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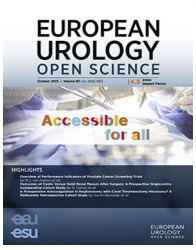


European Association of Urology

Prostate Cancer

# Intraductal Carcinoma Predicts Poor Response to Neoadjuvant Therapy in High-risk Prostate Cancer: A Retrospective Analysis of a Prospective Trial

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**Article info**

***Article history:***
Accepted September 29, 2025

***Associate Editor:***
Roderick C.N. van den Bergh

***Keywords:***
Prostatic neoplasms
Neoadjuvant treatment
Intraductal carcinoma
Androgen deprivation therapy

**Abstract**

***Background and objective:*** High-risk localized prostate cancer (PCa) patients may require neoadjuvant treatment (androgen deprivation therapy [ADT] plus abiraterone with or without taxane-based chemotherapy) before radical prostatectomy (RP). Intraductal carcinoma of the prostate (IDC) is an aggressive histological variant of prostate adenocarcinoma. This study aims to evaluate the association of IDC on biopsy with pathological response in such PCa patients.
***Methods:*** A retrospective analysis was conducted using the prospective trial data from 75 patients with high-risk localized/locally advanced PCa treated with 24 wk of neoadjuvant therapy comprising ADT and abiraterone, with or without taxane-based chemotherapy, followed by RP. Pathological responses, including pathological complete response (pCR), minimal residual disease (MRD), and adverse pathology outcomes (ypN1 or ≥ypT3b), were analyzed. Multivariable logistic regression identified the predictors of poor pathological response.
***Key findings and limitations:*** Among 75 patients, 35 (47%) had IDC on biopsy. Patients with IDC had worse pathological outcomes: 32 of 35 (91%) failed to achieve a favorable response (pCR or MRD) compared with 26 of 40 (65%) in those without IDC. IDC was also associated with higher rates of adverse pathology at RP,

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https://doi.org/10.1016/j.euros.2025.09.015

occurring in 27 of 35 patients (77%) versus nine of 40 patients (22%) without IDC. IDC independently predicted poor response (odds ratio 6.18, 95% confidence interval 1.16–32.8; $p$ = 0.032) after adjusting for tumor volume, Gleason grade, and prostate-specific antigen (PSA). In contrast, cribriform (Crib) pattern at biopsy did not impact response significantly. Metastatic progression and survival data were unavailable.

***Conclusions and clinical implications:*** IDC, but not Crib, on biopsy predicts poor pathological response to neoadjuvant therapy (ADT plus abiraterone with or without taxane-based chemotherapy) in high-risk PCa after adjusting for tumor volume and PSA. An understanding of this treatment-resistant phenotype will improve PCa biology insights and guide novel therapeutic strategies.

***Patient summary:*** Intraductal carcinoma (IDC) is a more aggressive form of prostate cancer that does not respond well to treatment. In our study, we found that 91% of patients who had IDC detected in their biopsy before surgery did not show a good response to presurgery therapy.



## 1. Introduction

Radical therapy typically results in excellent oncological outcomes for most patients with clinically localized prostate cancer (PCa). However, approximately 65% of patients with high-risk localized disease have recurrence requiring treatment following radical prostatectomy (RP) [1–4]. Even with intensified treatment using adjuvant or salvage radiation and/or chemohormonal therapy, the 15-yr mortality rate remains over 30% [3]. These poor outcomes suggest that micrometastatic disease is present at the initial diagnosis [5,6]. Early treatment intensification with neoadjuvant therapy has previously been explored to improve oncological outcomes for high-risk PCa patients.

A series of neoadjuvant clinical trials have shown mixed results among patients with high-risk PCa receiving androgen deprivation therapy (ADT) [7–11]. However, most of those studies were conducted in the pre–androgen receptor pathway inhibitor era and did not utilize metastasis-free survival as an endpoint [12,13]. A randomized trial of neoadjuvant docetaxel chemotherapy plus ADT has suggested a small benefit [14].

