Title

Refractive Corneal Inlay Implantation Outcomes: A Preliminary Systematic Review

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Abstract

Purpose

To review all case series of refractive corneal inlay implantation: Flexivue (Presbia, Netherlands), Invue (BioVision, Brügg, Switzerland) and Icolens (Neoptics, Hünenberg, Switzerland) performed in presbyopia patients and to evaluate the reported visual outcomes. In addition, our aim is to provide assessment for complications and to report the satisfaction rates.

Methods

PubMed, Web of Science and Scopus databases were consulted using "refractive corneal inlay", "Flexivue Inlay", "Invue Inlay" and "Icolens inlay" as keywords. 147 articles were found, and they were assessed considering the inclusion and exclusion criteria. After filtering, this systemic review included ten articles, published between 2011 and 2020.

Results

308 eyes from 308 participants were enrolled in this systematic review. Mean maximum follow-up was 13.9 months. Nine of the ten case series included used femtosecond laser for the corneal pocket creation. Mean pocket depth was 293.75 µm. 77.5 % of the eyes reported a postoperative uncorrected near visual acuity of 20/32 or better, and 19.20 % of the inlay-implanted eyes achieved an uncorrected distance visual acuity of 20/20 or better. The most prominent complications were halos, pain, photophobia, and poor distance visual acuity. 27 eyes (8.7 %) had to be explanted due to complications, such as near-distance spectacle dependence or blurred distance vision.

Conclusion

Refractive corneal inlay outcomes demonstrated high efficacy, safety, and satisfaction rates. Furthermore, it is a reversible technique. However, the findings must be viewed with caution due potential conflict of interest. Further research with higher sample size is needed to validate these findings.

Introduction

Presbyopia is the progressive loss of the eye's ability to focus on nearby objects.[1] It is the most frequent refractive error, and its incidence and prevalence increase every year.[2] Reduced spectacle dependence is a common expectation among people with active lifestyles.[3] Currently, there are different surgical and non-surgical approaches to try to solve this problem.[4] Refractive lens exchange with monofocal intraocular lens (IOL) targeting monovision, or more recently with trifocal IOL, has proved good outcomes.[1, 3] Furthermore, presbyopia laser corneal correction has also reported optimal results.[5] The most recent approach to treat presbyopia is the implantation of corneal inlays. These devices are implanted in the non-dominant eye within a corneal pocket, or under a stromal flap created using a mechanical microkeratome[6] or femtosecond laser.[7] Their aim is to improve near and intermediate visual acuity while preserving a good distance visual acuity in the fellow eye. Currently, there are three different types of presbyopia corneal inlays with different mechanisms of action.[2] The first type are corneal reshaping inlays, that modify the anterior corneal curvature to produce a multifocal cornea (Raindrop, ReVision Optics, Lake Forest, CA, USA; no longer marketed).[8] The second type, small-aperture intracorneal inlays (SAICI), commonly known as KAMRA (KAMRA™, AcuFocus Inc., Irvine, CA, USA),[9] act as a pinhole, creating a light channel through the small opening aperture, hence avoiding peripheral unfocused light from passing through and increasing the focus depth. Finally, refractive inlays modify the refractive index of the cornea using a bifocal optic (Flexivue, Presbia, Netherlands; Icolens, Neoptics, Hünenberg, Switzerland and Invue Inlay BioVision AG, Brügg, Switzerland).[1] The depth of the pocket is related to the design of each inlay. Inlays designed to vary refraction are deeply implanted, while inlays that attempt to modify corneal curvature are implanted more superficially.[2]

The Presbia Flexivue Microlens^{TM} (Presbia, Irvine, California, USA) is a clear hydrogel implant made from hydroxyethylmethacrylate and methylmethacrylate with a diameter of 3.2 mm. It has a central plano area of 1.6 mm. surrounded by multiple rings of progressively increasing powers from +1.50D to +3.50 D, creating a multifocal effect. The lens has 15-20 µm thickness from the center to its periphery, and it varies depending on the additional power. It acts by modifying the cornea's refractive index. At the center of the disc, a 0.50-mm diameter hole enables the transference of oxygen and nutrients into the cornea through the lens.[10]

