we preferentially use the term “MRI-negative epilepsy” instead of “nonlesional epilepsy.” Our reason for this preference is that MRI of patients with refractory epilepsy not infrequently shows structural lesions or alterations which are not the immediate cause of the epilepsy. Some of these lesions or abnormalities that are noncausative for epilepsy are cerebral atrophy, nonspecific white matter signal changes, and slight asymmetry in size or shape of regions in the brain. In these situations, the MRI cannot be said to be normal. Therefore, we avoided the use of the term “epilepsy with normal MRI.”

Another reason for our preferential use of the term “MRI-negative epilepsy” is that histopathological examination of resected tissues has revealed lesions in as many as 50% of nonlesional MRI patients, especially neuronal migrational abnormalities such as microdysgenesis and focal cortical dysplasias [1]. Conversely, histopathologically proven cortical dysplasia lesions are undetectable by MRI in 30% of the patients [2]. For these reasons, the term “nonlesional epilepsy” would be literally and technically incorrect. The term “MRI-negative epilepsy” better conveys the context in which it is used, in that the presurgical MRI is devoid of a structural abnormality as the probable cause of the epilepsy, and for which epilepsy surgery evaluation could be considered.

The term “cryptogenic epilepsy” has also been used in reference to MRI-negative epilepsy [3]. Whereas there is some overlap between the population of patients with cryptogenic epilepsy and the population with MRI-negative epilepsy, the two conditions do not always coexist in patients. The term “cryptogenic epilepsy” arose from the concept of classifying different types of epilepsy according to etiology [4]. An example of the complex interface between epilepsy etiology and MRI findings is in familial focal epilepsies. Unless clinical and laboratory investigations are conducted to establish the heredofamilial basis of the epilepsy, familial temporal or frontal lobe epilepsy could be classified as cryptogenic epilepsy. Some members in affected families have negative MRI, whereas others have epileptogenic lesions such as mesial temporal atrophy [5]. Yet, epilepsy surgery has been effective in some MRI-positive and some MRI-negative familial focal epilepsies. Nonetheless, MRI findings have overall been consistently a more important factor than epilepsy etiology in identifying patients for epilepsy surgery, and in prognosticating the outcome of the surgery.

Implications of MRI-negative epilepsy

Despite the use of optimal conventional MR-imaging techniques, the proportion of epilepsy surgery candidates with MRI-negative epilepsy still ranges from 20% to 40% among epilepsy centers. Moreover, data from the USA show a trend of declining hospitalizations in large epilepsy centers over about 20 years [6]. Some large epilepsy centers have verbally reported increasing proportions of MRI-negative patients, and declining volumes of resective surgeries. A study is underway to verify these observations.

Epilepsy surgery is less likely to be considered in MRI-negative epilepsy patients than in MRI-positive patients. Up to 30% of patients prospectively evaluated in experienced epilepsy surgery centers were not
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deemed to be surgical candidates, and a major factor for not undergoing surgery is the absence of an MRI lesion and other localizing evidence [7]. In a single-center study of both temporal and extratemporal epilepsy patients who had modern MRI imaging, only 15% of MRI-negative patients were offered surgery vs. 73% of MRI-positive patients [8].

One reason why only a minority of MRI-negative refractory epilepsy patients proceed to surgery is that seizure localization evidence in MRI-negative patients is often lacking. Localization to the epileptogenic zone by seizure semiology was correct in only about 34% of the patients, 14% by interictal scalp EEG, 28% by ictal scalp EEG, 29% by PET, and 15% by SISCOM. The rate of discordance between the results of these tests is also high in MRI-negative patients. This overall deficiency in concordant seizure-localizing findings often necessitates intracranial electrode implantation to identify the ictal onset zone. A retrospective study of patients who underwent epilepsy surgery evaluation shows that all MRI-negative patients, compared with 50% of MRI-positive patients, had undergone intracranial electrode implantation [9]. The extent and complexity of intracranial electrode implantation are often greater in MRI-negative than in MRI-positive patients, in whom the cerebral lesion would have guided the extent of intracranial electrode coverage. The risk of complications with intracranial electrode implantation is associated with the extent of the implantation. The risk has been reported to increase by 40% for every additional 20 subdural electrodes implanted [10]. Yet, extensive intracranial electrode implantation may not assure higher probability of postsurgical seizure control. It has been reported that neither the extent nor the type of intracranial ictal EEG discharge predicts postsurgical seizure freedom in MRI-negative epilepsy surgery [11].

