Incidental prostate cancer after holmium laser enucleation of the prostate—A narrative review

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Summary
Prostate cancer can be detected incidentally after surgical therapy for benign prostatic obstruction such as holmium laser enucleation of the prostate (HoLEP), thus called incidental prostate cancer (iPCa). We aimed to review the studies on iPCa detected after HoLEP and investigate its prevalence. A detailed search of original articles was conducted via the PubMed-MEDLINE, Web of Science, Wiley Online Library and Cochrane Library databases in the last 10 years up to 1 May 2021 with the following search string solely or in combination: "prostate cancer", "prostate carcinoma", "holmium laser enucleation of the prostate" and "HoLEP". We identified 19 articles to include in our analysis and divided them into six main categories: HoLEP versus open prostatectomy and/or transurethral resection of the prostate in terms of iPCa, oncological and functional outcomes, the role of imaging modalities in detecting iPCa, predictive factors of iPCa, the role of prostate-specific antigen kinetics in detecting iPCa and the management of iPCa after HoLEP. We found that the iPCa after HoLEP rate ranges from 5.64% to 23.3%. Functional and oncological outcomes were reported to be encouraging. Oncological treatment options are available in a wide range.

KEYWORDS
benign prostatic hyperplasia, HoLEP, holmium laser enucleation of the prostate, incidental prostate cancer

INTRODUCTION

Lower urinary tract symptoms caused by benign prostatic obstruction (BPO) is one of the most common health problems in adult males (Gratzke et al., 2015). In the last decade, holmium laser enucleation of the prostate (HoLEP) has come to the fore in the surgical treatment of BPO as an alternative to transurethral resection of the prostate (TURP) and open prostatectomy (OP) in efficiency, safety and complication terms (Nair et al., 2016; Patel et al., 2014; Rieken et al., 2010; Sivarajan et al., 2015; Vincent & Gilling, 2015). There is evidence that HoLEP is feasible regardless of the prostate size (Cornu et al., 2015).

Prostate cancer (PCa) is the second most common cancer in men, accounting for 15% of all cancers diagnosed (Ferlay et al., 2015). In addition to prostate-specific antigen (PSA) screening and subsequent prostate biopsy, PCa can be detected incidentally after the surgical treatment for BPO such as HoLEP, referred to as incidental prostate cancer (iPCa) (Kim et al., 2014). Although studies have reported iPCa...
after HoLEP (Elkousy et al., 2015; Nunez et al., 2011; Rosenhammer et al., 2018b), its clinical prevalence and relevance have not been well investigated. A literature review is therefore needed. In this study, we aimed to review the studies on iPCa detected after HoLEP, to investigate its prevalence, to assess the functional and oncological outcomes as well as the role imaging modalities play, predictive factors and iPCa management.

2 | MATERIAL AND METHODS

2.1 | Literature search

A comprehensive search was conducted using the PubMed-MEDLINE, Web of Science, Wiley Online Library and Cochrane Library databases over the last 10 years until 1 May 2021 with the following search string solely or in combination: “prostate cancer”, “prostate carcinoma”, “holmium laser enucleation of the prostate” and “HoLEP”. After the titles and abstracts of selected articles were retrieved, the full texts of related articles were screened. Our article selection process complying with the PRISMA criteria is shown in Figure 1. The PICOS (population [P], intervention [I], comparator [C], outcomes [O] and study design [S]) approach was used to determine the eligibility criteria (Liberati et al., 2009). We thus selected the studies providing that benign prostate hyperplasia (BPH)/BPO patients (P) had undergone HoLEP (I) as a single operation, or when they were compared with patients who had undergone TURP or OP (C), and if iPCa (O) had been revealed/diagnosed in prospective or retrospective studies (S).

We included studies reporting iPCa after HoLEP addressing functional and oncological outcomes, the role of imaging modalities, predictive factors, PSA kinetics and iPCa management. Studies not reporting iPCa after HoLEP, unassociated with HoLEP, not written in
English, case reports, conference abstracts, review articles, editorials and replies to the authors were excluded.

2.2 | Data extraction

Articles relevant to our subject of interest were retrieved and evaluated independently by two authors (M.Y. and T.T). A total of 434 articles were identified after the search query. Authors and date of study, study design, number of patients included and mean age, preoperative prostate volume (ml), total serum PSA (ng/ml), PSA density (ng/ml²), prostate biopsy history, the use of 5α-reductase inhibitors (5-ARI), tissue weight (g) removed at operation, iPCa ratio, Gleason score (GS) and T stage were recorded. We assessed the quality of evidence in the studies according to their study design applying National Institutes of Health (NIH) quality assessment tool for before-after (Pre-Post) studies with no control group or NIH assessment tool for observational cohort and cross-sectional studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). These tools consist of 12 and 14 questions to evaluate studies’ quality, respectively, according to "yes", "no", "cannot determine", "not applicable" or "not reported" options for each question. The following quality ratings were indicated: poor (<60%), adequate/fair (60%–69%), good (70%–79%) and strong (80%) (Linde et al., 2020; Musshafen et al., 2021). Discrepancies between two authors were resolved through discussion. A quality percentage score was calculated based on ‘yes’ responses divided by the total number of valid questions. The data were extracted by the authors (M.Y. and T.T) for qualitative and quantitative evidence and a narrative synthesis.

3 | RESULTS

Overall, 388 publications had to be excluded after title and abstract review for the following reasons: not reporting iPCa after HoLEP (n = 261), unassociated with HoLEP (n = 21), not written in English (n = 3), case reports (n = 12), review articles (n = 57), conference abstracts (n = 10), editorials (n = 9) and reply to the authors (n = 5).

