Suitability of conventional systematic vs. MRI-guided targeted biopsy approaches to assess surgical treatment delay for radical prostatectomy

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Abstract
Objectives To assess if systematic (SBx) vs. transrectal or transperineal mpMRI-ultrasound targeted combined with systematic (TBx + SBx) biopsy confer different effects on treatment delay to radical prostatectomy measured as Gleason grade group (GGG) upgrade of prostate cancer (PCa).

Materials and methods We relied on a multi-institutional cohort of localized PCa patients who underwent RP in Martini-Klinik, Hamburg, or Prostate Center Northwest, Gronau, between 2014 and 2022. Analyses were restricted to PCa GGG 1–3 diagnosed at SBx (n = 4475) or TBx + SBx (n = 1282). Multivariable logistic regression modeling (MVA) predicting RP GGG upgrade of ≥ 1 was performed separately for SBx and TBx + SBx.

Results Treatment delay to RP of <90, 90–180 and 180–365 days was reported in 59%, 35% and 6.2% of SBx and in 60%, 34% and 5.9% of the TBx + SBx patients, respectively. Upgrade to GGG ≥ 4 at RP was detected in 15% of SBx patients and 0.86% of TBx patients. In MVA performed for SBx, treatment delay yielded independent predictor status (OR 1.17, 95% CI 1.02–1.39, p = 0.028), whereas for TBx + SBx MVA, statistical significance was not achieved.

Conclusion Treatment delay remained independently associated with radical prostatectomy GGG upgrade after adjustment for clinical variables in the patients diagnosed with SBx alone, but not in those who received combined TBx + SBx. These findings can be explained through inherent misclassification rates of SBx, potentially obfuscating historical observations of natural PCa progression and potential dangers of treatment delay. Thus, mpMRI-guided combined TBx + SBx appears mandatory for prospective delay-based examinations of PCa.

Keywords mpMRI · Systematic biopsy · Targeted biopsy · Prostate cancer · Delay · Outcomes

Abbreviations
SARS-CoV-2 Severe acute respiratory syndrome coronavirus type 2
PCa Prostate cancer
SBx Systematic prostate biopsy

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mpMRI Multiparametric magnetic resonance imaging
TBx Targeted prostate biopsy
RP Radical prostatectomy
GGG Gleason grade group
AS Active surveillance
OR Odds ratio
CI Confidence interval
IQR Interquartile ranges
SPCG-4 Scandinavian Prostate Cancer Group
PIVOT Prostate Cancer Intervention Versus Observation Trial

Introduction

The SARS-CoV-2 pandemic situation raised a long-forgotten question: How to redirect and reprioritize medical resources through the triage of elective surgical procedures in times of need [1].

In the field of uro-oncology, potential effects of surgical treatment delay in patients with prostate cancer (PCa) are often debated [2]. Aging population demographics and age-related comorbidity burden demonstrate a necessity for triage to evaluate and prevent possible perioperative risks [3]. To achieve this, it should be clarified in which patients a treatment delay would be feasible without worsening oncologic prognosis. According to earlier reports, a delay in treatment of D’Amico low-risk PCa may not affect PCa outcomes in the timeframe of 6–12 months [2, 4], comparable to rebiopsy recommendations within active surveillance (AS) protocols [5]. But data on intermediate- and high-risk PCa patients are conflicting. One of two systematic reviews on the treatment delay published in 2021 stated that the timeframe of three months is generally safe in these patients [6], whereas the other estimated four months and one month for intermediate- and high-risk PCa, respectively [4]. These controversies result from a variety of endpoints chosen by previous series and significant heterogeneity across the studies in terms of treatment delay definition [2, 4, 6].

However, previous series did not account for additional factors potentially affecting the robustness of their delay models, such as biopsy technique or multiparametric MRI (mpMRI) guidance at primary diagnosis. Thus, inherently high misclassification rates of systematic biopsy (SBx) could obfuscate the influence of treatment delay [7, 8]. Only a limited number of series examined treatment delay by relying on the mpMRI-guided targeted biopsy (TBx) of prostate, but are restricted by small sample sizes [4, 6, 9].

To address this unmet need, our study aims to assess if SBx vs. TBx + SBx confers different effects on surgical treatment delay measured as Gleason grade group (GGG) upgrade at radical prostatectomy (RP) focusing primarily on the low- and intermediate-grade PCa patients.