The Invue lens (BioVision AG, Brügg, Switzerland) is a transparent hydrogel-based disc with a 3mm. diamater and an approximate thickness of 15 to 20 μm, depending on the added power. The central 1.8mm center diameter has no power, and the annular peripheral zone has an added power. At the center of the disc, it has a 0.15 mm hole to allow the transference of oxygen and nutrients into the cornea through the lens. The power varies from +1.25D to +3.00 D in 0.25-D increments.[11]

The Icolens inlay (Neoptics, Hünenberg, Switzerland) is a 3 mm hydrogel microlens made of a copolymer of 2-hydroxyethyl methacrylate and methyl methacrylate. It possesses a bifocal design, a central zone for distance vision and a peripheral positive refractive zone for near vision (Figure 1). The central zone has a 1.8 mm. diameter, an edge thickness of 15 mm., and a 150 mm. central hole to facilitate nutrient flow.[12] The main difference compared to the others is that Icolens is available with some refractive power in the central zone to correct distant vision.

Presbyopia correction using these refractive inlays is based on the fact that in far vision, the rays that pass through the central zone of the implant and the peripheral corneal tissue, free from the lens' added refractive effect, will be sharply focused on the retina. Conversely, rays that pass through the refractive peripheral zone of the inlay will be focused in front of the retina; whilst in near vision, due to the miosis-convergence-accommodation triad, the rays passing through the central zone of the implant will be unfocused behind the retina, and rays passing through the peripheral clear cornea will be blocked by the pupil. The rays passing through the peripheral refractive zone of the inlay will be focused on the retina.[10]

The purpose of this study is to review all case series of refractive corneal inlay implantation (Flexivue Inlay, Invue Inlay, and Icolens Inlay) in presbyopic patients reported in the literature in order to evaluate the visual outcomes, postoperative complications, and satisfaction rates.

Methods

This systematic review was carried out by searching in PubMed, Web of Science and Scopus databases on June 10, 2020. The study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement recommendations.[13] An initial search, focused on obtaining case studies of refractive corneal inlays in presbyopic patients, was firstly carried out. The keywords used were

''refractive corneal inlay'', "Flexivue inlay", "Invue inlay" and ''Icolens inlay''. From the initial search, a total of 147 articles were identified, which were evaluated and selected according to inclusion and exclusion criteria. Inclusion criteria were: (I) Flexivue, Invue or Icolens inlays implantation in presbyopia patients with or without prior surgery. The exclusion criteria were: (II) narrative reviews; (III) animal studies; (IV) non-English publications; (V) corneal shape-changing inlays, such as Raindrop or small-aperture corneal inlay KAMRA inlays; (VI) articles with no findings or conclusions; (VII) articles in non-indexed scientific journals.

The recorded data were; (1) authors and year of publication, (2) conflicts of interest, (3) study design, (4) maximum follow-up period expressed in months, (5) number of patients, (6) number of eyes implanted, (7) sex, (8) inlay type (Flexivue, Invue or Icolens inlay), (9) intrastromal flap / pocket creation technique (mechanical microkeratome or femtosecond laser), (10) pocket depth (expressed in microns, μm), (11) patients' past history and previous surgeries, (12) visual postoperative improvements of uncorrected near visual acuity (UNVA) and uncorrected distance visual acuity (UDVA), (13) patients' satisfaction rate, (14) postoperative complications, (15) postoperative cell density count, and finally, (15) postoperative corneal central thickness. To assess the risk of bias of the included studies, a summary table (Table 1) based on the Quality Assessment Tool for Case Series Studies from the National Heart, Lung, and Blood Institute was elaborated.[14] Questions included in the mentioned table were: (1) Is the study oriented to a clear question?; (2) Were all the patients results taken into account?; (3) Was the follow-up complete?; Were the same conditions used in surgical treatment?; (5) Was the intervention clearly described?; (6) Was the duration of follow-up adequate?; (7) Were the results described correctly? This analysis did not result in the exclusion of any article. However, articles with a higher risk of bias had a lower weight for the data synthesis. Risk of bias was assessed by C-RL and JM.SG. There were no disagreements in the assessment among the authors.

Statistical Analysis

Data was analyzed using SPSS statistics software (version 26.0 for Windows; SPSS Inc, Chicago, IL, USA). Descriptive analysis was carried out with values expressed as mean ± SD and range. For all tests, level of significance was established as 95% ($P < 0.05$).

