Therapeutic use of the HPV vaccine on recurrent respiratory papillomatosis: a systematic review and meta-analysis

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Brief summary
This updated and thorough review and meta-analyses supports the continued use of the HPV vaccine as an adjuvant treatment of RRP as significantly fewer surgeries per month are required after vaccination.
Abstract

Background: Recurrent respiratory papillomatosis is a benign condition caused by human papilloma virus (HPV). Surgery is the mainstay of treatment, but numerous adjuvant therapies have been applied to improve surgical outcome. Recently, HPV vaccination has been introduced, but only smaller studies of its effect have been published. The present meta-analysis is intended as a possible substitute for a proposed, but not yet realized multicenter randomized controlled trial.

Methods: A systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement. PubMed, Embase, and Cochrane were systematically searched. All retrieved studies (n=593) were reviewed and qualitatively assessed. In addition, two previously unpublished datasets were included. The systematic review included 11 studies, comprising 133 patients, of whom 63 patients from five studies were eligible for meta-analysis. A random-effects meta-analysis was conducted for the mean difference in number of surgeries per month before and after vaccination.

Results: Number of surgeries per month was significantly reduced after HPV vaccination (estimated mean 0.06) than before vaccination (estimated mean 0.35). Mean intersurgical interval increased from 7.02 months (range 0.30-45) before vaccination to 34.45 months (range 2.71-82) after HPV vaccination.

Conclusion: The present study supports the continued use of the HPV vaccine as an adjuvant treatment for recurrent respiratory papillomatosis.

Keywords: RRP, Recurrent respiratory papillomatosis, laryngeal papillomatosis, HPV vaccination, therapeutic vaccination, immunization.
Introduction
In recent years, human papilloma virus (HPV) vaccination has been debated frequently among the medical professions and in the news and social media. Most scientific studies have focused on cervical cancer and its prevention, but other cancers and benign diseases caused by HPV are gaining attention [1, 2].

The first HPV vaccine targeting the two oncogenic HPV subtypes 16 and 18 (Cervarix, GlaxoSmithKline Biological) was introduced in 2004, primarily to prevent cervical cancer [3]. In 2006, a new vaccine targeting the HPV subtypes 6, 11, 16, and 18 (Gardasil®, MerckSharpDohme) were released thus preventing not only cervical cancer but also benign diseases such as genital warts in the cervix, vulva or vagina and anus and recurrent respiratory papillomatosis (RRP). Most recently these vaccines have been followed by a 9-valent HPV vaccine (Gardasil®9, MerckSharpDohme) targeting five additional oncogenic subtypes (31, 33, 45, 52, and 58). Several countries have introduced prophylactic HPV vaccination for adolescents [4, 5], and this may reduce the incidence of HPV-related diseases such as cervical cancer, oropharyngeal cancer, genital warts, and recurrent respiratory papillomatosis (RRP) [6]. Therapeutic use of the HPV vaccine is controversial, but a positive effect in patients with various clinical manifestations of HPV has been suggested [7].

RRP is characterized by recurrent papillomatous lesions that occur primarily in the larynx, but occasionally involve other parts of the aero-digestive tract. Although it is a benign condition, malignant transformation has been described [8, 9]. Traditionally, RRP has been subdivided into juvenile onset RRP (JoRRP, age < 18 years) and adult onset RRP (AoRRP, age ≥ 18 years) [10], however in a recent study a trimodal distribution (peaking around the ages of 7, 35, and 64 years) has been suggested [11]. JoRRP is most likely caused by HPV transmission during labor whereas AoRRP may be caused by sexual transmission (the peak around 35 years) or activation of a latent viral infection (the peak around 64 years) [6, 11]. The clinical course of RRP varies, as some individuals require only one or a few treatments in a lifetime, and others need several treatments a year for many years despite repeated and careful removal of all visible lesions. RRP can thus be a frustrating disease due to its unpredictable nature and potential for producing airway compromise [6, 12]. Multiple endolaryngeal procedures can lead to glottic synechia and irreversible damage to the vocal cords [13] as well as discomfort, anxiety, absence from work and school, and impaired social life [14].

Surgical treatment with cold instruments, laser, or microdebrider is usually preferred. To improve the surgical outcome and prolong the symptom-free interval, numerous adjuvant therapeutic modalities have been applied [15, 16], including photodynamic therapy [17], indole-3-carbinol [18], interferon-a [19], Cidofovir [20], Bevacizumab [21] and most recently and therapeutic use of the HPV vaccine [22-24].