Material and methods

Patient selection

We relied on a multi-institutional cohort of localized PCa patients. A total of 4817 patients (84%) underwent RP between 2014 and 2022 in Prostate Center Northwest, Gronau, Germany, and 940 (16%) in Martini-Klinik, Hamburg, Germany. Analyses were restricted to the patients with biopsy GGG 1–3 diagnosed with SBx (n = 4475) or combined TBx + SBx (n = 1282). Patients were excluded if they had surgical- or radiotherapy prostate procedures or neoadjuvant treatment prior to biopsy.

All patients were registered within a prospective ethics committee-approved databases after informed consent.

mpMRI protocol and interpretation

In-house mpMRI examinations were performed in both institutions with a 3-T scanner (Gronau: Philips Achieva, Netherlands; Hamburg: Philips Igenia, Netherlands) according to previously described protocols [10]. External mpMRIs were included in case of acceptable quality after central review. MpMRI scans were reported according to the PI-RADS v.2 recommendations. MpMRI images performed before 2015 were reassessed accordingly.

Systematic biopsy

Patients underwent SBx at the discretion of the treating urologist and received TRUS-guided transrectal SBx, with cores taken systematically from at least apex, mid and base of the gland for each side. All SBx patients were subsequently treated at Prostate Center Northwest, Gronau.

mpMRI/ultrasound fusion-guided targeted biopsy

TBx + SBx in Gronau was performed transperineally with the BiopSee-platform (Medcom, Germany). TBx + SBx in Hamburg was performed transrectally with Urostation (Koolis, France). TBx protocols in both institutions were complemented with SBx, which included sampling of all regions outside the aforementioned contours. TBx + SBx protocols of both institutions were previously described [10, 11]. All biopsy cores were separately documented.
Histopathology

In both institutions, respective histopathological analyses were performed according to International Society of Urological Pathology guidelines. Pathological GGG upgrade at RP was defined as a GGG difference of ≥ 1 at RP vs. biopsy. Similarly, strong GGG upgrade was defined as GGG difference of ≥ 2. Finally, any upgrade to RP GGG ≥ 4 was evaluated separately.

Statistical analyses

TBx + SBx databases of both institutions were merged for analyses. For the descriptive analysis of the cohorts, frequencies and proportions were used for categorical variables and the median with interquartile range for continuously coded variables. The Chi-square test was used for categorical variables and the t test for continuously coded variables.

Multivariable logistic regression analysis (MVA) predicting GGG upgrade at RP was performed separately in SBx and TBx + SBx cohorts. The SBx MVA included following variables: age (cont.), PSA density (cont.), clinical tumor stage (cT1c [REF] vs. cT2), number of prior biopsy sessions (0 [REF] vs. ≥ 1), percent of PCa positive SBx cores (cont.), biopsy-based GGG (1 [REF] vs. 2 vs. 3) and treatment delay (days; cont.) between SBx and RP. The TBx + SBx MVA relied on same variables but also included maximum PI-RADS score (3 [REF] vs. 4 vs. 5) and percent of PCa positive TBx cores (cont.).

All tests were two-sided with a statistical significance set at p < 0.05. Statistical analyses are performed using the statistical package for R (R Foundation for Statistical Computing, v.4.1.1).

Results

Demographics

Within the SBx cohort, median age, PSA level and prostate volume were 65 years (IQR 59–70), 7.0 ng/ml (IQR 5.3–10) and 40 ml (IQR 30–53), respectively (Table 1). A total of 83% of patients were biopsy naïve. Median number of sampled SBx cores was 12 (IQR 10–12). A total of 7122 (38%), 1898 (43%) and 865 (19%) patients in this cohort were diagnosed with PCa GGG 1, 2 and 3, respectively. A time interval between positive SBx and RP of < 90, 90–180 and 180–365 days was reported in 2635 (59%), 1561 (35%) and 279 (6.2%) of the patients.

Within the TBx + SBx cohort, median age, PSA level and prostate volume were 66 years (IQR 60–70), 8.3 ng/ml (IQR 6–12) and 41 ml (IQR 32–58), respectively (Table 1). The maximum PI-RADS score proportions of 3, 4 and 5 were 166 (13%), 836 (65%) and 280 (22%). A total of 63% of patients were biopsy naïve. TBx + SBx were performed transperineally vs. transrectally in 27% and 73% of patients. A total of 322 (25%), 663 (52%) and 297 (23%) patients in this cohort were diagnosed with PCa GGG 1, 2 and 3, respectively. A treatment delay between positive TBx + SBx and RP of < 90, 90–180 and 180–365 days was reported in 764 (60%), 443 (34%) and 75 (5.9%) of the patients.