Results

The selection process of this systematic review was presented with a flow chart diagram in Figure 1. A total of ten articles[6, 7, 10–12, 15–19] published between 2011 and 2020 were included. All of them were case series or case reports and no randomized clinical trial was included. They were all prospective, except for Bouzoukis et al[7], Duignan et al.[6] and Han et al.[18]. None had a control group. We included presbyopic patients between 45 and 65 years old, with a preoperative manifest refractive spherical equivalent between -0.75D and +1.00D, with no more than -0.75D of refractive cylinder, uncorrected near visual acuity under 20/50 (Snellen scale) or 0.4 (Logarithm of the Minimum Angle of Resolution, LogMAR scale). Near addition required was between +1.00 diopter (D) and +2.50 D an minimum central corneal thickness (CCT) was established in 500 µm for most of the articles. A minimum central endothelial cell count (ECC) of 2000 cells/mm^2 or more and a corneal power from 41.00 D to 47.00 D in all meridians was required. According to the exclusion criteria, patients with anterior or posterior segment diseases, or degeneration (except for cataracts), any type of immunosuppressive disorder, patients using systemic medications with associated side effects, and those with latent hyperopia, were not included. Patients' and surgeries' characteristics of the selected articles were summarized in Table 2.

This systematic review included 308 eyes from a total of 308 patients (no study reported two eyes of the same patient), and a maximum postoperative follow-up that ranged from 1 week to 36 months, with the mean maximum follow-up of 13.9 months. Six studies[7, 10, 15–17, 19] declared conflicts of interest as medical advisor or consultant. Eight studies reported findings with Flexivue inlay,[6, 7, 10, 15–19] one study with Invue inlay[11] and one study with Icolens inlay[12]. It is also important to indicate the surgical technique used in each case, as well as the corneal pocket depth. Nine articles[6, 7, 10, 12, 15–19] used femtosecond laser for intrastromal pocket creation, and only one study[11] used a mechanical microkeratome approach. Regarding the pocket depth, it ranged from 280 µm to 300 µm and the mean pocket depth was 293.75 µm. Results after all corneal refractive inlays available in scientific literature were presented in Table 3. Concerning the past ocular history of the patients, there were nine articles[6, 7, 10–12, 15, 17–19] with emmetropic presbyopia, and one case series[16] recruited patients with previous cataract surgery. In the postoperative period, we highlighted the improvement in UNVA. In the last follow-appointment, UNVA ranged between 22% to 100% of eyes with 20/32 or better (J2, Jaeger), with a mean UNVA of 77.75 % of eyes with 20/32 or better. UIVA was not reported by any study. Eye

157 treated UDVA was reported in percentage of eyes with 20/20 or better, and it ranged between 0% to 100% with a
158 mean UDVA of 19.20% of eyes with 20/20 or better.

159 Pain, photophobia, and halos were the most reported complications. The latter, near distance spectacle
160 dependence and visual complaints were responsible for the explantation of the refractive inlays together. The
161 number of explanted refractive inlays were 27 (8.7 % of the total implanted). Patients' satisfaction was presented
162 in different formats. The best satisfaction reports were obtained in five studies,[10, 15–18] while the worst ones
163 were achieved by three of them.[11, 12, 19] Finally, the studies were grouped into three categories based on the
164 risk of bias assessment tool: low evidence (yeses = 0 to 2); medium evidence (yeses = 3 to 5); high evidence
165 (yeses = 6 to 7). Duignan et al.[6] obtained a low evidence level. Bouzoukis et al.,[7] Malandrini et al.,[15] and
166 Stojanovic et al.[16] achieved a medium evidence level. Finally, Bouzoukis et al.,[11] Limnopoulou et al.,[10]
167 Baily et al.[12] Beer et al.,[17] Han et al.,[18] and Beer et al.[19] obtained a high evidence level.