After full-text evaluation, we had to exclude another 27 more articles not fulfilling the inclusion criteria. The remaining 19 articles were finally incorporated in our review. Table 1 illustrates the baseline characteristics of all studies. One compared HoLEP with both OP and TURP (Capogrosso et al., 2018). Regarding the quality of the studies, 52.6% of our studies were adequate/fair (Capogrosso et al., 2018; He et al., 2020; Herlemann et al., 2017; Kim et al., 2014; Martos et al., 2021; Nunez et al., 2011; Otsubo et al., 2015; Rivera et al., 2014; Rosenhammer et al., 2018b). In another study, Rosenhammer et al. conducted a case-by-case matched-pair analysis to evaluate the iPCa detection rates after HoLEP and bipolar TURP (Rosenhammer et al., 2018a). In iPCa terms, their cancer detection rate after surgery was significantly higher in the HoLEP group (23.3% vs. 8.3%; p = 0.043). The majority of patients’ GSs were Gleason 3 + 3 in both groups (Rosenhammer et al., 2018a). There was only one patient with GS 3 + 4 iPCa in each group. The authors note that the higher percentage of prostate tissue removed during the HoLEP procedure compared HoLEP with OP (Rosenhammer et al., 2018b). Instead of drawing comparisons with other treatment approaches, other studies reported HoLEP’s oncological and functional outcomes (Nunez et al., 2011; Rivera et al., 2014; Tominaga et al., 2019), the role of imaging modalities in detecting iPCa (Kim et al., 2014; Porreca et al., 2019, 2020; Wenzel et al., 2021), the predictive factors of iPCa after HoLEP (Bhojani et al., 2015; Elkousy et al., 2015; Ohwaki et al., 2017; Porreca et al., 2017) and the role of PSA kinetics in detecting iPCa after HoLEP (Abedali, Calaway, Large, Lingeman, et al., 2020; Magistro et al., 2020; Martos et al., 2021; Otsubo et al., 2015). We collated iPCa after HoLEP management strategies from the studies we reviewed, and summarise them below.

3.1 | HoLEP versus OP and/or TURP in iPCa terms

Table 2 presents our data on the comparative studies including HoLEP, OP and TURP. Capogrosso et al. investigated the rate of iPCa after HoLEP, OP and TURP surgeries (Capogrosso et al., 2018). They reported a 6.4% overall iPCa rate. The majority of their patients had GS 6 (91%). The authors stated that patients underwent HoLEP were more likely to be diagnosed with iPCa postoperatively (OR: 2.28; 95% CI: 1.30–4.00; p = 0.004).

He et al. (2020) compared the diagnostic value of HoLEP to TURP in terms of iPCa. They identified a statistically significant difference in the total iPCa detection rate between HoLEP and TURP groups respectively (6.24% vs. 3.94%, p = 0.005). The authors divided all their patients into three groups: PSA <4 ng/ml, PSA 4–10 ng/ml and PSA >10 ng/ml. For those with PSA <4 ng/ml and PSA 4–10 ng/ml, iPCa detection rates were higher in the HoLEP group (4.6% vs. 2.7%, p = 0.014 and 13.9% vs. 5.0%, p = 0.023 respectively). They found no significant difference in the PSA >10 ng/ml subgroup (25.9% vs. 22.8%, p = 0.691) between groups (He et al., 2020), nor did they detect any significant difference in the GSs in any subgroups.

Herlemann et al. compared the oncological parameters following HoLEP and TURP (Herlemann et al., 2017). They found no significant difference in the iPCa detection rates between groups (15% for HoLEP vs. 17% for TURP, p = 0.593). The rates of the GS ≤6 were also insignificant between the HoLEP and TURP groups (86% vs. 84%, p = 0.779 respectively).