There has been interest in utilizing localized disease response in neoadjuvant trials as surrogate of long-term outcome [15–17]. Residual disease in post-treatment pathological response can offer insight into mechanisms of drug sensitivity and resistance. In this context, it is crucial to identify pretreatment prognostic factors to predict pathological response, as only 22–45% of patients experience a favorable pathological response following neoadjuvant ADT combined with androgen receptor pathway inhibitors or taxane-based chemotherapy [18–21].

Intraductal carcinoma of the prostate (IDC) is an aggressive histological variant of prostate adenocarcinoma, characterized by the presence of malignant cells within the prostatic ducts [22]. The biological distinction between IDC and cribriform (Crib) morphology has been investigated, and although a consensus on their independent clinical relevance is lacking [23–25], prior studies suggest that even minimal IDC on biopsy may portend aggressive behavior, independent of the Crib architecture [26]. Retrospective studies have demonstrated that IDC is strongly linked to higher tumor grades [27], higher odds of lymphatic metastasis [28,29], and worse oncological outcomes [30]. In experimental patient-derived xerograph models, IDC can persist after castration, with a subpopulation of castrate-tolerant cells capable of regenerating upon testosterone restoration [31]. Similarly, local recurrence after radiotherapy shows enrichment for IDC and Crib [32]. This suggests that IDC contributes to therapy resistance and highlights the need to understand how patients with this feature at biopsy respond to neoadjuvant systemic therapy. In this study, we examined the association between biopsy-derived IDC and pathological response in patients who underwent neoadjuvant treatment, including abiraterone plus or minus taxane-based chemotherapy, using pathological complete response (pCR)/minimal residual disease (MRD) as the surrogate endpoint as defined in the original ACDC trial [21].

## 2. Patients and methods

### 2.1. Study design, setting, and patients

We performed a retrospective analysis of prospectively collected data. As the data were collected retrospectively, no formal sample size calculation was conducted. From December 2016 to October 2023, a total of 75 patients with high-risk localized/locally advanced PCa (defined as prostate-specific antigen (PSA) >20 ng/ml, or Gleason score $\geq$8 with two or more positive cores, or Gleason score 4 + 3 = 7 with PSA >10 ng/ml and three or more positive cores) underwent neoadjuvant treatment with abiraterone acetate (1000 mg/d) plus prednisone (5 mg twice daily), leuprolide acetate (22.5 mg subcutaneously every 12 wk), and cabazitaxel (25 mg/m$^2$ body surface area; arm A) or abiraterone acetate plus prednisone and leuprolide acetate only (arm B) in a prospective randomized trial

(NCT02543255—ACDC trial). The planned treatment duration was 24 wk in each arm, following which patients underwent RP with standardized pelvic lymph node dissection to the level of the aortic bifurcation.

All RP specimens were fixed in formalin within 30 min of excision. The specimens were painted as per institutional protocol, and the apex and bladder neck were removed, sliced in serial transverse sections (5 mm in thickness), blocked in toto for paraffin embedding, and further processed for routine hematoxylin-eosin slides. The presence or absence of IDC and Crib in biopsies and RP specimens was adopted as a mandatory element in synoptic reporting in the Department of Pathology of our institution in 2015. All pathological biopsy slides were read by dedicated genitourinary pathologists, and re-reviewed as part of this study (T.v.K.). This study was approved by local institution review board (IRB – 24-5174).

### 2.2. Study variables

Patient-level variables were extracted from the trial data and included the following parameters: age at the time of RP, serum PSA level measured within 30 d prior to the start date of neoadjuvant treatment, diagnostic biopsy grade group (GG) and presence of IDC and/or Crib on prostate biopsy specimen, percent of biopsy cores positive, and highest core percentage. The following variables were retrieved from the final RP pathological examination: pathological stage, presence of IDC and/or Crib, margins, pelvic lymph node status, and pathological response to neoadjuvant treatment.

All prostate biopsies were reported as per international recommendations, with routine documentation of IDC and Crib. Definitions followed the 2021 International Society of Urological Pathology consensus for Crib [33] and the 2022 World Health Organization classification for IDC [34]. IDC was defined as lumen-spanning proliferation of carcinoma cells distending antecedent ducts or glands. Crib was defined as an expansile area of carcinoma cells without intervening stroma or vasculature and at least the size of an average (200 μm in diameter) benign gland and with multiple punched-out lumina. Immunostaining for basal cell markers to help distinguish between IDC and Crib was performed on a case by-case basis. Presence of IDC/Crib was based on a central review and blinded to outcomes.