The presence of an epileptogenic lesion in a surgically safe and accessible location is the single most favorable factor in determining outcome of epilepsy surgery. Numerous studies have consistently contrasted the prognosis between MRI-positive and MRI-negative epilepsy surgery. Meta-analysis of studies on the subject shows that, compared with MRI-negative patients, MRI-positive or histopathology-positive patients have a 2.5 times higher chance for seizure freedom following epilepsy surgery. Selected groups of lesional temporal lobe epilepsy surgeries are associated with a 90% chance of excellent postsurgical seizure control, whereas the rate is only 65% in MRI-negative temporal lobe surgeries [12]. Similarly, lesional frontal lobe epilepsy surgeries have a 72% probability of excellent postsurgical seizure control, whereas the rate is only 41% in MRI-negative frontal lobe surgery [13]. In one study of both temporal and extratemporal refractory epilepsy, surgery resulted in seizure freedom in only 38% of the MRI-negative patients vs. 76% of the MRI-positive patients [8]. However, many studies have shown that the outcome of MRI-negative epilepsy can be improved with the use of modern diagnostic measures, with instances of excellent surgical outcome rates approximating those in MRI-positive epilepsy [14]. Therefore, a major objective of this book is to critically assess and identify measures that can improve the surgical outcome of MRI-negative epilepsy surgery.

MRI-negative epilepsy surgeries also carry a higher risk for postoperative functional deficits than surgeries involving an MRI lesion. MRI-demonstrated lesions such as tumors or encephalomalacias are generally expected to be devoid of intrinsic cortical function; thus, their borders provide good, though imperfect, demarcation between nonfunctioning and functioning tissues. Such anatomical guidance is lacking in MRI-negative epilepsy. Additionally, a greater degree of intrinsic cortical function resides in epileptogenic tissues that are MRI-negative than in MRI-demonstrated lesions. Helmstaedt and colleagues have observed that MRI-negative patients experience more prominent memory loss after temporal lobectomy than MRI-positive patients [15].

MRI-negative refractory epilepsy patients could still benefit from surgery [16, 17], especially if a more modest postsurgical prognosis than seizure freedom is acceptable to the patient. Alarcon and colleagues found that postsurgical seizure frequency of three seizures or less per year is as likely to be achieved in MRI-negative surgeries as in MRI-positive surgeries (74% vs. 73%) [9]. Nonetheless, in their subgroup of extratemporal epilepsy, MRI-negative patients had a much lower rate of achieving seizure freedom than MRI-positive patients (16.7% vs. 39.1%). The putative goal of surgery for medically refractory epilepsy should be seizure freedom, given that improvement in quality of life after surgery is best associated with the achievement of complete seizure control [18].

The less favorable outcome of MRI-negative epilepsy surgery may be due to a number of factors. Without a visible potentially epileptogenic lesion, the epileptogenic zone may be missed or underestimated. In some MRI-negative patients with extratemporal...
epilepsy as proven by intracranial EEG and favorable postsurgical outcome, presurgical video-scalp EEG recordings had wrongly localized seizure onset to the temporal lobe [19]. The pathology underlying MRI-negative epilepsy is also poorly understood and possibly widespread or multifocal. Although cortical dysgenesis is increasingly found in resected tissues from patients with MRI-negative epilepsy, the histopathology in as many as 50% shows only nonspecific changes such as “gliosis.” In fact, the absence of a clear-cut epileptogenic lesion in the histopathology and the persistence of seizures after surgery in many MRI-negative patients may be consequences of misguided resection which failed to include the epileptogenic histopathological lesion, or the absence of a well-delineated epileptogenic lesion for resection. In the latter situation, the pathophysiology of epileptogenesis might involve molecular or cellular abnormalities affecting large portions of the brain, which constitutes a more widespread epileptogenic network than that of epilepsy with a definite MRI-detectable or histopathology-proven lesion. Examples of this concept include focal epilepsies associated with mutations of the nicotinic acetyl-choline receptor subunit (autosomal dominant nocturnal frontal lobe epilepsy) or of the leucine-rich glioma-inactivated 1 gene (autosomal dominant focal epilepsy with auditory features), or multifocal type 1 cortical dysplasia.