In a retrospective matched-pair study, Rosenhammer et al. compared HoLEP with OP and found similar iPCa detection rates (9.7% and 8.3%, respectively; p = 1.000) (Rosenhammer et al., 2018b). In another study, Rosenhammer et al. conducted a case-by-case matched-pair analysis to evaluate the iPCa detection rates after HoLEP and bipolar TURP (Rosenhammer et al., 2018a). In iPCa terms, their cancer detection rate after surgery was significantly higher in the HoLEP group (23.3% vs. 8.3%; p = 0.043). The majority of patients’ GSs were Gleason 3 + 3 in both groups (Rosenhammer et al., 2018a). There was only one patient with GS 3 + 4 iPCa in each group. The authors note that the higher percentage of prostate tissue removed during the HoLEP procedure...
| Author (year)            | Study design and type | Number of patients | Patients’ age Mean ± SD or median (min–max; years) | Preop PV-TRUS or TAUS Mean ± SD or median (min–max) | Preop tPSA Mean ± SD or median (min–max) ng/ml |
|-------------------------|----------------------|--------------------|---------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| Rosenhammer et al. (2018b) | R, matched pair, C   | 72                 | 69.9 ± 7.9                                        | 112.9 ± 25.8 ml                                  | 7.32 ± 4.37                                       |
| Tominaga et al. (2019)   | R, nonrandomized, NC | 418                | 71.9 ± 8.2                                        | 47.0 ± 26.8 ml                                   | 5.32 ± 6.65                                       |
| Porreca et al. (2019)    | R, multicentric, NC  | 228                | 64.9 (7.3)                                        | 86.9 ± 34.4 ml                                   | 7.09 ± 3.9                                        |
| Rivera et al. (2014)     | R, NC                | 450                | 70.5 (65.0–80.0)                                  | 82.0 ml (24.6–210.0)                             | N/A                                              |
| He et al. (2020)         | R, C                 | 1362               | 72.4 ± 6.7                                        | 59.1 ± 19.2 g                                    | 3.3 ± 2.3                                         |
| Elkoushy et al. (2015)   | R, NC                | 1242               | 75.8 ± 8.7 for iPCa group                         | 85.97 ± 46.2 ml for iPCa group                   | 3.6 ± 15.7 ng/dl for iPCa group                   |
| Ohwaki et al. (2017)     | R, NC                | 654                | 70.0 (50.0–91.0)                                  | 66 ml (50–91)                                    | 6.15 (3.61–10.55)                                 |
| Nunez et al. (2011)      | R, NC                | 240                | 73.0 (54.0–87.0) for iPCa group                   | 71.2 ml (26.9–140.0) for iPCa group              | 3.3 (0.7–56.8) for iPCa group                     |
| Herlemann et al. (2017)  | R, C                 | 289                | 71.0 (65.0–76.0)                                  | 80.0 ml (67.3–100.0)                             | 5.5 (3.5–8.8)                                     |
| Otsubo et al. (2014)     | R, NC                | 365                | 70 (55–82) for iPCa group                         | 47 ml (25–100) for iPCa group                    | 7.14 (1.26–37.3) for iPCa group                   |
| Bhojani et al. (2015)    | R, NC                | 1272               | 74.5 ± 9                                          | 85.2 g (23–231) for iPCa group                   | 7.2 (0.04–121)                                    |
| Rosenhammer et al. (2018a)| R, matched pair C  | 60                 | 71.5 ± 7.9                                        | 74.2 ± 13.9 ml                                   | 4.99 ± 3.12                                       |
| Magistro et al. (2020)   | R, NC                | 1125               | For PSA <10: 70 (65–75) For PSA >10: 70 (64–76)   | For PSA <10: 75 ml (60–100) For PSA >10: 105 ml 80–140 | For PSA <10: 4 (2.4–6.0) For PSA >10: 14.2 (11.5–19.9) |
| Porreca et al. (2020)    | R, NC                | 117                | 65.0 (59.5–70.0)                                  | 80.0 ml (60.0–101.0)                             | 6.20 (5.40–9.90)                                  |
| Capogrosso et al. (2018) | R,C                  | 540                | N/A for HoLEP group                               | 87.6 ml (60–115)                                 | N/A for HoLEP group                               |
| Kim et al. (2014)        | R,NC                 | 458                | 68.4 ± 6.6                                        | 58.0 ± 24.9 ml                                   | 3.38 ± 4.16                                       |
| Martos et al. (2021)     | R,NC                 | 90                 | 69.19 ± 7.21                                     | N/A                                              | 6.3 ± 5.9                                         |
| Abedali et al. (2020)    | R, NC                | 1202               | Biopsy group: 72.4 ± 7.5 Nonbiopsy groups: 70.2 ± 7.6 | Biopsy group: 99.81 g ± 70.41 Nonbiopsy group: 103.73 g ± 51.60 | Biopsy group: 7.72 ± 7.08 Nonbiopsy group: 8.06 ± 9.47 |
| Wenzel et al. (2021)     | R, NC                | 76                 | 66 (61–72)                                        | 84 ml (65–121)                                   | 8.9 (5.6–14.4)                                    |