### 2.3. Study outcomes

Our study objectives were thus to determine whether the presence of IDC in prostate biopsy is associated with a pathological response of primary PCa to neoadjuvant treatment (ADT plus abiraterone with or without taxane-based chemotherapy). A favorable pathological response was defined as the presence of a pCR or MRD in the RP specimen; pCR was defined as the absence of morphologically identifiable carcinoma in the prostatectomy specimen, and MRD was defined as residual cancer burden tumor volume (tumor percentage × prostate size) $\leq$0.5 $cm^3$. Adverse pathology at RP was defined as ypN1 or $\geq$ypT3b. We also investigated whether IDC in prostate biopsy was associated with adverse RP pathology (ypN1 or $\geq$ypT3b).

### 2.4. Statistical analysis

Demographic and clinicopathological characteristics were summarized using descriptive statistics. Differences in pathological response (pCR/MRD vs no pCR/MRD) and adverse RP pathology were stratified by the presence of IDC on biopsy, presence of Crib on biopsy, and type of neoadjuvant treatment, and the differences in distribution were assessed using Fisher's exact test.

To assess whether neoadjuvant treatment or presence of IDC or Crib on biopsy was independently associated with unfavorable pathological response (defined as an absence of pCR/MRD), multivariable logistic regression models were fit. Each model was adjusted for the following covariates: PSA before neoadjuvant treatment (continuous), percent of biopsy cores positive ($\leq$50% vs >50%), and GG (2, 3, and 4–5), as confounders were fit. Separate multivariable models were constructed for neoadjuvant treatment regimen (cabazitaxel plus abiraterone vs abiraterone alone), IDC, and Crib. As PSA distribution was significantly skewed, log PSA was used in the model. We dichotomized the percent of positive cores at 50% ($\leq$50% vs >50%) because >50% denotes high-volume disease; given the variable's right-skewed distribution, categorization at this clinically meaningful threshold improved model stability and interpretability. If IDC or Crib was statistically significant in the multivariable regression models, an additional multivariable model incorporating the same confounders along with an interaction term between IDC/Crib (whichever was significant) and neoadjuvant treatment regimen was fit, to evaluate whether the effect was consistent across treatment groups.

All statistical analyses were performed using R version 4.2.0 (The R Foundation for Statistical Computing, Vienna, Austria). All hypothesis tests were two sided and $p$ values of <0.05 were considered statistically significant. All analyses were conducted using complete cases; no missing data were imputed.

## 3. Results

This study included 75 patients who underwent neoadjuvant treatment prior to RP between 2016 and 2021. Among the 75 patients, 36 (48%) had Crib and 35 (47%) had IDC on prostate biopsy, with 19 (25%) patients having both IDC and Crib. Table 1, and Supplementary Tables 1 and 2 summarize cohort characteristics by IDC status, Crib status, and IDC and/or Crib status, respectively. Compared with IDC-negative patients, those with IDC on biopsy showed markedly greater tumor burden at baseline, with higher percent of biopsy cores positive (median 92% vs 65%, $p < 0.001$. When stratified by biopsy IDC and/or Crib status, baseline characteristics were broadly similar, with no statistically significant differences in PSA (median 20.8 vs 15.3 ng/ml, $p = 0.16$), GG distribution ($p = 0.65$), or neoadjuvant regimen allocation (ADT + abiraterone vs ADT + cabazitaxel + abiraterone, $p = 0.38$). At final RP specimen, IDC and Crib were frequent in both strata, with no significant differences (IDC: 21% vs 4.3%, $p = 0.091$; Crib: 12% vs 0%, $p = 0.17$).