Therefore, the critical issue in the presurgical evaluation of refractory MRI-negative epilepsy is the development and validation of diagnostic strategies for localizing the epileptogenic zone and surgical approaches for resecting the zone. Accordingly, “biomarkers” could be developed to identify subgroups of MRI-negative patients with favorable surgical prognosis, such as those with MRI-occult focal cortical dysplasia (FCD). When used alone or in combination, clinical information, scalp EEG, MEG, SPECT, or PET may in the future presurgically distinguish between MRI-occult type II FCD where surgical prognosis is favorable, and type I multifocal/extensive cortical dysplasia where the prognosis is poorer. It is also conceivable that advances in current and future diagnostic techniques may prove that a comprehensive understanding of the pathophysiology underlying each case of MRI-negative epilepsy is more important for postsurgical outcome than the current strategy of identifying the seizure onset zone.

Scope of the issues

Our terminology of “MRI-negative epilepsy” includes instances when MRI shows a subtle focal finding that is suspected or disputed to be the cause of the refractory epilepsy [20, 21] (Figure 1.1) The reason is that evaluation for epilepsy surgery is just as complex and
rigorous whether or not a subtle or disputable finding is present on the MRI. The tests and strategies available for localizing and resecting the ictal onset zone are applicable in either case.

There are also instances when the histopathological examination of resected tissues disclosed lesional pathology, which then prompted reassessment of the presurgical MRI that was perviously pronounced to be negative [20]. With reassessment of the presurgical MRI, a subtle lesion or alteration at the location of the surgery was then recognized. Visual reassessment of the MRI combined with morphometric analysis have retrospectively identified a subtle lesion in eight of nine patients whose presurgical MRI was deemed negative, but postsurgical tissue examination showed lesional pathology [8]. These situations should still be considered as MRI-negative epilepsy, because the presurgical knowledge of the MRI result had been the basis for developing the strategies in identifying and resecting the ictal onset zone, and also in prognosticating the surgical outcome.

Both presurgically and postsurgically detected subtle MRI alterations should be further scientifically investigated, because studies have suggested that subtle focal alterations in otherwise MRI-negative epilepsy could be associated with excellent postsurgical seizure control [8, 20]. With continuing advancements in MRI imaging, MRI findings that are currently negative, subtle, or disputable for epilepsy surgery consideration may eventually be detected and recognized as definite anatomical lesions with potential epileptogenicity. Even before then, advancements in functional imaging and electrophysiology may establish subtle alterations to be highly probable ictal onset zones, which may be targeted for further seizure localization studies and subsequent surgical resection. Accumulation of experience in surgery of patients with subtle MRI alterations will lead to better understanding of their histopathological nature [3].

There are many types of MRI-negative epilepsies that are of generalized or indeterminate onset, but this book concentrates on the surgical evaluation and treatments of refractory focal epilepsy. Nonetheless, much of the methods and approaches in searching for the seizure onset zone for focal resective surgery are also applicable in evaluating patients with suspected generalized or indeterminate seizure onset. When the evaluation process has more confidently excluded focal refractory epilepsy, and the generalized-onset nature of the epilepsy is affirmed, the appropriate pharmacologic or surgical treatments for the nonfocal epilepsy may then be considered.

In concentrating the treatise of this book on refractory focal epilepsy, the authors make no presumptive restriction regarding the size or extent of the seizure focus for inclusion in this book. The extent of the seizure focus or foci, and their relationship to eloquent cortex, is at the crux of the complexities and nuances of MRI-negative epilepsy surgery evaluation. We have also specifically included in this book the discussion of temporal-plus epilepsy and posterior cortical epilepsy, in which the clinical and scalp EEG findings appear to involve the parietal, occipital, or temporal lobe, or a combination of these lobes, and the intracranial recording subsequently confirming either a unilobar or multilobar region of seizure onset.