168 **Discussion**

169

170 *Visual outcomes*

171 Refractive addition corneal inlay proved an improvement in UNVA in all studies. Refractive inlays were designed
172 with a central zone free from refractive power, and a peripheral zone with standard positive refractive power.[19]
173 UNVA improved due to myopic shift in spherical equivalent and negative spherical aberrations.[10] 77.5% of
174 eyes reported UNVA of 20/32 or better. The best near visual outcomes were reported in five studies,[7, 11, 15,
175 16, 19] although they might be biased as they are published by members of the Presbia™ company medical advisor
176 board or consultants for Presbia™. Lowest UNVA were found in the Icolens inlay.[12] Significant decrease of
177 UDVA was observed in most of the studies. 19.20% of eyes reported a UDVA of 20/20 or better. Pocket
178 intrastromal creation improves centering and requires a smaller incision, hence fewer corneal nerves are cut and
179 there is less chance of causing dry eye.[20] Usually, a femtosecond laser was used to create an intrastromal pocket,
180 which works using the photo disruption principle emitting infrared pulses and achieving tissue separation at a
181 molecular level without affecting the surrounding tissue. However, there were two cases in which a mechanical
182 microkeratome was used.[21, 22] In accordance with various authors,[23, 24] femtosecond laser should be used
183 to obtain better results in surgery, or else, an automatic microkeratome. The use of mechanical microkeratome
184 should be avoided due to its imprecision and its worse results.[25] Limnopoulu et al.[10] found that the root mean
185 square (RMS) of the spherical aberration was increased at 3-mm pupil diameter. It was estimated that corneal and

total eye high aberrations are affected by the refractive inlay. The inlay centration could be a possible justification for this increase. In the daily practice, the refractive inlay surgeon should try to align the device coaxially with the corneal reflex. Till today, it remains unclear whether another position would enhance optical quality.

Complications & Safety

Small-aperture inlays have reported a few anecdotical complications, such as epithelial ingrowth, corneal edema, stromal thinning flap striae or decentration. Conversely, patients with refractive inlay implantation included in this systematic review did not present serious complications,[26] except those reported by Duignan et al.,[6] where two eyes in two patients with Flexivue inlay suffered a painful infectious corneal infiltrate three and two days after the implantation, respectively, affecting UCVA and BCVA, and isolating Corynebacterium pseudodiphtheriticum, a Gram-positive bacillus, in one of the cases. In these two cases, it was not necessary to explant the inlay. Inlay implantation is a very similar procedure to the insertion of intrastromal corneal ring segments (ICRS) for the treatment of keratoconus or other ectasia, where a synthetic foreign body is permanently placed within the corneal stroma. There are hardly any published data regarding the incidence of infectious keratitis in these patients. In the Phase II and III studies of ICRS, only one out of 449 patients developed infectious keratitis.[27] Although we have only been able to observe two reported cases,[6] it is important to try to minimize the possibility of developing infectious keratitis, as it is a serious and possible complication that can be devastating in patients undergoing an elective presbyopia treatment with corneal inlay implantation. Risk factors for infectious keratitis after flap or surface ablation procedures are known to involve patient-specific factors, such as blepharitis or dry eye disease; intra-surgical components, such as intraoperative epithelial defects or suboptimal asepsis; and postoperative traumatisms.[6, 28] Although these conditions were not reported in the study by Duignan et al,[6] these risk factors could similarly be the cause of infectious keratitis in patients who are going to undergo implantation of corneal incrustations such as presbyopia inlays or ICRS.

Patient satisfaction

Most studies have reported excellent levels of near vision satisfaction without changing their distance vision satisfaction among patients with inlay implantation. We only found 27 explanted inlays out of 308 eyes in this systematic review. One of the main problems of the inlays is the decrease in the contrast sensitivity and the

increase in the higher order aberrations, that along with the decrease in the CDVA and UDVA, were the main reasons for the explantation. Authors have hypothesized that guaranteeing a good centration is essential for the optimum functioning of the inlay, and an inadequate centration in certain cases may have contributed to inferior refractive outcomes.[12] Baily et al.[12] reported that the main cause of explantation in all of their reported eleven cases was a poor refractive outcome. The indications were inadequate centration in seven cases, ambiguous ocular dominance in three cases, and exaggerated expectations in one case.

It is known that contrast sensitivity is an important indicator of functional vision.[29] The loss of contrast sensitivity after femtosecond laser has been recognized as a factor that could decrease visual quality.[30] Stojanovic et al.[16] found that monocular contrast sensitivity in inlay-implanted eyes at frequencies of 12 and 18 cycles-per-degree (cpd) was lower in all of their patients under both mesopic and photopic conditions, compared to contrast sensitivity of the fellow eyes. Similarly, Beer et al.[17] reported that contrast sensitivity had decreased significantly ($p < 0.05$) in all eyes of their treated patients 3 years after surgery. In the same line, Bouzakis et al.[11] reported that contrast sensitivity in the operated eye decreased at all spatial frequencies at 1, 3, and 12 months postoperatively under mesopic and photopic conditions.

