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Incidental Prostate Cancer (cT1a–cT1b) Is a Relevant Clinical and Research Entity and Should Be Fully Discussed in the International Prostate Cancer Guidelines

1. Introduction

International guidelines for prostate cancer (PCa) represent a valuable aid for urologists and other health care professionals engaged in the management of PCa patients [1–3]. We commend the authors of international guidelines for systematically reviewing and critically analyzing a monumental amount of scientific literature, and developing evidence-based recommendations for practicing clinicians.

During the past decade, incidental (cT1a–cT1b) PCa has almost disappeared from international guidelines [1–3]. Stages T1a and T1b have been merged with T1c cancers, and thus have essentially vanished as a distinct clinical entity. This circumstance can be explained by a number of factors: (1) aggregation of T1a, T1b, and T1c cancers into one group with a homogeneous natural history [1–3]; (2) widespread PCa screening using prostate-specific antigen (PSA) and other tools; (3) the introduction and widespread implementation of multiparametric magnetic resonance imaging (mpMRI) of the prostate; (4) increased use of benign prostatic enlargement (BPE) treatments in which tissue is not available for pathologic evaluation (eg, GreenLight photoevaporation, "button" electroevaporation, water jet ablation); and (5) lack of high-level evidence regarding specific management of T1a and T1b PCa.

We believe that none of the above reasons justifies consigning cT1a and cT1b to history, mainly because incidental PCa is a common condition and its clinical implications differ from those for biopsy-detected tumors.

2. cT1a–cT1b PCa is still a very frequent diagnosis

With the wide availability of PSA measurement and the introduction of mpMRI, the vast majority of PCa cases are now identified before BPE treatment [4]. However, a not-insignificant number of patients undergoing BPE surgery (5–11% according to the most recent reports [5–8]) are still diagnosed with "incidental" PCa. Worldwide, this means many thousands of cases annually, as many patients will have a "normal" PSA level or no PSA measurement before BPE treatment. The further adoption of mpMRI in the PCa diagnostic pathway may increase this phenomenon. Many patients with elevated PSA and negative prostate mpMRI may undergo BPE surgery without a preoperative systematic prostate biopsy. Prostate mpMRI has relatively low sensitivity for low-grade tumors, and could eventually lead to an increase in the proportion of patients with incidental PCa detection [5].

3. cT1a–cT1b PCa assessment, treatment, and natural history: not the same as T1c cases

Patients with incidental PCa show a different natural history relative to biopsy-detected cases [9]. Incidental PCa cases include tumors that may involve the prostate transitional zone (TZ) in three distinctive ways, with different clinical implications [10]. PCa can involve the TZ: (1) by originating in the TZ only; (2) by originating in the peripheral zone (PZ) and subsequently infiltrating the TZ; and (3) through multifocal PCa simultaneously affecting all prostate zones. TZ cancer exhibits unique histological, molecular, and genetic characteristics that are different from those for tumors originating from the PZ. Indeed, relative to classical biopsy-detected cT1c cancers, TZ cancers are International Society of Urological Pathology (ISUP) grade group 1 in more than 90% of cases at diagnosis [5], and have lower expression of nuclear and nucleolar areas, human epidermal growth factor receptor [10], α-methylalacyl coenzyme A racemase, Ki67, topoisomerase IIα, and somatostatin receptors [10,11].

Furthermore, most clinical and pathological features (PSA, prostate volume, and histology) may be affected by prior BPE surgery. Therefore, statistical models predicting extracapsular extension, lymph node invasion, and risk of progression—originally and intentionally developed for biopsy-detected cancers—cannot be directly applied to cT1a–cT1b PCa [12].

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4. Additional considerations in relation to cT1a–cT1b PCa management

4.1. The key role of an expert pathologist

The cT1a–cT1b subclassification is based on the proportion of tumoral cells in the resected tissue. It was historically created to establish which cancers were at low (tumor incidental finding in ≥5% of resected tissue) versus high risk of progression (>5% or ISUP grade group >1). However, the volume-based distinction between T1a and T1b is limited by many potential methodological shortcomings which reduce its reliability and reproducibility (eg, the amount of specimen that is processed, pathologist expertise) [10]. Moreover, it has been demonstrated that the cT1a–cT1b subclassification does not increase the accuracy in predicting residual tumor at radical prostatectomy and clinical progression relative to the use of standard variables such as pathological ISUP grade and total PSA, which remain the most informative predictors in the cT1a–cT1b PCa setting [13,14].

4.2. The importance of postoperative PSA

The presence of incidental PCa at final pathology for BPE surgery reflects the poor performance of PSA as the sole screening test for PCa before BPE surgery. This can be attributed to many potential confounders (eg, large gland volume, concomitant inflammatory components, presence of an indwelling catheter) and to the fact that the true cancer burden for men with cT1a–cT1b PCa is usually small and of low grade [8].