Abbreviations: 5-ARI, 5-alpha reductase inhibitor; C, comparative; HoLEP, holmium laser enucleation of the prostate; iPCa, incidental prostate cancer; N/A, not applicable; NC, noncomparative; OP, open prostatectomy; PV, prostate volume; R, retrospective; SD, standard deviation; TAUS, transabdominal ultrasonography; tPSA, total prostate-specific antigen; TRUS, transurethral ultrasonography.
| Preop PSA density | History of bx, n (%) | Resected weight (g) Mean ± SD or median (min–max) (IQR) | The use of 5-AI, n (%) | Gleason score, n (%) | T stage, n (%) |
|-------------------|----------------------|------------------------------------------------------|------------------------|---------------------|----------------|
| Mean ± SD or median (min–max) ng/ml² | | | | | |
| 0.067 ± 0.037 | 24 (33.3) | 71.0 ± 27.5 | 13 (18.1) | 7 (9.7) | GS 6: 6 (85.7) GS 7 (3 ± 4): 1 (14.3) pT1a: 5 (71.4) pT1b: 2 (28.6) |
| 0.11 ± 0.10 | N/A | 22.5 ± 20.9 | N/A | 25 (6) | GS 6 ≤: 21 (84) GS 7: 4 (16) cT1a: 24 (96) cT1b: 1 (4) |
| 0.09 ± 0.06 | N/A | 47.1 ± 27.7 | 10 (4.4) | 24 (10.5) | GS 6 ≤: 21 (87.5) GS 7: 3 (12.5) pT1a: 22 (91.7) pT1b: 2 (8.3) |
| N/A | N/A | 37.8 (2.6–166.5) for iPCa group | N/A | 43 (9.6) | N/A |
| N/A | 147 (10.7) | N/A | N/A | 85 (6.24) | GS 6: 40 (2.93) GS 7: 29 (2.12) GS ≤: 16 (1.17) N/A |
| 0.22 ± 0.42 ng/dl/ml for iPCa group | N/A | N/A | N/A | 70 (5.64) | GS 6 ≤: 56 (80) GS 7: 4 (5.7) GS ≥: 10 (14.3) pT1a: 54 (77.1) pT1b: 16 (22.9) |
| N/A | 253 (38.6) | N/A | 81 (12.3) | 41 (6.3) | GS 6 ≤: 25 (3.8) GS ≥: 16 (2.5) pT1a: 25 (3.8) Other pT: N/A |
| N/A | 14 (50) for iPCa group | N/A | N/A | 28 (11.7) | GS 6: 15 (53.6) GS ≥: 13 (46.4) cT1a: 14 (50) cT1b: 14 (50) |
| 0.063 (0.042–0.104) | 100 (35) | 60 (42.8–80) | N/A | 43 (15) | GS 6 ≤: 37 (86) GS 7: 4 (9) GS ≥: 2 (5) pT1a: 38 (88) pT1b: 5 (12) |
| 0.155 (0.027–0.533) for iPCa group | 126 (34.5) | 20 (10–75) for iPCa group | N/A | 25 (6.8) | GS 6: 20 (80) GS ≥: 5 (20) pT1a: 17 (68) pT1b: 8 (32) |
| 0.19 (0.0–6.6) for iPCa group | N/A | 78.9 ± 53 | N/A | 103 (8.1) | GS 6 ≥: 80 (78) GS 7: 14 (14) GS ≥: 9 (8) N/A |
| 0.067 ± 0.041 | 12 (20) | 47.6 ± 16.3 | 12 (20) | 14 (23.3) | GS 6: 13 (92.9) GS 7: 1 (7.1) pT1a: 8 (57.1) pT1b: 6 (42.9) |
| For PSA <10: 0.05 (0.03–0.07) | 305 (27.1) | For PSA <10: 55 (40–74.5) For PSA >10: 81 (63–115) | 200 (17.8) | 108 (9.6) | GS 6 ≥: 95 (88) GS 7: 6 (5.6) GS ≥: 6 (5.5) pT1a: 103 (95.4) pT1b: 5 (4.6) |
| 0.08 (0.06–0.13) | 117 (100) | 30.0 (20.0–55.0) | 12 (10.3) | 14 (12) | GS 6: 11 (78.6) GS 7: 3 (3 ± 4): 3 (21.4) pT1a: 10 (71.4) pT1b: 4 (28.6) |
| N/A | N/A for HoLEP group | N/A for HoLEP group | N/A for HoLEP group | N/A for HoLEP group | N/A for HoLEP group |
| 0.055 ± 0.051 | 174 (38) | 21.3 ± 17.3 | N/A | 27 (5.9) | GS 6: 25 (92.6) GS 7 (3 ± 4): 2 (7.4) pT1a: 23 (85.2) pT1b: 4 (14.8) |
| N/A | 32 (35.6) | 165.9 ± 144.7 | 38 (42.2) | 7 (7.8) | GS 6: 5 (2.2) GS 7: 2 (5.6) N/A |
| Biopsy group: 0.084 ± 0.055 Nonbiopsy groups: 0.094 ± 0.221 | N/A | N/A | N/A | 147 (12.2) | N/A for iPCa N/A |
| 0.09 (0.07–0.15) | 26 (34.2) | N/A | 6 (7.9) | 9 (11.8) | GS 6: 7 (77.8) GS 7: 2 (22.2) pT1a: 8 (10.5) pT1b: 1 (1.3) |
| Author (year) | Procedure | Number of patients | PSA (ng/ml) | Resected weight (g) | iPCa, n (%) | Gleason score, n (%) | Main findings |
|--------------|-----------|--------------------|-------------|---------------------|-------------|---------------------|--------------|
|              |           |                    | Mean ± SD or median (min–max) | Mean ± SD or median (min–max) | iPCa, n (%) | Gleason score, n (%) |              |
| Rosenhammer et al. (2018b) | HoLEP    | 72                 | N/A         | 71.0 ± 27.5         | 7 (9.7)     | GS 6: 6 (85.7) GS 7: 1 (14.3) | No significant difference for age, PV, PSA, PSA density, history of biopsy, use of 5-ARI, iPCa |
|              | OP        | 72                 | N/A         | 69.8 ± 28.2         | 6 (8.3)     | GS 6: 5 (83.3) GS 7: 1 (16.7) |
| He et al. (2020) | HoLEP    | 1362               | <4          | 35.5 ± 12.4         | 55 (4.03)   | GS 6: 40 (2.93) GS 7: 29 (2.12) GS ≥8: 16 (1.17) | No statistical difference between patients’ baseline characteristics. HoLEP with significantly higher total iPCa detection rate (p < 0.05) |
|              | TURP     | 1547               | 4-10        | 41.8 ± 9.4          | 15 (1.1)    | GS 6: 29 (1.87) GS 7: 20 (1.29) GS ≥8: 12 (0.77) |
|              |          |                    | >10         | 51.6 ± 6.8          | 15 (1.1)    | Age, PSA, PV, PSA density, history of biopsy and resected weight were significantly higher in the HoLEP group. No significant difference for the iPCa detection rate |
| Herlemann et al. (2017) | HoLEP    | 289                | 5.5 (3.5–8.8) | 60 (42.8–80)        | 43 (15)     | GS 6 ≤: 37 (86) GS 7: 4 (9) GS ≥8: 2 (5) |
|              | TURP     | 229                | 2.3 (1.2–4.4)| 20 (15–35)         | 38 (17)     | GS 6 ≤: 32 (84) GS 7: 5 (13) GS ≥8: 1 (3) |
| Rosenhammer et al. (2018a) | HoLEP    | 60                 | 4.99 ± 3.12 | 47.6 ± 16.3         | 14 (23.3)   | GS 6: 13 (92.9) GS 7: 1 (7.1) |
|              | TURP     | 60                 | 4.91 ± 3.01 | 36.2 ± 11.6         | 5 (8.3)     | GS 6: 4 (80) GS 7: 1 (20) |
| Capogrosso et al. (2018) | HoLEP    | 540                | N/A         | 74 (6.4) for all groups | GS 6: 67 (91) GS ≥7: 7 (9) for all groups | The HoLEP group with a higher chance of iPCa detection |
|              | OP       | 139                | N/A         | 74 (6.4) for all groups |
|              | TURP     | 498                | N/A         | 74 (6.4) for all groups |