Other secondary and less likely reasons for explantation reported were certain photopic complaints, mainly glare and halos. Malandrini et al.[15] reported that all their explanted inlays were due to halos and glare complaints, in addition to a reduction in the UDVA. Han et al.[18] reported two eyes that required inlay explantation due to patients' complaints concerning blurred vision, glare and low UDCA. In contrast, Limnopoulu et al.[10] reported that only 12.5% of their patients experienced halos, and 12.5% experienced glare one year after implantation, although not affecting their daily activities.

Similar to small-aperture inlay implantation and to any refractive surgery, it is necessary to guarantee an optimal ocular surface. Therefore, in the case of a pre-surgical dry eye condition or any ocular surface disease, it is necessary to treat it appropriately prior to intervention,[31] since any corneal surgery may aggravate this condition. As the tear film is the first optical surface of the eye, management of dry eye disease is essential to ensure optimal function of corneal inlays.[2, 32] According to Han et al.,[18] corneal inlay implantation leads to a risk of corneal nerve fiber loss, although regeneration to the preoperative state was relatively rapid. Authors suggest that corneal inlay implantation requires a shorter side cut and smaller lamellar cut then SMILE, therefore they could experience a faster nerve regeneration.

Strengths and Limitations

To the best of our knowledge, this is the first systematic review of refractive corneal inlays available in the scientific literature. PRISMA statement recommendation improves the evidence level. Regarding the limitations of our study, only ten studies could be enrolled in this review. There is a lack of literature with no conflicts of interest, and a shape-changing comparison research could be performed in future research. Sixty percent of the studies included had conflict of interest. This means that 188 eyes (61.03%) were from authors with an interest disclosure, such as being the medical advisor or consultant for the manufacturing company of the respective inlay. None of these studies with conflicts of interest compared different inlays and, furthermore, none had a control group to make the comparison. Therefore, the reader must take into consideration the possible limitations derived from the conflict of interest after reading this systematic review.

In conclusion, refractive corneal inlays, such as Flexivue inlay, Invue inlay and Icolens inlay, achieved a high efficacy, safety, and satisfaction rate. These inlays improve near vision and clearly affect distance visual acuity. Furthermore, it is a reversible technique, hence it can be explanted if necessary. Postoperative complications have been reported, sometimes requiring inlay explantation. The type of surgical procedure, patient selection, and pocket depth are essential for successful surgery outcomes. However, the findings must be viewed with caution due potential conflict of interest.

Declarations

Conflicts of interest: All authors declare no competing interest

Source of Funding: No funding support

Ethics approval: This study was conducted in accordance with the tenets of the Helsinki Declaration and obtained Institutional Review Board approval.

Consent to participate: All patients included in this work were adequately informed verbally and in writing of the benefits, characteristics, and risks of the surgeries. All patients signed an informed consent prior to the surgery and after the interview performed with the ophthalmologist.

Consent for publication: All authors consent publication of this article

Availability of data and material: Data available on demand

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Figure legends

Figure 1. Study selection process according to the PRISMA statement.

Table legends

Table 1. Quality Assessment Tool for Case Series Studies.

Table 2: Study characteristics and patient population.

Table 3: Evaluation of the visual results after the implantation of Small-Aperture Intracorneal Inlay.