Assessment of the effect of treatment delay between SBx and RP on pathological upgrade

Concordant GGG findings at SBx and RP were reported in 50% (n = 2237) of the cases. Upgrading and strong upgrading were reported in 21% (n = 961) and 18% (n = 799) of the cases, respectively. It is of note that upgrading to GGG ≥ 4 occurred in 15% (n = 664) of cases. Pathological downgrading was observed in 11% (n = 478) RP specimens (Table 1).

Assessment of the effect of treatment delay between TBx + SBx and RP on pathological upgrade

Concordant GGG findings at TBx + SBx and RP were reported in 61% (n = 781) of the cases. Upgrading and strong upgrading were reported in 18% (n = 227) and 8.7% (n = 112) of the cases, respectively. Noteworthy is that upgrading to GGG ≥ 4 occurred in only 0.86% (n = 11) of the cases. Pathological downgrading was observed in 13% (n = 162) RP specimens (Table 1).

Factors influencing pathological upgrade at RP in the patients diagnosed with SBx vs. those with TBx + SBx

In MVA predicting GGG upgrade at RP, performed in the patients diagnosed with SBx, treatment delay yielded an independent predictor status (OR 1.17 95% CI 1.02–1.39, p = 0.028). Clinical variables such as age, PSA density, clinical tumor stage (cT1c [REF] vs. cT2), percent of PCa positive SBx cores, number of prior biopsy sessions (0 [REF] vs. ≥ 1), and GGG at SBx (1 [REF] vs. 2 vs. 3) achieved independent predictor status as well (Table 2).

In MVA performed in the patients diagnosed with TBx + SBx, treatment delay yielded no statistical significance (OR 0.96 95% CI 0.73–1.26, p = 0.8), whereas clinical variables such as age, PSA density, percent of PCa positive TBx cores, GGG at TBx + SBx (1 [REF] vs. 2 vs. 3) achieved an independent predictor status (Table 3).
Table 1 Baseline characteristics of the patients diagnosed with localized prostate cancer Gleason grade group 1–3 at systematic biopsy (n=4,755) at Prostate Center Northwest, Gronau, and at combined targeted and systematic biopsy (n=1282) at Martini-Klinik, Hamburg, or Prostate Center Northwest, Gronau, prior to radical prostatectomy, between 2014 and 2022