Only a few original studies addressing the therapeutic use of the HPV vaccine as treatment for RRP have been published [13, 16, 25-32] along with a small number of case reports [33-39]. The reported outcomes vary, and a proposed large-scale multicenter study has not yet been undertaken.

The aim of this study was to estimate the effect of therapeutic use of the HPV vaccine on RRP by conducting a systematic literature review and meta-analysis and thus provide a possible substitute for a multicenter study.
Methods
A systematic literature review and meta-analysis was performed in accordance with the guideline "Preferred Reporting Items for systematic Reviews and Meta-Analysis statement" (PRISMA) [40].

The review protocol has been registered in the PROSPERO International Prospective Register of Systematic Reviews, registration number CRD42017069515.

Systematic literature search
A PICOS (Population, Intervention, Comparison, Outcome, and Study design) strategy [41] was adopted for the search. The target population consisted of patients diagnosed with RRP. The intervention was HPV vaccination, and the comparator comprised other treatment modalities prior to HPV vaccination. The outcomes were the number of, and the time interval between, surgical procedures before and after HPV vaccination. The study design was without restrictions if original data for at least five patients were available.

On March 3, 2018 we searched the electronic bibliographic databases PubMed, Embase, and Cochrane without restrictions on publication date. The search strategy was based on a combination of all available free text and Medical Subject Heading terms for RRP, HPV, and vaccination (see supplementary data for the complete search strategy for each electronic database). The search strategy was developed with help from a scientific librarian, and the electronic search was performed by the first author (TR).

Study selection
Studies identified by the literature search were entered into EndNote version X8 (Thompson Reuters, Carlsbad, CA). Duplicates were removed manually. To assess the eligibility of studies, two authors (TR and BP) independently screened the titles and the abstracts using predefined criteria for inclusion and exclusion and subsequently, the same authors independently evaluated the full text version of all publications that passed the first step. Any discrepancies were solved by discussion and if needed, a third evaluator (CSM) acted as arbitrator. In case of doubt, the article proceeded to the next level. In case of missing data, an attempt was made to obtain these by contact to the corresponding author of the study in question.

Conference abstracts, case reports (n<5) and publications without relevant data were excluded.

The systematic review thus included publications with original data for at least five patients with RRP treated with HPV vaccine and that were written in English, Swedish, Norwegian, German, or Danish. Publications that provided sufficient individual data on number of surgeries and duration of observation period before and after vaccination proceeded to the meta-analysis.

Two unpublished datasets that met all the above inclusion criteria were identified and included in both the systematic review and the meta-analysis.

Unpublished data
The data from Romania were collected between September 2012 and December 2015 on patients referred for treatment of RRP at Otorhinolaryngology Department of Emergency, County Hospital of Cluj-Napoca, Romania. Children and adults with histopathological confirmed RRP treated with HPV vaccine and followed up for at least six months were included. Demographic characteristics, such as gender and age were registered as well as the onset of RRP, the HPV sub-type (detected by polymerase-chain reaction with
colorimetric detection), previous adjuvant therapy, the number of surgeries for RRP per year before and after the vaccination with Silgard 4 (MerckSharpDohme, Netherlands), the follow-up time before and after vaccination (months), and any malignancy. All data were collected into a database (Microsoft Excel 2007). See Supplementary Table 2 for more details. The data concerning age at onset of RRP have been published in a distribution analysis of onset of RRP by San Giorgi et al. [11] The remaining data have never been published.

The data from Denmark were collected on patients treated with HPV vaccine for RRP between December 2009 and March 2012 at the Department of Otorhinolaryngology – Head & Neck Surgery and audiology, Odense University Hospital, Denmark. Children and adults with histopathological confirmed RRP were included. Demographic characteristics, such as gender and age were registered as well as the onset of RRP, the HPV sub-type (detected by polymerase chain reaction (PCR) using INNO-LiPA® HPV for genotyping), previous adjuvant therapy, the number of surgeries for RRP per year before and after the vaccination with Gardasil (MerckSharpDohme, Netherlands), and the follow-up time before and after vaccination (months). All data were collected into a database (Microsoft Excel 2007). These data have never been published. See Supplementary Table 3 for more details.

**Data items and collection process**

Two authors (TR and BP) performed data extraction, and any discrepancies were resolved through discussion. Data were extracted on number of patients, age at RRP onset/age at diagnosis (full years), HPV subtype, age at HPV vaccination (full years), number of previous surgeries, and duration of observation period before and after vaccination. To complete all datasets, eight authors were contacted. One author returned a full dataset, and another returned a full dataset together with unpublished data on 20 additional patients. The remaining six authors did not supplement their datasets.