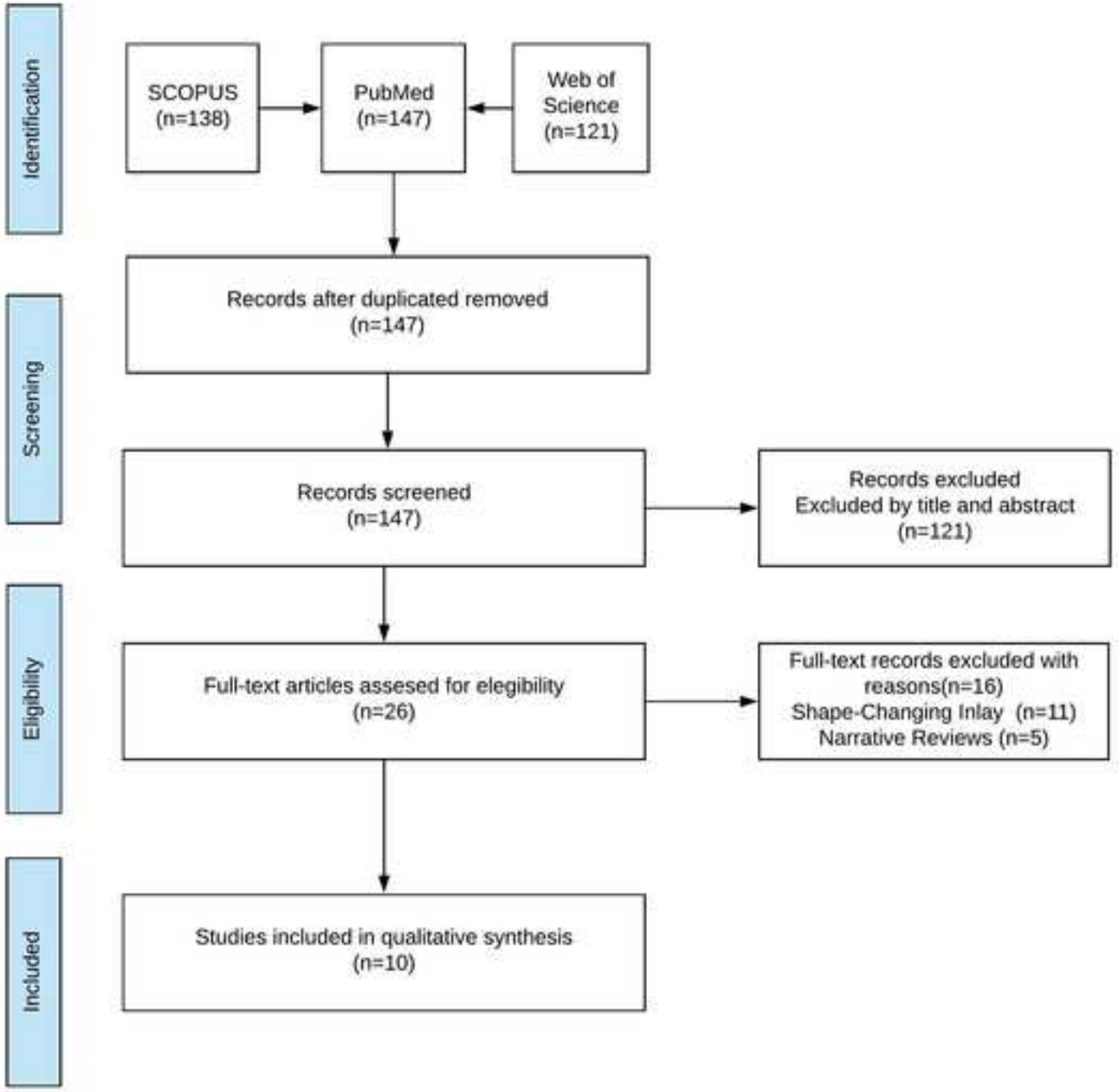

Table 1. Quality assessment of articles

Author (date)	Q1	Q2	Q3	Q4	Q5	Q6	Q7
Bouzoukis et al.[1] (2011)	Yes	NA	Yes	NA	Yes	No	No
Bouzoukis et al.[2] (2012)	Yes	Yes	Yes	Yes	Yes	Yes	No
Limnopoulu et al.[3] (2012)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Baily et al.[4] (2014)	Yes	Yes	Yes	Yes	No	Yes	Yes
Malandrini et al.[5] (2015)	Yes	Yes	No	No	Yes	Yes	Yes
Duignan et al.[6] (2016)	Yes	Yes	No	No	No	No	No
Stojanovic et al.[7] (2016)	No	Yes	Yes	No	Yes	Yes	Yes
Beer et al.[8] (2017)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Han et al.[9] (2019)	Yes	Yes	Yes	Yes	Yes	No	Yes
Beer et al.[10] (2020)	Yes	Yes	Yes	Yes	Yes	Yes	Yes

NA: Not applied; NR= Not reported; Q= Question; (Q1): Is the study oriented to a clear question?; (Q2): Were all the patients results taken into account?; (Q3): Was the follow-up complete?; (Q4): Were the same conditions used in surgical treatment?; (Q5): Was the intervention clearly described?; (Q6): Was the duration of follow-up adequate?; (Q7): Were the results described correctly?