| Value                                                      | Systematic biopsy (n=4475) | Combined targeted and systematic biopsy (n=1282) | p value |
|------------------------------------------------------------|-----------------------------|-------------------------------------------------|---------|
| Age, years (median, IQR)                                   | 65 59–70                    | 66 60–70                                       | 0.035   |
| PSA, ng/ml (median, IQR)                                   | 7 5.3–10                    | 8.3 6–12                                       | <0.001  |
| Clinical tumor stage (n, %)                                |                             |                                                 |         |
| cT1c                                                       | 2827 63%                    | 934 73%                                        | <0.001  |
| ≥cT2                                                       | 1648 37%                    | 348 27%                                        |         |
| Prostate volume, ccm (median, IQR)                         | 40 30–53                    | 41 32–58                                       | <0.001  |
| PSA density, ng/ml/ccm (median, IQR)                       | 0.18 0.12–0.27              | 0.17 0.11–0.26                                | 0.007   |
| Number of prior biopsies of prostate (n, %)                |                             |                                                 |         |
| 0                                                          | 3725 83%                    | 809 63%                                        | <0.001  |
| ≥1                                                         | 750 17%                     | 470 37%                                        |         |
| Biopsy source (n, %)                                       |                             |                                                 | NA      |
| Gronau                                                     | 4475 100%                   | 342 27%                                        |         |
| Hamburg                                                    | 0 0%                        | 940 73%                                        |         |
| Number of SBx cores (median, IQR)                          | 12 10–12                    | 9 7–12                                         | <0.001  |
| Percent of PCa positive SBx cores                          | 33% 17%–50%                 | 20% 8.3%–36%                                  | NA      |
| SBx Gleason grade group (n, %)                             |                             |                                                 | <0.001  |
| No tumor                                                   | 247 19%                     |                                                 |         |
| GGG 1                                                      | 1712 38%                    | 514 40%                                        |         |
| GGG 2                                                      | 1898 43%                    | 403 31%                                        |         |
| GGG 3                                                      | 865 19%                     | 118 9.2%                                       |         |
| Maximum PI-RADS score (n, %)                               |                             |                                                 | NA      |
| 3                                                          | NA NA                       | 166 13%                                        |         |
| 4                                                          | NA NA                       | 836 65%                                        |         |
| 5                                                          | NA NA                       | 280 22%                                        |         |
| Number of TBx cores (median, IQR)                          | NA NA                       | 7 5–10                                         | NA      |
| Percent of PCa positive TBx cores                          | NA NA                       | 43% 17%–75%                                   | NA      |
| TBx Gleason grade group (n, %)                             |                             |                                                 | NA      |
| No tumor                                                   | NA NA                       | 112 8.7%                                       |         |
| GGG 1                                                      | NA NA                       | 318 25%                                        |         |
| GGG 2                                                      | NA NA                       | 600 47%                                        |         |
| GGG 3                                                      | NA NA                       | 252 20%                                        |         |
| Combined TBx + SBx Gleason grade group (n, %):              |                             |                                                 | NA      |
| GGG 1                                                      | NA NA                       | 322 25%                                        |         |
| GGG 2                                                      | NA NA                       | 663 52%                                        |         |
| GGG 3                                                      | NA NA                       | 297 23%                                        |         |
| Days from biopsy to prostatectomy, intervals (n, %)         |                             |                                                 | 0.8     |
| <90                                                        | 2635 59%                    | 764 60%                                        |         |
| 90–180                                                     | 1561 35%                    | 443 34%                                        |         |
| >181                                                       | 279 6.2%                    | 75 5.9%                                        |         |
| Prostatectomy Gleason grade group (n, %)                   |                             |                                                 | <0.001  |
| GGG 1                                                      | 1097 24%                    | 146 11%                                        |         |
| GGG 2                                                      | 1911 43%                    | 949 74%                                        |         |
| GGG 3                                                      | 803 18%                     | 176 14%                                        |         |
| GGG ≥ 4                                                    | 664 15%                     | 11 0.86%                                       |         |
| Gleason Grading Group reclassification at radical prostatectomy (n, %) |                             |                                                 | <0.001  |
| Downgrading                                                | 478 11%                     | 162 13%                                        |         |
| Same GGG                                                   | 2237 50%                    | 781 61%                                        |         |
| Upgrading of 1 GGG                                         | 961 21%                     | 227 18%                                        |         |
| Strong upgrading of ≥ 2 GGG                                | 799 18%                     | 112 8.7%                                       |         |

IQR interquartile ranges, SBx systematic biopsy of prostate, TBx targeted biopsy of prostate, PI-RADS Prostate Imaging Reporting and Data System, PCa prostate cancer, GGG Gleason Grade Group
Discussion

PCa is known for its rather slow biological progression and advanced age at primary diagnosis which may allow treatment delay without worsening oncologic prognosis [12]. However, the evidence on supposedly safe time-frames of the treatment delay remains highly heterogeneous [6]. Some studies consider treatment delay of up to 12 months in men with intermediate- and high-risk disease as safe [13, 14], whereas most of the series suggest a significantly shorter time period of 3–6 months [15–17]. Moreover, the results of SPCG-4 and PIVOT trials demonstrate that longer expectant management should be avoided in patients with intermediate-risk PCa [18, 19]. However, many series fail to provide a deeper assessment of additional factors affecting the outcomes, such as possible misclassification bias at primary diagnosis, e.g., biopsy. Thus, we aimed to investigate whether SBx compared to TBx + SBx confers different effects on treatment delay measured as RP GGG upgrade of PCa in a large multi-institutional cohort. Our study reveals important findings:

First, pathological upgrading at RP to high-risk disease defined as GGG ≥ 4 PCa was more often observed in the SBx- than in the TBx + SBx cohort, 15% (n = 664) vs. 0.86% (n = 11). These rates are highly consistent with previous studies [7, 20]. Specifically, Ahdoot et al. reported in a prospective trial that examined diagnostic accuracy of TBx, SBx and combined TBx + SBx in the men with MRI visible lesions upgrading to GGG ≥ 4 on SBx in 16.8% and on TBx + SBx in 3.5% of the patients [7]. Similarly, Diamond et al. reported upgrading to GGG ≥ 4 PCa of 3.8% in TBx + SBx cohort [20]. High SBx misclassification rates may result in false disease management decisions, for example including patients in AS protocols and complementary vs. omitted pelvic lymph node dissection at RP. Moreover, GGG upgrade to high-risk PCa in RP specimen should be taken into account when biopsy is considered, accounting for the detrimental impact of high-risk PCa on oncological outcomes previously reported [18, 19]. An observed upgrading from an indolent GGG1 at biopsy to GGG ≥ 2 at RRP can be explained through insufficient lesion sampling, e.g., limited number of cores [21] and as a result failed detection of the lowest Gleason pattern 4 burden [22].

Second, treatment delay achieved statistically independent predictor status for any GGG upgrade in MVA of the SBx cohort (OR 1.17, 95% CI 1.02–1.39, p = 0.028), whereas it did not in MVA of the TBx + SBx cohort. If our analyses were restricted to biopsy GGG 3, a similar pattern was observed namely treatment delay as a significant predictor for GGG upgrade as well as strong GGG upgrade in the SBx cohort, but not in the TBx + SBx cohort.

Table 2

| Value                        | OR   | 95% CI      | p value |
|------------------------------|------|-------------|---------|
| Age, years                   | 1.04 | 1.03–1.05   | <0.001  |
| PSA density, ng/ml/ccm       | 2.07 | 1.86–2.32   | <0.001  |
| Clinical tumor stage         |      |             |         |
| cT1c [REF]                   | –    | –           | –       |
| cT2                          | 1.97 | 1.71–2.27   | <0.001  |
| Number of prior biopsy sessions |      |             |         |
| 0 [REF]                      | –    | –           | –       |
| ≥ 1                          | 0.83 | 0.70–0.99   | 0.045   |
| Percent of positive SBx cores |      |             |         |
| GGG 1 [REF]                  | –    | –           | –       |
| GGG 2                        | 0.28 | 0.24–0.32   | <0.001  |
| GGG 3                        | 0.21 | 0.17–0.26   | <0.001  |
| Days to prostatectomy        | 1.17 | 1.02–1.39   | 0.028   |

OR hazard ratio, CI confidence interval, SBx systematic prostate biopsy, GGG Gleason Grade Group

Table 3

| Value                        | OR   | 95% CI      | p value |
|------------------------------|------|-------------|---------|
| Age, years                   | 1.04 | 1.02–1.07   | <0.001  |
| PSA density, ng/ml/ccm       | 1.98 | 1.54–2.57   | <0.001  |
| Clinical tumor stage         |      |             |         |
| cT1c [REF]                   | –    | –           | –       |
| cT2                          | 1.37 | 0.98–1.91   | 0.067   |
| Number of prior biopsy sessions |      |             |         |
| 0 [REF]                      | –    | –           | –       |
| ≥ 1                          | 1.03 | 0.75–1.40   | 0.9     |
| Maximum PI-RADS score        |      |             |         |
| 3 [REF]                      | –    | –           | –       |
| 4                            | 1.31 | 0.84–2.08   | 0.2     |
| 5                            | 1.63 | 0.97–2.74   | 0.064   |
| Percent of positive TBx cores |      |             |         |
| GGG 1 [REF]                  | –    | –           | –       |
| GGG 2                        | 2.59 | 1.56–4.32   | <0.001  |
| GGG 3                        | 1.54 | 0.78–3.03   | 0.2     |
| Days to prostatectomy        | 0.96 | 0.73–1.26   | 0.8     |

OR hazard ratio, CI confidence interval, SBx systematic biopsy of prostate, TBx targeted biopsy of prostate, PI-RADS Prostate Imaging Reporting and Data System, GGG Gleason Grade Group
findings might be explained with the inherent misclassification rate of SBx reported in the previous series [7, 8]. This may limit the assessment of the treatment delay effects as demonstrated by contradictory results of the earlier studies [13–17, 23–28].