References


Seizure semiology and scalp EEG in MRI-negative refractory focal epilepsy

Soheyl Noachtar and Elisabeth Hartl

The rationale of epilepsy surgical intervention depends on the localization of the epileptogenic zone and its complete removal [1]. The following methods were used to delineate the epileptogenic zone [2]:

- seizure description and patient history
- MRI
- interictal EEG
- ictal EEG–video monitoring
- ictal (and interictal) SPECT
- interictal PET
- neuropsychological evaluation

Several studies have shown that it is more difficult to identify the epileptogenic zone if MRI does not reveal any abnormality [2, 3]. In general, the chance of a postoperative seizure freedom outcome from epilepsy surgery is less favorable in nonlesional MRI-negative patients as compared to patients with MRI-documented lesions [3]. However, thanks to advances in MRI technology, the sensitivity in detecting epileptogenic lesions improved dramatically over the last two decades [4]. It is, therefore, mandatory to perform state of the art epilepsy-oriented MRIs before stating that a given patient has MRI-negative epilepsy.

Concordance of noninvasive results implicating a resectable focus is usually considered the prerequisite to proceed to epilepsy surgery based on noninvasive studies only. This is mostly true in temporal lobe epilepsy, which is the most common focal epilepsy that is referred to epilepsy surgery centers. However, in a large series of unselected patients with extra-temporal lesions, discrepancy of EEG and MRI localization was more common than congruence [5]. Discrepancy did not necessarily imply that resective epilepsy surgery was associated with poor postsurgical outcome [5]. Invasive evaluation may be used in patients in whom noninvasive studies are inconclusive or reveal discrepant results, but still support a testable hypothesis of a resectable focus. Under these circumstances, properly placed invasive electrodes frequently provide useful additional information about the localization and extent of the epileptogenic zone. If MRI is negative, the definition of the epileptogenic zone has to rely on localization information derived from methods such as seizure semiology and EEG, which then become more important. Frequently, in MRI-negative patients, invasive studies are required to define the localization of the epileptogenic zone.

Interictal EEG

Electroencephalography is the most specific method to define the epileptogenic cortex. Interictal epileptiform discharges, particularly if consistent over time, can provide useful information [6]. In temporal lobe epilepsy, consistently unitemporal interictal epileptiform discharges (IED) have a better prognosis for seizure freedom than bilateral IEDs. Focal, particularly extratemporal, epilepsies in which the EEG shows active regional polyspikes are more likely associated with cortical dysplasia as etiology of the epilepsy than patients with other IEDs [7]. Rhythmic midline theta activity, which is distinct from patterns of drowsiness of mental activation, is highly significant for frontal lobe epilepsy and rarely seen in temporal lobe epilepsy [8]. This is particularly interesting since one out of four of these frontal lobe epilepsy patients did not show any interictal epileptiform discharges on noninvasive long-term EEG-monitoring and the rhythmic midline theta was the only interictal EEG abnormality [8].

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Ictal EEG–video monitoring

Ictal EEG–video recording is critical in localizing the epileptogenic zone. A careful analysis of the first clinical signs and symptoms of a seizure and of the evolution of the seizure symptomatology can provide important clues on the epileptogenic zone [9–11]. One must keep in mind, however, that often an epileptic seizure arises from a “silent” region of cortex and would remain asymptomatic unless it spreads to “eloquent” cortex such as primary motor, primary sensory, or supplementary sensorimotor areas (Figure 2.1). Unfortunately, ictal EEG frequently documents discrepant results in extratemporal epilepsies [5]. Good concordance to MRI lesions and interictal EEG is only typical for temporal lobe epilepsy [5].

Seizure semiology

Careful clinical observations and detailed reports of seizure semiology by the patient or observers have been used since the 18th century to classify epileptic seizures and epileptic syndromes. A detailed analysis of seizure semiology is still essential for the proper management of epileptic patients. A clear definition of the seizure type is important for classifying the epilepsy syndrome of the patient. The syndrome, together with the etiology of the epilepsy, are the essential factors determining the prognosis as well as the most effective pharmacological treatment. Seizure semiology plays an important role in the presurgical work-up, particularly when analyzed independently of other presurgical tests (EEG monitoring, neuroradiology, etc.). In addition, seizure semiology can be used effectively to differentiate between epileptic and nonepileptic seizures.