**Table 1 – Overall cohort patient characteristics, stratified by biopsy IDC status**

| Variable | Overall ($n$ = 75) | IDC absent ($n$ = 40) | IDC present ($n$ = 35) | $p$ value |
|---|---|---|---|---|
| Age at biopsy (yr), median (IQR) | 69 (64–73.5) | 69 (64–72) | 70 (63–75) | 0.6 |
| Serum (before neoadjuvant) PSA (ng/ml), median (IQR) | 20.1 (9.9–37.1) | 18.4 (9.2–31.9) | 23.7 (13.0–38.1) | 0.17 |
| Biopsy grade group, $n$ (%) | | | | 0.053 |
| Grade group 1 | 0 | 0 | 0 | |
| Grade group 2 | 6 (8.0) | 3 (7.5) | 3 (8.6) | |
| Grade group 3 | 18 (24) | 14 (35) | 4 (11) | |
| Grade group 4 | 16 (21) | 5 (12) | 11 (31) | |
| Grade group 5 | 35 (47) | 18 (45) | 17 (49) | |
| Biopsy cribriform, $n$ (%) | 36 (48) | 17 (42%) | 19 (54%) | 0.4 |
| Percent of cores positive (%), median (IQR) | 73.5 (55.7–98.1) | 64.7 (47.6, 78.6) | 91.7 (71.4, 100.0) | <0.001 |
| Highest core percentage (%), median (IQR) | 90.0 (7.5–100) | 65 (0–100) | 95 (77.5–100) | 0.10 |
| Presence of intraductal carcinoma on radical prostatectomy specimen, $n$ (%) | 12 (16) | 2 (5%) | 10 (29%) | 0.009 |
| Presence of cribriform on radical prostatectomy specimen, $n$ (%) | 6 (8.1) | 1 (2.5%) | 5 (15%) | 0.088 |
| Missing | 1 | 0 | 1 | |
| Neoadjuvant treatment, $n$ (%) | | | | 0.075 |
| ADT + abiraterone | 35 (47) | 23 (58) | 12 (34) | |
| ADT + cabazitaxel + abiraterone | 40 (53) | 17 (42) | 23 (66) | |

ADT = androgen deprivation therapy; IDC = intraductal carcinoma; IQR = interquartile range; PSA = prostate-specific antigen.

Pathological response and adverse pathology rates stratified by IDC, Crib, and neoadjuvant treatment are summarized in Supplementary Tables 3–6. Multivariable regression models are summarized in Table 2. A poor pathological response occurred in 91% of patients with IDC versus 65% without IDC; after adjusting for PSA, GG, and percent of biopsy cores positive, IDC remained independently associated (odds ratio [OR] 6.18, 95% confidence interval [CI] 1.16–32.8, $p$ = 0.032). The interaction between IDC and neoadjuvant treatment was not statistically significant ($p$ = 0.7), suggesting no difference in association across treatment groups. Rates were similar with and without Crib (75% vs 80%), and Crib was not independently associated (OR 0.59, 95% CI 0.17–2.06, $p$ = 0.4). Response rates were also comparable between abiraterone alone and abiraterone + cabazitaxel (74% vs 80%), with no independent association of treatment (OR 1.46, 95% CI 0.41–5.23, $p$ = 0.6).

Adverse RP pathology was more frequent in patients with IDC on biopsy (77%) than in those without (22%; difference 55%, 95% CI 33–76%, $p$ < 0.001). Patients lacking both IDC and Crib had lower rates (17%) than those with either feature (62%; difference 45%, 95% CI 21–68%, $p$ < 0.001). No significant differences were observed by Crib status alone (56% and 41% in patients with and without Crib, respectively; difference 15%, 95% CI –10% to 40%, $p$ = 0.3) or by type of neoadjuvant treatment (58% in cabazitaxel + abiraterone vs 37% in abiraterone alone; difference 21%, 95% CI 4.5–45%, $p$ = 0.13).