Further strengthening these notions, out of two systematic reviews on the treatment delay published in 2021 one stated that the timeframe of three months is generally safe in patients with intermediate- and high-risk PCa [6], whereas the other estimated four months for intermediate- and one month for high-risk PCa, respectively [4]. Interestingly both systematic reviews relied on the virtually same studies, with a few exemptions of the studies conveying contradictory messages [17, 23–28]. This only confirms the general uncertainty in this field and demonstrates the need for further trials. Moreover, it is noteworthy that in the real-life scenario, various factors such as administrative delay, compliance as well as recent pandemic issues are to be taken into account if definitive treatment is planned. These factors however may affect the assessment of treatment delay to RP.

Finally, as opposed to the SBx MVA, MVA of treatment delay in the TBx + SBx cohort did not yield an independent predictor status for pathological GGG upgrade (OR 0.96, 95% CI 0.73–1.26, \( p = 0.8 \)). This, taking into account high accuracy and reliability of mpMRI-guided TBx + SBx, could represent the true, slow biological progression of the PCa [12]. Moreover, this reflects previous dedicated series on mpMRI-TBx delay which found no effect on TBx csPCa yield [9] as well as modern mpMRI-based AS protocols demonstrating that 85% and 72% of patients remain on AS at 3 and 5 years, respectively [29].

Another important aspect to consider is the TBx-effect of grade inflation, which also might reduce upgrading at RP [30]. Moreover, it is important to acknowledge that the time interval between any biopsy and local treatment does not include complementary analyses such repeated digital rectal exams or longitudinal mpMRIs that would highlight any changes or discordant findings early on. In our setting, however, the time interval essentially passes without additional diagnostics since the treatment decision is already finalized. Our study aimed to provide first evidence on the effect of biopsy technique on RP GGG upgrade in the treatment delay scenario relying on the large multi-center cohort. Due to the primary surgical focus, we assessed only the effects of biopsy on RP timespan. However, only limited number of series provided evidence on the safe timespan between diagnostic modalities such mpMRI and TBx + SBx, demonstrating clear, unmet need for future prospective studies [9, 29].

Our study is not devoid of limitations. First, our data originate from two highly specialized tertiary referral centers and are not necessarily generalizable. Second, our data represents transperineal and transrectal biopsies, non-academic and academic centers including both in- and out-house performed mpMRIs. Finally, patients included in the study were diagnosed and received subsequent RP between 2014 and 2022 which also represents a limitation because of the refinement of biopsy and imaging technology at this time. On the other side, analyses were consistent if restricted to those diagnosed and treated from 2016 to the present (data not shown).

## Conclusion

In the patients diagnosed with SBx, treatment delay was independently associated with RP GGG upgrade after adjustment for clinical variables, but not in the cohort of TBx + SBx patients. These discordant findings might be explained through inherent misclassification rates of SBx, potentially obfuscating historical observations of natural PCa progression and potential dangers of treatment delay. Thus, mpMRI-guided TBx or at least SBx protocols with complementary MRI appears mandatory for prospective delay-based examinations of PCa.

### Author contributions

PR, MK, LB and SRLB 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 was done by PR, MK and SRLB. Acquisition of data was done by PR and MK. Analysis and interpretation of data were carried out by PR, MK and SRLB. Drafting of the manuscript was done by PR, MK, LB, JHW and SRLB. Critical revision of the manuscript for important intellectual content was done by PR, MK, JZ, TS, DB and SRLB. Statistical analysis was carried out by PR, MK and SRLB. Obtaining funding: NA. Administrative, technical, or material support was carried out by LB, JHW, CW, JZ, TS, DB and MG. Supervision was done by LB, JHW, CW, MG, MK and SRLB. Other: none.

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### Availability of data and material

Full availability.

### Code availability

Full availability.

### Declarations

**Conflict of interest** The authors declare that they have no conflict of interest according to the current manuscript.

**Ethical approval** The institutional review board at the St. Antonius-Hospital, Gronau as well as at the Martini-Klinik, Hamburg, and the local ethics committee at University of Münster and University of Hamburg approved the retro- und prospective study design and access to the patients’ medical records. All methods were carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from individual participants in the study.

**Ethical standards** All authors of this research paper have directly participated in the planning, execution or analysis of the study. All authors of this paper have read and approved the final version submitted. The contents of this manuscript have not been copyrighted or published.
previously. The contents of this manuscript are not under consideration for publication elsewhere.

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