Patient subgroups not relevant to our study were excluded from the study population before statistical analysis along with patients with any malignant disease or pre-malignant laryngeal lesions (n=3) [13]. In the meta-analysis, we further excluded seven patients with less than 24 months of follow-up after vaccination (four patients from Hočevar-Boltežar et al. [28] and three patients from Goon et al. [31])

**Risk of bias assessment**

Risk of bias in individual studies was assessed using the SIGN Checklist for Cohort Studies [42]. Each study was evaluated according to three domains (selection of subjects, study design, and statistics), leading to an overall assessment for each study. The evaluations were based on the research question in the present review.

**Statistical methods and synthesis of results**

The primary outcome was the average number of surgeries per month (SPM), both before and after vaccination. As initial analysis, we estimated the mean difference of SPM and corresponding 95% confidence interval for each study and reported the p-value of the corresponding paired t-test. To synthesize study results, we did a two-level approach and performed a random effects meta-analysis [43] based on the study-specific estimated means and confidence intervals. Additionally, we tested for homogeneity across studies and calculated Higgins I² as an estimate of the heterogeneity between studies [44].
To ensure comparability with previous studies the average intersurgical interval (ISI) was calculated for both the period before vaccination and the period after vaccination by dividing the length of follow-up for each patient by the number of surgeries. In case of no observed recurrences (n=24), the ISI was determined to equal the time of follow-up after vaccination.

All statistical analyses were carried out in Stata 15 (StataCorp, College Station, TX). A p-value below .05 was considered statistically significant.

Results

Study selection and characteristics
The systematic literature search resulted in 781 publications (n=593 after removal of duplicates). The study selection process is illustrated in Figure 1. Thirty-four publications were analyzed as full text, and their quality was assessed according to the SIGN recommendations. Nine of these publications met all eligibility criteria and were included in the review, as were two unpublished datasets that met all inclusion criteria (see Supplementary table 2 and 3 for details). Thus, data from a total of 133 patients were available for review.

Table 1 shows the characteristics of the 11 datasets included in the systematic review, including number of patients, gender, time of RRP onset (JoRRP/AoRRP), and HPV subtype together with individual data from each study, i.e. number of surgeries, duration of observation period, SPM and ISI before and after vaccination. Only Goon et al. did not provide information on how subtyping was performed [31]. The remaining studies used PCR [13, 16, 25, 26, 28-30, 32].

Data from 63 patients derived from four published and two unpublished datasets were suitable for the meta-analysis. The four studies suitable for the meta-analysis [25, 28, 29, 31] included 42 patients in all, but we excluded seven patients due to less than 24 months follow-up (four patients from Goon et al. [31] and three from Hočevar-Boltežar et al. [28]). All of the 28 patients from the two unpublished datasets were eligible for metaanalyses.

Risk of bias assessment
Of nine published, original studies included in the systematic review, four studies were of acceptable quality and five were of high quality (Supplementary table 1).

Synthesis of results
The meta-analysis included four studies and two unpublished datasets. As we found no important differences between the published and unpublished data from Chirilă et al. (data not shown), we handled these two datasets from Romania as one study in the meta-analysis (with a total study population of 33 patients). The other unpublished dataset was from Denmark (DK). Study populations ranged from six to 33 with a total of 63 patients. SPM estimates before and after vaccination for each study as well as individual curves are displayed in Figure 2. For the 63 patients included in the meta-analysis, mean SPM prior to vaccination was 0.35 (range 0.02-3.29), translating to 4.14 surgeries per year. Mean SPM after vaccination was 0.06 (range 0-0.37), translating to 0.68 surgeries per year. Correspondingly, mean ISI prior to vaccination was 7.02 months (range 0.30-45) and the mean ISI after vaccination was 34.45 months (range 2.71-82) (data not reported elsewhere). We found no statistically significant differences of gender, RRP...
onset, or HPV subtype distribution between the studies included in the meta-analysis (p-values of Fisher’s exact test (.076, .607 and .456).