## 4. Discussion

We examined the correlation between the presence of IDC in prostate biopsy and both the pathological response and the adverse pathology at RP in men with high-risk PCa who received 6-mo neoadjuvant ADT combined with abiraterone plus or minus taxane-based chemotherapy. IDC on prostate biopsy was a significant predictor of poor pathological response (91% did not achieve pCR/MRD) and adverse pathology at RP (77%). Additionally, IDC was the only independent predictor of poor pathological response, with patients demonstrating a six-fold higher likelihood of experiencing a poor pathological outcome. Neither Crib status on biopsy nor type of neoadjuvant treatment significantly influenced pathological response or adverse pathology at final RP. Notably, IDC prevalence on biopsy was high in our cohort (≈46.7%). This likely reflects the ACDC trial's enrichment for high-risk disease and a centralized, blinded review by genitourinary pathologists, and aligns with the rates reported in similarly aggressive populations (eg, 56% in the study of Porter et al [35]).

There is considerable variability in treatment response among men undergoing neoadjuvant therapy, with a pCR

**Table 2 – Multivariable logistic regression models for predictors of poor pathological response**

| Variable | IDC | | Crib | | Neoadjuvant treatment | |
|---|---|---|---|---|---|---|
| | OR (95% CI) | $p$ value | OR (95% CI) | $p$ value | OR (95% CI) | $p$ value |
| IDC present on biopsy (ref = absent) | 6.18 (1.16, 32.8) | 0.032 | | | | |
| Crib present on biopsy (ref = absent) | | | 0.59 (0.17, 2.06) | 0.4 | | |
| CABA + ABI neoadjuvant treatment (ref = ABI only) | | | | | 1.46 (0.41, 5.23) | 0.6 |
| Log PSA at diagnosis | 2.20 (1.00, 4.83) | 0.050 | 2.38 (1.11, 5.11) | 0.026 | 2.26 (1.05, 4.87) | 0.037 |
| >50% percent cores positive (ref = ≤50%) | 2.02 (0.51, 8.06) | 0.3 | 3.01 (0.79, 11.4) | 0.11 | 2.85 (0.76, 10.7) | 0.12 |
| Gleason grade group (ref = GG2) | | | | | | |
| GG 3 | 1.00 (0.07, 14.7) | 1 | 0.62 (0.05, 7.68) | 0.7 | 0.56 (0.04, 7.11) | 0.7 |
| GG 4–5 | 1.98 (0.14, 27.1) | 0.6 | 1.75 (0.15, 20.5) | 0.7 | 1.53 (0.12, 18.9) | 0.7 |

ABI = abiraterone; CABA = cabazitaxel; CI = confidence interval; Crib = cribriform pattern; GG = grade group; IDC = intraductal carcinoma; MRD = minimal residual disease; OR = odds ratio; pCR = pathological complete response; PSA = prostate-specific antigen.
An OR of >1 denotes no response (not pCR/MRD).

occurring in only 5–13% of cases and a favorable pathological response observed in 22–45% of cases [21,36] depending on the definition of pathological response. Understanding the mechanisms of drug sensitivity and resistance in this model can lead to enhanced drug development as well as personalized cancer therapies. Porter et al [31] found that IDC can persist after castration, with a subpopulation of castrate-tolerant cells capable of regenerating upon testosterone restoration in patient-derived xenografts models. Wang et al [37] demonstrated that the presence of IDC in biopsy samples is an independent predictor of poor pathological response, with a 3.8-fold increased likelihood of not achieving a favorable pathological response. However, their study did not adequately define IDC and Crib on biopsy, as it included the Crib pattern within the IDC definition and did not adjust for important confounding factors such as tumor volume (ie, the number of positive biopsy cores).

Molecular markers have also been proposed to be associated with poor neoadjuvant response. McKay et al [18] also observed that PTEN loss and IDC at RP were associated with an increased risk of biochemical recurrence in the neoadjuvant pre-RP setting. However, among 117 patients in the cohort, 65 did not have annotations for IDC status at the final pathology report. Additionally, baseline biopsy IDC status was not routinely available, preventing the authors from correlating it with the final outcomes. Kato et al [38] evaluated the response of IDC to neoadjuvant ADT in patients undergoing RP. This analysis involved 145 patients treated with neoadjuvant ADT, assessing the presence of IDC in prostate biopsy and RP specimens. The key findings included that IDC persistence after ADT was associated with poorer disease-free survival, cancer-specific survival, and overall survival compared with biopsies IDC-negative or IDC disappearance cases at final pathology. These data collectively suggest that IDC contributes to therapy resistance and underscores the need for new therapeutic strategies to target these resistant cancer cells [31].