It is very important to emphasize that as a rule epileptic discharges limited to the seizure onset zone do not cause clinical symptoms unless located in an eloquent area (Figure 2.1). This is because the epileptogenic zone does not necessarily overlap with the symptomatic zone [1]. The term symptomatic zone refers to the area of the cortex that produces certain clinical symptoms as a result of epileptic activation. For example, seizures that originate in the frontal convexity remain asymptomatic as long as they do not spread into the symptomatic zones. If the epileptic activation reaches the primary motor area, versive or focal clonic seizures result (Figure 2.1). If the supplementary sensorimotor area is activated, focal tonic or hypermotor seizures occur; and if the activation spreads into the limbic system (cingulate gyrus), features of the seizure possibly become those of automotor seizures [12] (Figure 2.1). There is some association of specific seizure types with brain regions: seizures characterized by oral and manual automatisms (automotor seizures) [13, 14] are more common in temporal lobe epilepsy than in extratemporal epilepsy [15]. However, the specificity to temporal lobe epilepsy is much higher if automotor seizures are preceded by epigastric (abdominal) auras [15]. Similarly, unilateral clonic seizures of the face are frequently seen in patients with paracentral epilepsies. However, the same seizure type may occur in patients with temporal lobe epilepsy but then is usually preceded by manual and oral automatisms (automotor seizure. In fact, this evolution is more likely to occur in

Figure 2.1 Illustration of the relation of the seizure onset and symptomatic zones. Seizure onset in the prefrontal region is likely to stay unnoticed unless the epileptic activity spreads into symptomatic cortex:
1. Spread into the supplementary sensorimotor area leads to bilateral asymmetric tonic seizure
2. Spread into the somatosensory hand area leads to right face clonic seizure
3. Spread into the frontal eye field leads to right versive seizure
4. Spread into frontal speech area leads to aphasic seizure
Seizure onset in the left occipital lobe leads to the following seizure evolution:
5. Right visual aura ⇒ right versive seizure
Seizure onset in the temporal lobe leads to the following seizure evolution:
6. Acoustic aura/abdominal aura ⇒ automotor seizure ⇒ right face clonic seizure.
lateral than mesial temporal lobe epilepsy [16]. Unilateral clonic seizures may be associated with both frontal and temporal lobe epilepsies. However, the sequence of the seizure evolution makes a major difference. In temporal lobe epilepsy, unilateral facial clonic seizures are typically preceded by manual and oral automatisms, which are rarely the case in frontal lobe epilepsy. Thus, the association of single-seizure types to particular localizations of the epileptogenic zones is not as strong as the association of the evolution of seizure types to specific brain regions. This may explain why several studies which neglected this fact found poor localizing value of seizure semiology [17]. Another limitation is that many studies relied on the description of seizures rather than investigating adequate video-recorded seizures [17]. Patients’ or witnessess’ descriptions of seizure are subject to bias and not sufficiently reliable.

Table 2.1 summarizes studies on nonlesional epilepsy patients. A computerized online search via MEDLINE (online PubMed from first available year to April 2013) using the search term “nonlesional epilepsy” identified 121 studies, of which 78 were excluded for being review articles (n = 16), meta-analysis (n = 1), or a commentary (n = 1). Animal studies (n = 2), genetic studies (n = 4), as well as ten studies investigating symptomatic epilepsy and 19 not clearly differentiating between nonlesional and lesional epilepsy patients (n = 19) were excluded. Seven publications including patients with status or witnessess of epilepsy syndromes were excluded, as they do not localize in early infancy. In addition, studies were excluded if they did not use MR imaging (n = 6) or were written in languages other than English or German (n = 9). Two publications were excluded, because the full text was not available online. In total, 43 studies met our inclusion criteria.

Different terminologies were used to classify or label seizure semiology. It was mostly labeled after the lobe, such as temporal lobe seizure or frontal lobe seizure, providing no reliable clinical information on the seizure characteristics. Other studies used the seizure classification system of the International League against Epilepsy with terms such as complex partial seizures (CPS) or simple partial seizures (SPS). These terms only provide the information whether consciousness is disturbed or not in patients with focal epilepsies regardless of the actual seizure semiology. Only few publications of case series provide detailed information on seizure semiology and EEG findings [18–20]. We, therefore, use the semiological seizure classification to provide clinically localizing information [13, 14]. With the help of EEG–video-recorded seizures, several very reliable lateralizing signs have been identified which have an accuracy of 80–100% (Table 2.2) [12, 21].