For all studies, the estimated mean difference in SPM was negative, ranging from -0.06 (Unpublished, DK) to -0.44 (Chirilă et al.) (Table 2/Figure 3). Two studies showed a statistically significant reduction in SPM after HPV vaccination, whereas no statistically significant differences were seen in the other three original studies. The hypothesis of homogeneity between studies was rejected (p-value .023), and the Higgins $I^2$ was 64.6%. The meta-analysis showed a statistically significant reduction of SPM after HPV vaccination, with an overall mean difference of -0.18 (95% CI: -0.30; -0.06) (Figure 3).

Discussion

To our knowledge this is the first published meta-analysis concerning the effect of therapeutic use of the HPV vaccine as treatment of RRP. The analysis included four published, original studies and two unpublished datasets. A random effects meta-analysis indicated an overall statistically significant reduction of SPM after HPV vaccination. This new knowledge may benefit patients severely affected by RRP, for whom quality of life is often reduced [45].

The idea of immunological treatment of RRP is not new. The first attempts of such treatment were made in the 1960s with the use of bovine wart vaccines [46]. In the 1960s and 1970s, autogenous vaccines were tested [47, 48], and mumps vaccines were tried out around 1990 [49]. The quadrivalent HPV vaccine was introduced in 2006, primarily to prevent cervical cancer. In 2015, this was followed by a 9-valent HPV vaccine targeting five additional oncogenic subtypes [50]. In 2009, Gallagher et al. were among the first to suggest a therapeutic effect of the HPV vaccine on RRP [22]. It has been proposed that the antibody-mediated humoral immune response to the vaccine may inhibit a latent HPV infection in the mucosa surrounding the surgical site and thereby reduce the risk of both recurrence and reinfection [23]. Moreover, Goon et al. recently suggested that the cell-mediated response in the adaptive immune response may also be activated by vaccination [31].

Only few original studies have been published on the therapeutic use of the HPV vaccine for patients with RRP. Although most of these have suggested a positive effect of HPV vaccination, the true effect is still debated. Some authors argue that the reported increased ISI merely reflect the natural course of RRP, as remission or a tendency toward fewer relapses is described in non-vaccinated patients too [32]. In contrast, a recent cohort study demonstrated that ten vaccinated patients had significantly fewer surgeries per year compared to 57 comparable non-vaccinated patients [13]. In general, treatments prior to HPV vaccination have had limited success, and patients have usually volunteered for HPV vaccination based on their symptoms. It is therefore likely that the HPV-vaccinated patients represent the most severely affected RRP patients. This makes it more likely that a considerably increased ISI immediately after vaccination compared to before vaccination would be due to the vaccination. A large multicenter randomized controlled trial (RCT) would be needed to establish the true effect [28, 29], but to our knowledge this has not yet been realized. The present meta-analysis may thus be the best current substitute for such study.

In total, our study comprised 133 patients from eight different countries (USA, UK, Germany, Brazil, Holland, Romania, Slovenia, and Denmark). Common for all patients, the HPV vaccination was administered according to the standard approved dosing protocol. However, institutional guidelines for the treatment of RRP may vary, so patients may have been included differently across studies. Also, information on how HPV
subtyping was performed was limited in several papers and this may hamper the specificity and sensitivity of the subtyping.

The studies that were excluded from the meta-analysis due to missing individual data reported on 63 patients in total. One study [16] included 18 patients and described partial or complete response to HPV vaccination in nine patients and no response in the other nine patients; they provided no details about number of operations or time of follow up. Hermann et al. [26] reported no significant changes in the ISI before and after vaccination in nine patients. The patients were however only followed up for 12 months and therefore it is unclear whether this outcome was due to the naturally fluctuating course of RRP or a true missing effect of vaccination. From a German study by Papaioannou et al. [13], seven patients were included in our review of whom four patients showed complete response and the other three showed partial response. Another recent study [32] included 12 HPV vaccinated patients and described significantly longer ISIs after vaccination than before; three patients were reported to have complete response. However, the authors argued that it might be due to the natural course of RRP as also the ISIs for their 16 non-vaccinated patients were increased. Lastly, Young et al. [30] included 17 patients and reported complete response in eight patients, partial response in five patients and no response in four patients.