Conversely, PSA assessment after surgery for BPE is relevant. BPE surgery reverses many PSA confounders. PSA after BPE surgery correlates more closely with the characteristics of the residual PZ tissue. Although imprecise, a comparison of the proportion of tissue resected (or ablated) with the percentage reduction in total PSA after BPE surgery can be informative. Indeed, in the case of incidental cancer, it was shown that a PSA level >1 ng/ml after surgery for BPE was associated with a worse natural history relative to patients whose PSA decreased to <1 ng/ml [9].

4.3. cT1a–cT1b PCa management: available data

In contrast to an earlier era when radical prostatectomy or radiation was frequently considered for men with favorable-risk PCa [13], active surveillance (AS) is now the standard of care for most of these patients. HAROW was an observational outcomes study on the management of localized PCa that enrolled more than 3000 patients with newly diagnosed localized (≤T2c) PCa in the period between 2008 and 2013 [7]. The study compared patients with cT1a–cT1b PCa undergoing AS with their counterparts with T1c–T2a PCa. The dropout rate from the AS protocol was significantly lower in the cT1a–cT1b group (12.1%) compared to the group with biopsy-detected tumors (25.9%) and—even more importantly—only 6% of the cT1a–T1b group undergoing AS switched to invasive treatment for clinical progression [7]. However, only 25.3% of the patients in cT1a–cT1b PCa group underwent at least one biopsy after their incidental PCa diagnosis [7].

No high-level evidence is available to define the optimal clinical decision pathway after detection of incidental cT1a–cT1b PCa. In this context, we propose some recommendations that are based on the retrospective and real-life data available:

(1) Strong collaboration with an expert uropathologist is required to ensure that the disease is correctly staged and graded (see the previous subsection) [10].
(2) Postoperative measurement of PSA, which is an informative predictor of residual disease and of the subsequent natural history of PCa [9,15], should be carried out. For instance, when postoperative PSA is >1 ng/ml, the probability of residual significant cancer is higher.
(3) If mpMRI has not been performed before surgery for BPE (eg, in cases of normal preoperative PSA), its use after BPE surgery for men who are found to have PCa is suggested to better characterize the residual part of the gland if PSA remains elevated [8,15].
(4) If a patient's life expectancy is <10 yr, watchful waiting should be considered, since the probability of clinical progression is virtually zero when balanced with competing risks [6,7,9,16].
(5) For patients with a life expectancy of >10 yr, biopsy of the PZ may be warranted to exclude large-volume or higher-grade PZ cancer [6,7,9].

In the era of mpMRI, cT1a–cT1b PCa remains a common condition (up to 11% of all BPE surgeries) with its unique natural history and biological behavior that differ in many ways from T1c and higher stage disease. While future research endeavors should target areas of uncertainty, this clinical entity should be fully recognized and thoroughly reflected in contemporary international guidelines.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Mottet N, Cornford P, van den Bergh RCN, et al. EAU guideline: prostate cancer. European Association of UrologyArnhem, The Netherlands https://uroweb.org/guideline/prostate-cancer/ 2020
[2] Mohler JL, Antonarakis ES, Armstrong AJ, et al. NCCN Clinical practice guidelines in oncology - prostate cancer, version 2.2019 short. J Natl Compr Cancer Netw 2019;17:479–505. http://dx.doi.org/10.6004/jnccn.2019.0023.
[3] Sanda MG, Cadeddu JA, Kirkby E, et al. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part I: risk stratification, shared decision making, and care options. J Urol 2018;199:683–90. http://dx.doi.org/10.1016/j.juro.2017.11.095.