The EEG data were mostly reported as being concordant or discordant with the other diagnostic findings (Table 2.1). Highest diagnostic sensitivity in the localization of epileptogenic foci and seizure lateralization was demonstrated for ictal scalp EEG. Concordance rate was higher in the good than in the poor surgical outcome group [22].

The lateralizing and localization value of seizure semiology, and their role in MRI-negative surgery, are further discussed elsewhere in this book according to the brain regions affected by epilepsy (Chapters 14, 15, 16, and 18), in children (Chapter 17), and with relevance to cortical mapping (Chapter 13).

### Illustrative patients

How seizure semiology and EEG help to develop a hypothesis on the epileptogenic zone in patients with negative MRI is illustrated by the following two patients:

**Patient 1:** This 27-year-old, right-handed female bank clerk has had epileptic seizures since the age of 8 years. She had frequent predominantly nocturnal hypermotor and asymmetric bilateral tonic seizures which were sometimes preceded by an aura of fear. Her MRI was normal. Interictal EEG revealed evenly distributed right and left mesial temporal interictal epileptiform discharges and slowing. Ictal EEG showed frontal, nonlateralized seizure patterns. Postictally, the patient was at times aphasic and her generalized tonic–clonic seizures were preceded by right versive seizures. Her medical history was unremarkable. Antiepileptic medications in monotherapy and several combinations did not control the seizures.

In summary, MRI was negative, ictal EEG showed nonlateralized frontal abnormalities, and interictal EEG demonstrated bitemporal discharges. However, semiology was pointing to a left hemisphere and a likely frontal onset (sleep predominance, hypermotor seizure, bilateral asymmetric tonic seizures, right versive seizure, postictal aphasia). Based on these noninvasive findings, an invasive evaluation was performed with subdural grid electrodes covering the left frontal convexity, and strip electrodes over the left mesial frontal and right lateral frontal region. Seizure onset could be identified over wide areas of the mesial and lateral left frontal lobe.
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<td>13 (5/8)</td>
<td>13 CPS</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a. (4)</td>
<td>N</td>
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<td>Nakayama et al. (2009)[42]</td>
<td>CR</td>
<td>1 (1/0)</td>
<td>1 CPS, 1 GTC</td>
<td>a.</td>
<td>-</td>
<td>-</td>
<td>Y</td>
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<tr>
<td>Tanriverdi et al. (2009)[43]</td>
<td>uCCT</td>
<td>393 (191/202)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>N</td>
<td>185</td>
<td>208</td>
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<tr>
<td>Velasco et al. (2009)[44]</td>
<td>CR</td>
<td>2 (1/1)</td>
<td>2 SPS, 2 SGC</td>
<td>a.</td>
<td>a.</td>
<td>a. (2)</td>
<td>N</td>
<td>2</td>
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<td>Aubert et al. (2009)[45]</td>
<td>uCCT</td>
<td>8 (3/5)</td>
<td>-</td>
<td>n.a.</td>
<td>n.a.</td>
<td>a. (8)</td>
<td>N</td>
<td>5</td>
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<tr>
<td>Poon et al. (2010)[46]</td>
<td>CR</td>
<td>1 (0/1)</td>
<td>1 CPS</td>
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<td>a.</td>
<td>a. (1)</td>
<td>Y</td>
<td>1</td>
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<td>Lowe et al. (2010)[47]</td>
<td>uCCT</td>
<td>76 (-/-)</td>
<td>-</td>
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<td>n.a. (24)</td>
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<td>Oliva et al. (2011)[48]</td>
<td>uCCT</td>
<td>12 (4/8)</td>
<td>-</td>
<td>a.</td>
<td>-</td>
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<td>N</td>
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<td>Mankinen et al. (2011)[49]</td>
<td>pCCT</td>
<td>21 (10/11)</td>
<td>-</td>
<td>a.</td>
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<td>N</td>
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