The four studies suitable for the meta-analysis [25, 28, 29, 31] included 42 patients in all, but we excluded seven patients due to a short follow-up period. Tjon et al. [29] demonstrated a clinical effect of HPV vaccination with complete response in four of six vaccinated patients and no response in the remaining two patients during of 3-4 years of follow up. Chirilă et al. [25] included 13 patients with an aggressive form of RRP and found complete response in 11 patients and partial response in two patients. A more recent study by Goon et al. [31] reported a 7-fold decrease in the incidence rate of surgeries after vaccination compared to the period before vaccination. They included 12 patients of which nine showed complete response and three showed a partial response. Four of their patients were followed up less than 24 months after vaccination and were thus excluded from the present meta-analysis. Finally, Hočevar-Boltežar et al. [28] reported a significant increase in the ISI after HPV vaccination of 11 patients (complete response in one patient, partial response in seven patients and no response in three patients). Due to a short follow up period for three of their patients (12 months), we found only eight patients suitable for the meta-analysis. On the other hand, our meta-analysis was enriched with two previously unpublished datasets including a total of 28 patients.

Limitations
A number of aspects could have improved the present study. Most importantly, the ability to include data on all patients from the systematic literature review in the meta-analysis would have contributed to the strength of the statistical analyses and, consequently, the conclusions. Further details regarding the following aspects could also have added strength to the analyses and conclusions is 1) timing of surgeries (would have enabled analyses taking timing into account), 2) local clinical protocols (would have provided information on treatment strategies, surgical agenda and surgical preferences, and other applied treatment options), and 3) disease specific information including viral activity and more details on how HPV subtyping was performed.

The unpredictable course of RRP means that large-scale studies with long-term follow-up are needed to assess the effect of a treatment. A future multicenter RCT of the therapeutic use of the HPV vaccine should at the minimum standardize the inclusion and exclusion criteria, doses of vaccine, and treatment intervals.
Conclusion
This study supports the continued use of the HPV vaccine as an adjuvant treatment of RRP as significantly fewer surgeries per month are required after HPV vaccination. This is highly relevant for patients and their relatives, the surgeons, as well as for health care planning and the public debate of HPV vaccination. A large cross-national study in which patients are enrolled according to standardized inclusion criteria could contribute to further knowledge in the field.

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Conflict of interest
All authors declare no conflicts of interest

Originality
The information in the present study has not previously been presented

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References


32. Milner TD, Harrison A. A retrospective case-control analysis of the efficacy of Gardasil((R)) vaccination in 28 patients with recurrent respiratory papillomatosis of the larynx. 2018.


Figure 1. Study selection flowchart. In the meta-analysis, the two datasets from Romania (published and unpublished) from Chirilă et al. were handled as one study, giving five studies in all. Figure adapted from [40].

Figure 2. Boxplots of surgeries per month (SPM) before and after HPV vaccination, separately by study, and individual curves. * Chirilă includes both published and unpublished patients. ** Unpublished is the dataset from Denmark. Please note that four patients with SPM > 0.8 before vaccination were omitted from the figure for graphical reasons (three patients from Chirilă et al. and one patient from the unpublished Danish dataset.

Figure 3. Random effects meta-analysis results of surgeries per month differences. * Chirilă includes both published and unpublished patients. ** Unpublished is the dataset from Denmark. ES: (effect size): Mean difference.
Figure 1

PRISMA 2009 Flow Diagram

Identification

Records identified through database search (n = 781) (PubMed 304, Embase 447, Cochrane 10)

Records after duplicates removed (n = 593)

Records screened (n = 593)

Records excluded based on title and abstract (n = 559)

Screening

Full-text articles assessed for eligibility (n = 34)

Full-text articles excluded (n = 25),
Reason for exclusions:
No original data (12)
Inclusion criteria not met (13)

Eligibility

Studies included in qualitative synthesis (n = 11)

Studies included in quantitative synthesis (meta-analysis) (n = 5)

Included
Figure 2

- Chirilă et al.* [25] (N=30)
- Goon et al. [31] (N=8)
- Hocevar-Boltezar et al. [28] (N=8)
- Tjon et al. [29] (N=6)
- Unpublished** (N=7)
- All (N=59)
Figure 3

<table>
<thead>
<tr>
<th>Author</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chirila et al.* [25]</td>
<td>-0.44 (-0.64, -0.24)</td>
<td>17.75</td>
</tr>
<tr>
<td>Goon et al. [31]</td>
<td>-0.06 (-0.18, 0.01)</td>
<td>27.95</td>
</tr>
<tr>
<td>Hocevar-Boltezar et al. [28]</td>
<td>-0.14 (-0.27, -0.02)</td>
<td>24.63</td>
</tr>
<tr>
<td>Tjon et al. [29]</td>
<td>-0.23 (-0.48, 0.03)</td>
<td>13.32</td>
</tr>
<tr>
<td>Unpublished **</td>
<td>-0.06 (-0.27, 0.15)</td>
<td>16.35</td>
</tr>
<tr>
<td>Overall (I-squared = 64.6%, p = 0.023)</td>
<td>-0.18 (-0.30, -0.06)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis
Table 1. Study characteristics, calculated intersurgical interval, and calculated surgeries per months for 11 studies included in the systematic literature review.