Abbreviations: 5-ARI, 5-alpha reductase inhibitor; GS, Gleason score; HoLEP, holmium laser enucleation of the prostate; iPCa, incidental prostate cancer; N/A, not applicable; OP, open prostatectomy; PSA, prostate-specific antigen; PV, prostate volume; TURP, transurethral resection of the prostate.
and sampling of potentially tumour tissue from the region adjacent to the peripheral zone results in iPCa being detected more often during HoLEP.

3.2 | Oncological and functional outcomes of patients diagnosed with iPCa after HoLEP

Tominaga et al. reported on long-term oncological and functional iPCa outcomes after HoLEP. Twenty-five patients (6%) were diagnosed with iPCa after HoLEP, and 21 patients (84%) had GS 6 (3 + 3). The 5-year overall survival and progression-free survival rates were 100%. They found that iPCa did not affect American Urological Association Symptom Score, maximum flow rate (Qmax) and postvoid residual (PVR) (Tominaga et al., 2019). Another study including patients who had undergone HoLEP reported that 43 patients (9.6%) were diagnosed with iPCa (Rivera et al., 2014). They found that GS of iPCa did not affect American Urological Association Symptom Score (AUASS) and Qmax.

Nunez et al. investigated the incidence of T1a and T1b iPCa and functional and oncological outcomes of iPCa in patients diagnosed after HoLEP (Nunez et al., 2011) and found that iPCa was detected in 11.7% of patients (n = 28). Regarding T stage, 14 patients had cT1a stage and the other 14 individuals had cT1b stage. They reported that three patients with cT1b pathology needed additional treatment because of a rise in PSA during the follow-up. They also compared patients diagnosed with iPCa with patients whose surgical pathology finding was benign. Postoperative Qmax, average urinary flow rate, PVR and AUASS were similar between iPCa and BPH groups (p > 0.05). In another study, Elkoushy et al.’s estimated overall iPCa survival was 72.8% and 63.5% at 5 years and at 10 years respectively (Elkoushy et al., 2015).

3.3 | Role of imaging modalities in detecting iPCa after HoLEP

Porreca et al. investigated the association between preoperative negative multiparametric magnetic resonance imaging (mpMRI) and iPCa rates in patients who underwent HoLEP (Porreca et al., 2019) and found that iPCa was detected in 24 (10.5%) patients overall. They identified a statistically lower rate of iPCa in patients with negative MRI compared to patients with no MRI (6.2% vs. 14.8%; p = 0.03). However, there was no significant difference between their negative MRI and no MRI groups in terms of GS 3+3 (85.7% vs. 88.2%; p = 0.86 respectively). In another study, Porreca et al. compared negative in-bore mpMRI-guided biopsy and negative mpMRI + transrectal ultrasonography (TRUS)-guided biopsy in patients with suspected PCA in terms of iPCa findings after HoLEP (Porreca et al., 2020). They found no statistically significant difference in iPCa (14% vs. 10%; p = 0.50 respectively) between groups.

Kim et al. (2014) evaluated the significance of TRUS in patients who underwent HoLEP, detecting iPCa in 27 patients (5.9%). The detection of a hypoechoic lesion on TRUS was found to be the only independent predictive factor for iPCa (OR: 2.829; 95% CI 1.061–7.539; p = 0.038).

In their study investigating the value of mpMRI and prostate biopsy in diagnosing PCA in patients scheduled for HoLEP, Wenzel et al. reported iPCa in 9 (11.8%) patients with no previous PCA diagnosis who had undergone HoLEP (Wenzel et al., 2021). In their study, they reported that Prostate Imaging–Reporting and Data System 4 and five lesions detected via mpMRI before HoLEP function as independent predictors of PCA (OR: 9.91, p = 0.04).

3.4 | Predictive factors of iPCa after HoLEP

Bhojani et al. investigated iPCa after HoLEP in 1272 patients, ultimately diagnosing (8.1%) patients with iPCa (Bhojani et al., 2015). Factors significantly associated with iPCa were higher age (OR: 1.07; 95% CI 1.04–1.10; p < 0.001), increasing preoperative PSA (OR: 1.03; 95% CI 1.01–1.05; p = 0.003) and lower surgical specimen weight after HoLEP (Bhojani et al., 2015). Regarding GS, they noted a significant association between preoperative PSA value and an increased risk of a higher GS (p = 0.002).

Elkoushy et al. determined the prevalence and predictors of iPCa in 1242 patients who underwent HoLEP (Elkoushy et al., 2015). Of those, 70 patients (5.64%) were diagnosed as having iPCa. In terms of GS, the majority had a GS ≤6 (80%). These authors found that higher age (OR: 1.27; 95% CI 1.12–1.76; p = 0.03) and preoperative PSA density (OR: 3.62; 95% CI 1.81–5.12; p = 0.01) were independent predictors for iPCa after HoLEP (Elkoushy et al., 2015).