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[4] Patel S, Rongen JJ, Fütterer JJ, Boltyenkov A, Rovers MM. The role of multiparametric magnetic resonance imaging in active surveillance for men with low-risk prostate cancer: a cost-effectiveness modeling study. Eur Urol Oncol 2018;1:476–83. http://dx.doi.org/10.1016/j.euo.2018.05.007.
[5] Capogrosso P, Capitanio U, Vertosick EA, et al. Temporal trend in incidental prostate cancer detection at surgery for benign prostatic hyperplasia. Urology 2018;122:152–7. http://dx.doi.org/10.1016/j.urology.2018.07.028.
[6] Elkoushy MA, Elshal AM, Elhilali MM. Incidental prostate cancer diagnosis during holmium laser enucleation: assessment of predictors, survival, and disease progression. Urology 2015;86:552–7. http://dx.doi.org/10.1016/j.urology.2015.06.002.
[7] Herden J, Wille S, Weissbach L. Active surveillance in localized prostate cancer: comparison of incidental tumours (T1a/b) and tumours diagnosed by core needle biopsy (T1c/T2a): results from the HAROW study. BJU Int 2016;118:258–63. http://dx.doi.org/10.1111/bju.13308.
[8] Hutchison D, Peabody H, Kuperus JM, et al. Management of prostate cancer after holmium laser enucleation of the prostate. Urol Oncol. In press. https://doi.org/10.1016/j.urolonc.2020.11.003.
[9] Capitanio U. Contemporary management of patients with T1a and T1b prostate cancer. Curr Opin Urol 2011. http://dx.doi.org/10.1097/MOU.0b013e328344e4ad.
[10] Capitanio U, Cheng L, Lopez-Beltran A, et al. The importance of interaction between urologists and pathologists in incidental prostate cancer management. Eur Urol 2011;60:75–7. http://dx.doi.org/10.1016/j.eururo.2011.03.012.
[11] Fisher KW, Zhang S, Wang M, et al. TMPRSS2-ERG gene fusion is rare compared to PTEN deletions in stage T1a prostate cancer. Mol Carcinog 2017;56:814–20. http://dx.doi.org/10.1002/mc.22535.
[12] Fossati N, Sjoberg DD, Capitanio U, et al. Extended pelvic lymph node dissection in patients with prostate cancer previously treated with surgery for lower urinary tract symptoms. BJU Int 2015;116:366–72. http://dx.doi.org/10.1111/bju.12912.
[13] Capitanio U, Scattoni V, Freschi M, et al. Radical prostatectomy for incidental (stage T1a–T1b) prostate cancer: analysis of predictors for residual disease and biochemical recurrence. Eur Urol 2008;54:118–25. http://dx.doi.org/10.1016/j.eururo.2008.02.018.
[14] Capitanio U, Briganti A, Suardi N, et al. When should we expect no residual tumor (pT0) once we submit incidental T1a–b prostate cancers to radical prostatectomy? Int J Urol 2011;18:148–53. http://dx.doi.org/10.1111/j.1442-2042.2010.02689.x.
[15] Chung DY, Goh HJ, Koh DH, et al. Clinical significance of multiparametric MRI and PSA density as predictors of residual tumor (pT0) following radical prostatectomy for T1a–T1b (incidental) prostate cancer. PLoS One 2018;13:e0210037. http://dx.doi.org/10.1371/journal.pone.0210037.
[16] Soeterik TFW, van Melick HHE, Dijksman LM, Biesma DH, Witjes JA, van Basten JPA. Follow-up in active surveillance for prostate cancer: strict protocol adherence remains important for PRIAS-ineligible patients. Eur Urol Oncol 2019;2:483–9. http://dx.doi.org/10.1016/j.euo.2019.01.010.

Umberto Capitanio[a,b]
Riccardo Autorino[c]
Marco Bandini[a,b]
Alberto Briganti[a,b]
Liang Cheng[d]
Matthew R. Cooperberg[e]
Federico Dehò[f]
Andrea Gallina[a,b]
Laurence Klotz[g]
Brian Lane[h,i]
Rodolfo Montironi[j]
Andrea Salonia[a,b]
Christian Stief[k]
Bertrand Tombal[l]
Francesco Montorsi[a,b,*]

[a]*Unit of Urology, IRCCS Ospedale San Raffaele, Milan, Italy*
[b]*Division of Experimental Oncology, Urological Research Institute, IRCCS Ospedale San Raffaele, Milan, Italy*
[c]*Division of Urology, VCU Health, Richmond, VA, USA*
[d]*Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN, USA*
[e]*Departments of Urology and Epidemiology & Biostatistics, Helen Diller Family Comprehensive Cancer Center, University of California-San Francisco, San Francisco, CA, USA*
[f]*Unit of Urology, Ospedale ASST Sette Laghi, Varese, Italy*
[g]*Division of Urology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada*
[h]*Department of Surgery, Michigan State University College of Human Medicine, Grand Rapids, MI, USA*
[i]*Division of Urology, Spectrum Health Hospital System, Grand Rapids, MI, USA*
[j]*Section of Pathological Anatomy, Polytechnic University of the Marche Region, United Hospitals, Ancona, Italy*
[k]*Department of Urology, Ludwig-Maximilians University of Munich, Munich, Germany*
[l]*Service d'Urologie, Cliniques universitaires Saint Luc, Université Catholique de Louvain, Brussels, Belgium*

*Corresponding author. Department of Urology, San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy. Tel. +39 02 26437286; Fax: +39 02 26437298.
E-mail address: montorsi.francesco@hsr.it (F. Montorsi).

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