<table>
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<tr>
<th>Study</th>
<th>n</th>
<th>RRP</th>
<th>Gender (M/F)</th>
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<th>After vaccination</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Number of surgeries</td>
<td>Follow-up time (months)</td>
<td>ISI (months)</td>
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<td>Dedo et al. 2011</td>
<td>18</td>
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<td>12/6</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chirilă et al. 2013</td>
<td>13</td>
<td>4/9</td>
<td>9/4</td>
<td>10/3</td>
<td>8.92</td>
<td>38.9</td>
<td>5.46 ***</td>
</tr>
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<td>(Romania)</td>
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<td></td>
<td></td>
<td>(2-21)</td>
<td>(12-180)</td>
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<td>9</td>
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<td>6/3</td>
<td>8/1</td>
<td>1.00</td>
<td>12</td>
<td>10.6</td>
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<td>(Brazil)</td>
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<td>(0-2)</td>
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<tr>
<td>Hočevar- et al.</td>
<td>11</td>
<td>4/7</td>
<td>5/6</td>
<td>7/4</td>
<td>13.8</td>
<td>92</td>
<td>7.65*</td>
</tr>
<tr>
<td>2014 (Slovenia)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(3-42)</td>
<td>(14-261)</td>
<td>(2.57-12.8)</td>
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<tr>
<td>Goon et al.</td>
<td>12</td>
<td>NA</td>
<td>8/4</td>
<td>8/2</td>
<td>6.42</td>
<td>133.5</td>
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<td>(1-12)</td>
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<td>(4.38-45)</td>
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<td>8/4</td>
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<td>(0-2)</td>
<td>(9-66)</td>
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<td>NA</td>
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<td>2018 (Germany)</td>
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<td>(2-8)</td>
<td>(0-2)</td>
<td>(9-66)</td>
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<td>Tjon et al.</td>
<td>6</td>
<td>3/3</td>
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<td>5/1</td>
<td>20.2</td>
<td>94.0</td>
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<td>2016 (Holland)</td>
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<td></td>
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<td>(4-79)</td>
<td>(12-360)</td>
<td>(1.72-9.33)</td>
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<th>ISIs</th>
<th>ISIs</th>
<th>CR/P/P/N</th>
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<td>Young et al. 2014</td>
<td>USA</td>
<td>11/6</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>4.86</td>
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<td>NR 4 patients</td>
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<tr>
<td>Unpublished</td>
<td>Romania</td>
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<td>11/9</td>
<td>19/1</td>
<td>11.5</td>
<td>31.7</td>
<td>3.27</td>
<td>0.54</td>
<td>0.9</td>
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<td>39.63</td>
<td>CR 7 patients</td>
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<td>PR 13 patients</td>
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<td>4/4</td>
<td>6/2</td>
<td>14.6</td>
<td>85.0</td>
<td>5.97</td>
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<td>15.1</td>
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Table 2. Paired t-tests by study. Overall result based on random effects meta-analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Mean difference (95% CI)</th>
<th>p-value *</th>
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</thead>
<tbody>
<tr>
<td>Chirilă et al.\textsuperscript{25}</td>
<td>33</td>
<td>-0.44 (-0.64; -0.24)</td>
<td>.0001</td>
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<tr>
<td>Goon et al \textsuperscript{31}</td>
<td>8</td>
<td>-0.08 (-0.18; 0.01)</td>
<td>.0671</td>
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<tr>
<td>Hočevar-Boltežar et al.\textsuperscript{28}</td>
<td>8</td>
<td>-0.14 (-0.27; -0.02)</td>
<td>.0292</td>
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<tr>
<td>Tjon et al.\textsuperscript{29}</td>
<td>6</td>
<td>-0.23 (-0.48; 0.03)</td>
<td>.0741</td>
</tr>
<tr>
<td>Unpublished (DK)</td>
<td>8</td>
<td>-0.06 (-0.27; 0.15)</td>
<td>.5287</td>
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<tr>
<td>Overall</td>
<td></td>
<td>-0.18 (-0.30; -0.06)</td>
<td></td>
</tr>
</tbody>
</table>

CI: Confidence interval

*Two-sided paired t-test