Ohwaki et al. investigated predictive comorbidities of iPCa in patients who underwent HoLEP (Ohwaki et al., 2017). Of 654 men, 41 (6.3%) were diagnosed with iPCa. They categorised patients as low-risk (Gleason ≤6 and T1a; n = 25) versus high-risk (all others; n = 16) cancer groups. In terms of predictive comorbidities, diabetes proved to be an independent predictor of high-risk PCA (OR: 3.15; 95% CI 1.06–9.43; p = 0.04) (Ohwaki et al., 2017).

3.5 | Role of PSA kinetics in detecting iPCa after HoLEP

Magistro et al. evaluated whether a high preoperative PSA level has diagnostic value for detecting iPCa in 1125 patients who underwent HoLEP with a prostate volume above 100 cc (Magistro et al., 2020). Their study cohort was divided into two groups, one having a preoperative PSA value <10 ng/ml and the other >10 ng/ml. They observed no significant difference between groups in terms of the overall iPCa detection rate (9.5% vs. 9.9%; p = 0.83) or GS (p > 0.05) and found that PSA and PSA density were not associated with iPCa (p > 0.05) (Magistro et al., 2020).
Otsubo et al. (2015) evaluated PSA, PSA density and velocity in iPCA-diagnosed patients who underwent HoLEP. In their study, 25 patients (6.8%) were diagnosed with iPAs. They reported that a small prostate, higher preoperative PSA and higher PSA density were associated with iPAs. Furthermore, they found that preoperative PSA (6.06 ng/ml vs. 21.6 ng/ml, \( p = 0.0191 \)) and postoperative PSA velocity (0.185 ng/ml/year vs. 1.32 ng/ml/year, \( p = 0.0382 \)) differed significantly between GS 6 and >6 groups (Otsubo et al., 2015).

Martos et al. investigated the association of preoperative prostate size, urinary retention, urine culture, prostatitis and iPCA on baseline and 3-month nadir PSA values after HoLEP (Martos et al., 2021). Seven (7.8%) patients were diagnosed as iPAs. These authors stated that the histopathological diagnosis after HoLEP was not associated with PSA value at the 3-month follow-up after surgery (\( p = 0.724 \)).

Abedali, Calaway, Large, Lingeman, et al. (2020) investigated the positive predictive value of PSA and PSAD regarding the PCa after HoLEP. Fifty-five patients had undergone a TRUS biopsy the positive predictive value of PSA and PSAD regarding the PCa after HoLEP. They observed that patients with a PSAD above 0.1 ng/ml\(^2\) after HoLEP had a 95% probability of malignancy and an 88% risk of clinically significant PCa.

### 3.6 | Managing iPAs after HoLEP

In a study conducted by Gellhaus et al. (2015), robot-assisted radical prostatectomy (RARP) after HoLEP proved feasible and promising in terms of oncological results. Besides curative treatments, Elkousy et al. reported that active surveillance is a rational option for low-grade iPAs after HoLEP (Elkousy et al., 2015). Tominaga et al. (2019) stated that watchful waiting (WW) can be a useful approach for iPAs. However, it is unclear which patient group is suitable for WW. Rivera et al. reported that androgen deprivation therapy (ADT) can be applied alone or in combination with external beam radiation (XRT) in patients with a GS upgrade after HoLEP (Rivera et al., 2014). The authors stated that no stricture, bladder neck contracture, urinary retention or incontinence events were reported after XRT, radical prostatectomy or ADT (Rivera et al., 2014).

### 4 | DISCUSSION

Lower urinary tract symptoms caused by BPH is common in older men; it occurs in 70% of men over 60 years of age (Nafie et al., 2017). As with BPH, the PCa incidence is mainly age-related (Mottet et al., 2020). Although there is evidence that the iPAs detection rate fell from 31% to 5.4% through PSA screening, one can expect to detect iPAs after BPH surgery in older men (Bhojani et al., 2015; Elkousy et al., 2015). The incidence of iPAs after TURP has been reported to range from 5% to 14% (Abedi et al., 2020). Regarding the studies we reviewed, the rate of iPAs after HoLEP ranges between 5.64% and 23.3%. Although we would expect the iPAs rate to be higher because more tissue is removed in HoLEP surgery than during TURP, the outcomes of these comparative studies are conflicting. Herlemann et al. (2017) stated that there was no significant difference between HoLEP and TURP in assessing iPAs rates, whereas Rosenhammer et al. (2018a) and He et al. (2020) detected significantly more iPAs in patients who had undergone HoLEP. While there was no significant difference in iPAs detection in the study comparing OP and HoLEP (Rosenhammer et al., 2018b), another study including TURP, HoLEP and OP reported that their HoLEP group’s chance of having an iPAs detected was higher (Capogrosso et al., 2018).

Recently, multiparametric MRI of the prostate has gained popularity in PCa diagnosis, thanks to its high accuracy rates (Rhudd et al., 2017). Porreca et al. (2019) suggested that to rule out an iPAs, a negative mpMRI can benefit patients suspected of harbouring PCa who are undergoing HoLEP. Another study of the authors also proposed that in their patients with suspected PCa, in-bore mpMRI-guided biopsy is a potentially useful tool to avoid unnecessary TRUS-guided biopsy before HoLEP (Porreca et al., 2020). Kim et al. (2014) suggested that patients with abnormal PSA and negative DRE and hypoechoic lesions on TRUS can undergo a prostate biopsy before HoLEP. Overall, it probably makes good sense to carry out an MRI before biopsy in case of a hypoechoic lesion in TRUS. Clinicians should consider mpMRI before HoLEP, a rational option to detect PCa in case PCa is suspected.