Understanding the biological underpinnings that contribute to IDC therapeutic resistance remains an important research topic. We have previously reported via a proteomic approach that it has downregulation of androgen response proteins and upregulation of mesenchymal markers [39]. Additionally, others have noted that tumors with ERG positivity and PTEN loss are associated with larger residual disease and reduced androgen receptor expression, indicating a potential shift to androgen-independent survival mechanisms [40]. Further understanding these mechanisms will be instrumental in developing IDC-targeted therapies.

This study has some unique attributes unlike others published to date. First, the aforementioned studies did not differentiate between IDC and Crib in terms of oncological outcomes, grouping these together as a single entity. Additionally, unlike in our study, which utilized preoperative biopsy characteristics, IDC at final pathology was used as the independent variable, limiting clinical relevance since preoperative indicators that might predict poor oncological outcomes are more clinically applicable. To our knowledge, our study is the only one that analyzed IDC and Crib patterns separately. These entities should indeed be reported separately not only because of their morphological differences, with IDC characterized by cancer cells growing inside the ducts of the prostate gland and Crib characterized by cancer cells forming a sieve-like structure [29], but also due to their distinct oncological outcomes [28,29,41,42,43].

This study has several limitations that should be acknowledged. First, the relatively small sample size may limit the statistical power and generalizability of the findings to broader patient populations in this setting, and may also contribute to wider CIs. Second, data on long-term clinical outcomes such as metastasis-free survival and overall survival were not available, precluding direct assessment of the prognostic impact of IDC in this context. Nonetheless, the study benefits from high-quality data derived from a prospectively collected phase 2 clinical trial (ACDC), which employed standardized treatment protocols and rigorous data collection procedures, thereby enhancing the reliability and internal validity of the results. At this time, we do not recommend excluding IDC-positive patients from ongoing neoadjuvant treatment approaches, as the findings from this study are retrospective and should be interpreted with appropriate caution. Nevertheless, the results contribute important insights that inform the design of future prospective trials, particularly to validate the resistance of IDC to neoadjuvant therapies and to explore the role of novel agents or treatment intensification strategies in this high-risk subgroup.

## 5. Conclusions

In conclusion, IDC but not Crib on prostate biopsy is associated with poor pathological response to ADT plus abiraterone with or without taxane-based chemotherapy in men with high-risk PCa. These findings support routine assessment and reporting of IDC as a marker of inherent tumor aggressiveness and relative treatment tolerance, useful for risk stratification and trial design. Future prospective, biomarker-driven trials should test whether treatment intensification or novel agents will overcome this resistant phenotype.

***Author contributions:*** Rui M. Bernardino had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design*: Bernardino, Yin, Winqust, Jenjitranant, Henrique, Cockburn, van der Kwast, Joshua, Fleshner.
*Acquisition of data*: Bernardino, Yin.
*Analysis and interpretation of data*: Bernardino, Nguyen, Yin, Lajkosz, Cockburn, Matthiesen, Henrique, O'Connell, Benitez, van der Kwast, Fleshner.
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*Critical revision of the manuscript for important intellectual content*: Winqust, Yin, Lajkosz, Henrique, Cockburn, van der Kwast, Joshua, Fleshner.
*Statistical analysis*: Lajkosz.
*Obtaining funding*: Fleshner, Cockburn.
*Administrative, technical, or material support*: Cockburn, Benitez, Veloso.
*Supervision*: van der Kwast, Fleshner.
*Other*: None.

***Financial disclosures:*** Rui M. Bernardino certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

***Funding/Support and role of the sponsor:*** ACDC trial was supported by Ontario Institute for Cancer Research, Janssen, Sanofi, and Amgen. Rui M. Bernardino is supported by the Foundation for Science and Technology (FCT), Portugal (grant no. 2022.13386.BD).

***Ethics statement:*** Appropriate ethics approval was obtained from the University Health Network research ethics board.

***Data sharing statement:*** We have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The data sets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

***Acknowledgments:*** We acknowledge Princess Margaret Foundation.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2025.09.015.

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