We know that there is an association between PSA, PSA density and the clinical significance of PCa (Mottet et al., 2020). However, the role that PSA and PSA density play in iPAs after HoLEP is controversial. Otsubo et al. found that a higher preoperative PSA value and higher PSA density were associated with iPAs (Otsubo et al., 2015). In addition, higher PSA density was shown to be an independent predictor for iPAs after HoLEP (Elkousy et al., 2015; Herlemann et al., 2017). Rivera et al. suggested that in case of a change between preoperative and postoperative PSA values after HoLEP, clinicians should suspect a high-grade malignancy (Rivera et al., 2014). On the other hand, Magistro et al. found that PSA and PSA density were not associated with iPAs after HoLEP (Magistro et al., 2020).

However, PSA screening can raise the numbers of local disease diagnoses and lower the rates of advanced stage cancer. Kim et al. suggested a PCa screening strategy: in case of a previous negative biopsy, patients should be advised to undergo a transition zone biopsy or a transurethral surgical modality such as HoLEP enabling the retrieval of transitional zone tissue (Kim et al., 2019). They also found that the PSA level at the time of biopsy did not affect the iPAs detection rate following HoLEP. Otsubo et al. detected no significant difference in detecting iPAs between with- and without-biopsy groups in patients whose PSA measured >4 ng/ml before HoLEP (Otsubo et al., 2015). Considering the relevance of prostate biopsies before HoLEP, the PSA level's optimum range seems unclear in iPAs detection terms. Nevertheless, even if the biopsy is negative, it makes sense to follow-up PSA after HoLEP in patients in whom PCa was suspected preoperatively. Similarly, Martos et al. suggested that in case a PCa after HoLEP is undetected...
histopathologically and the patient’s nadir PSA level is higher, the patient should undergo investigation to enable an early diagnosis of PCa (Martos et al., 2021).

Hearing an unexpected cancer diagnosis after a benign disease surgery is difficult for both patients and their urologists, especially in terms of treatment choices. Since most iPcas detected after HoLEP are low grade, patients can be expected to benefit from curative therapies. Fortunately, there are various treatment options such as active surveillance, or treatment with curative intent after HoLEP such as open or RARP, XRT and intensity-modulated radiation therapy (Bhojani et al., 2015; Gellhaus et al., 2015; Kretschmer et al., 2020; Rivera et al., 2014). Bentafecta is a concept that includes urinary continence, potency, cancer control, postoperative complications and negative surgical margins after RARP and that shows the functional and oncological results of surgery (Patel et al., 2011). RARP after HoLEP does not preclude improved oncological outcomes, or alleviating incontinence and erectile function. In addition, positive surgical margins, biochemical recurrence rates and perioperative complication rates resembled those in HoLEP-naive patients (Abedali, Calaway, Large, Koch, et al., 2020; Gellhaus et al., 2015; Kretschmer et al., 2020). RARP after HoLEP appears to be a safe surgical and oncological method in suitable patients. Active surveillance, WW or ADT treatment options can also be considered in certain cases (Rivera et al., 2014; Tominaga et al., 2019).

We conducted a comprehensive review of iPca after HoLEP. However, this review has certain limitations. Firstly, retrospective nature of the studies, widely varying study designs, different study objectives/outcomes and large differences in patient numbers—all these factors make our data heterogeneous. Secondly, the paucity of comparative studies means that there are insufficient data to reveal differences in PCa detection between other transurethral surgical methods and HoLEP.

5 | CONCLUSIONS

We found that the iPca after HoLEP rate ranges from 5.64% to 23.3%. However, iPca was usually detected as lower GSs. There is a wide range of treatment options for iPca after HoLEP. Patients diagnosed with iPca after HoLEP should be informed about their treatment options. Nonrestricted postsurgical functional outcomes can be expected. The oncological follow-up should be individually discussed. An iPca diagnosis after HoLEP can be a serious concern for both patients and urologists. We believe that this review will be useful in the clinical practice of urologists who perform HoLEP.

CONFLICT OF INTEREST

Prof. Dr. Christian Gratze is advisor for Astellas Pharma GmbH, DE, Ipsen Pharma GmbH, DE, Steba Biotech S.A., LUX, Bayer Pharma, DE, Olympus Winter & Ibe GmbH, DE, Medi-Tate Ltd., IL, MSD, DE, Astra-Zeneca, UK and Roche, CH. He receives speaker fees from Amgen, USA, Astellas Pharma GmbH, DE, Ipsen Pharma GmbH, DE, Janssen-Cilag GmbH, BEL, Bayer Pharma, DE, Takeda Pharmaceuticals, JPN, and medac GmbH, DE. A. Miernik receives research funding from the German Federal Ministry of Education and Research, Berlin (D). He receives support for his travel activities from the European Society of Urology, Arnhem (NL), and German Society of Urology, Düsseldorf (D). A. Miernik is also a consultant for KLS Martin, Tuttingen (D), Avateramedical, Jena (D), LISA LaserProducts GmbH, Kalletsburg-Lindau (D), Schoelly fiberoptics GmbH, Denzlingen (D), Dornier MedTech Laser GmbH (D), MediTate Ltd. (IL, USA) and B. Braun Newventures GmbH, Freiburg (D). A. Miernik is speaker for the companies Richard Wolf GmbH (D) and Boston Scientific (USA). He also served as a reviewer for the Ludwig Boltzmann Gesellschaft, Wien (A). M. Yilmaz, T. Toprak, A. Sigle, R. Suarez-Ibarrola declare to have no conflicts of interest.

AUTHORS’ CONTRIBUTIONS

Study concept and design: Mehmet Yilmaz, Tuncay Toprak; acquisition of data: Mehmet Yilmaz, Tuncay Toprak; analysis and interpretation of data: Rodrigo Suarez-Ibarrola, August Sigle; drafting of the manuscript: Mehmet Yilmaz, Tuncay Toprak, Rodrigo Suarez-Ibarrola; critical review: Rodrigo Suarez-Ibarrola, Christian Gratze and Arkadiusz Miernik; supervision: Arkadiusz Miernik. All authors read and approved the final manuscript.

ETHICS

This research did not involve human subjects or animals. As this is a review of the literature, no ethics approval was necessary.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

Abedali, Z. A., Calaway, A. C., Large, T., Koch, M. O., Lingeman, J. E., & Boris, R. S. (2020). Robot-assisted radical prostatectomy in patients with a history of holmium laser enucleation of the prostate: The Indiana University experience. Journal of Endourology, 34(2), 163–168. https://doi.org/10.1089/end.2019.0436
Abedali, Z. A., Calaway, A. C., Large, T., Lingeman, J. E., Mellon, M. J., & Boris, R. S. (2020). The role of prostate specific antigen monitoring after holmium laser enucleation of the prostate. Journal of Urology, 203(2), 304–310. https://doi.org/10.1097/JU.0000000000005530
Abedi, A. R., Ghiasy, S., Fallah-Karkan, M., Rahavian, A., & Allameh, F. (2020). The management of patients diagnosed with incidental prostate cancer: Narrative review. Research and Reports in Urology, 12, 105–109. https://doi.org/10.2147/RRU.S245669
Bojani, N., Boris, R. S., Monn, M. F., Mandeville, J. A., & Lingeman, J. E. (2015). Coexisting prostate cancer found at the time of holmium laser enucleation of the prostate for benign prostatic hyperplasia: Predicting its presence and grade in analyzed tissue. Journal of Endourology, 29(1), 41–46. https://doi.org/10.1089/end.2014.0359
Capogrosso, P., Capitiano, U., Vertosick, E. A., Ventimiglia, E., Chièrio, F., Oreggia, D., Moretti, D., Briganti, A., Vickers, A. J., Montorsi, F., &
magnetic resonance imaging: A safe clinical practice to reduce incidental prostate cancer in Holmium laser enucleation of the prostate. *Central European Journal of Urology*, 72(2), 106–112. https://doi.org/10.5173/ceju.2019.1943

Rhudd, A., McDonald, J., Emberton, M., & Kasivisvanathan, V. (2017). The role of the multiparametric MRI in the diagnosis of prostate cancer in biopsy-naive men. *Current Opinion in Urology*, 27(5), 488–494. https://doi.org/10.1097/MOU.0000000000000415

Rieken, M., Ebinger Mundorff, N., Bonkat, G., Wyler, S., & Bachmann, A. (2010). Complications of laser prostatectomy: A review of recent data. *World Journal of Urology*, 28(1), 53–62. https://doi.org/10.1007/s00345-009-0504-z

Rivera, M. E., Frank, I., Viess, B. R., Rangel, L. J., & Krambeck, A. E. (2014). Holmium laser enucleation of the prostate and perioperative diagnosis of prostate cancer: An outcomes analysis. *Journal of Endourology*, 28(6), 699–703. https://doi.org/10.1089/end.2014.0009

Rosenhammer, B., Lausenmeyer, E. M., Mayr, R., Burger, M., & Eichelberg, C. (2018a). HoLEP provides a higher prostate cancer detection rate compared to bipolar TURP: A matched-pair analysis. *World Journal of Urology*, 36(12), 2035–2041. https://doi.org/10.1007/s00345-018-2353-0

Rosenhammer, B., Lausenmeyer, E. M., Mayr, R., Burger, M., & Eichelberg, C. (2018b). Holmium laser enucleation of the prostate provides similar incidental prostate cancer detection rates as open prostatectomy: A matched pair analysis. *Urologia Internationalis*, 101(4), 382-386. https://doi.org/10.1159/000492923

Sivarajan, G., Borofsky, M. S., Shah, O., Lingeman, J. E., & Lepor, H. (2015). The role of minimally invasive surgical techniques in the management of large-gland benign prostatic hypertrophy. *Reviews in Urology*, 17(3), 140–149.

Tominaga, Y., Sadahira, T., Mitsui, Y., Maruyama, Y., Tanimoto, R., Wada, K., Munemasa, S., Kusaka, N., Nishiyama, Y., Kurashige, T., Nasu, Y., & Hayata, S. (2019). Favorable long-term oncological and urinary outcomes of incidental prostate cancer following holmium laser enucleation of the prostate. *Molecular and Clinical Oncology*, 10(6), 605–609. https://doi.org/10.3892/mco.2019.1839

Vincent, M. W., & Gilling, P. J. (2015). HoLEP has come of age. *World Journal of Urology*, 33(4), 487–493. https://doi.org/10.1007/s00345-014-1443-x

Wenzel, M., Welte, M. N., Grossmann, L., Preisser, F., Theissen, L. H., Humke, C., Deuker, M., Bernatz, S., Gild, P., Ahyai, S., Karakiewicz, P. I., Bodelle, B., Kluth, L. A., Chun, F. K. H., Mandel, P., & Becker, A. (2021). Multiparametric MRI may help to identify patients with prostate cancer in a contemporary cohort of patients with clinical bladder outlet obstruction scheduled for Holmium Laser Enucleation of the Prostate (HoLEP). *Frontiers in Surgery*, 8, 633196. https://doi.org/10.3389/fsurg.2021.633196

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