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Diagnostic Value, Oncological Outcomes And Safety Profile Of Image-Guided Surgery Technologies During Robot-Assisted Lymph Node Dissection with Sentinel Node Biopsy For Prostate Cancer.

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Abstract

Rationale: Despite good sensitivity and negative predictive value, the implementation of sentinel node biopsy (SNB) in robot-assisted radical prostatectomy (RARP) with extended pelvic lymph node dissection (ePLND) for prostate cancer (PCa) is still controversial. Based on this premise, we aimed to define the added value of SNB (with different tracer modalities) to ePLND in the identification of nodal metastases. Complications rates and oncological outcomes were also assessed.

Methods: From January 2006 to December 2019, prospectively collected data were retrospectively analyzed from a single institutional database regarding PCa patients all treated with RARP and ePLND with or without additional use of SNB, either with hybrid tracer indocyanine green (ICG)–^{99m}Tc-nanocolloid (ICG-99mTc-nanocolloid) or free ICG. Multivariable logistic and Cox regression models tested the impact of adding SNB (either with hybrid tracer or free-ICG) on lymph nodal invasion detection, complications and oncological outcomes.

Results: Overall, 1680 patients were included in the final analysis. 1,168 (69.5%) were in the ^{non}SNB-group, 161 (9.6%) in the ^{ICG}SNB-group and 351 (20.9%) patients in the ^{Hybrid}SNB-group. ^{Hybrid}SNB-group (OR 1.61, 95%CI 1.18-2.20, p=0.002) was an independent predictor of nodal involvement, while ^{ICG}SNB-group did not reach the independent predictor status when compared to ^{non}SNB group (OR 1.35, 95%CI 0.89-2.03, p=0.1). SNB techniques were not associated with higher rates of complications. Lastly, use of ^{Hybrid}SNB was associated with lower rates of biochemical recurrence (0.79, 95%CI 0.63-0.98) and of clinical recurrence (HR 0.76, p=0.035) compared to ^{non}SNB group.

Conclusions: The implementation of hybrid sentinel node biopsy technique with ICG-^{99m}Tc-nanocolloid in prostate cancer improves detection of positive nodes and potentially lowers recurrence rates with subsequent optimization of patient management, without harming patient safety.

Introduction

During the last decade, there was an increasing interest to identify and implement new staging modalities for lymphatic metastatic dissemination in prostate cancer (PCa) patients. An extended pelvic lymph node dissection (ePLND) represents the best available staging tool for PCa patients with a risk of lymph node invasion (LNI) higher than 5% (*1*,*2*). Despite the invasive nature of this approach, it has been demonstrated that ePLND can still miss aberrant dissemination pathways to approximately 30% of lymph nodes that are located outside the ePLND template (*2*). Tailored staging modalities that help predict the routes of lymphatic spread, such as sentinel node biopsy (SNB), have been proposed to improve the accuracy of ePLND in identifying nodal metastases (*3*,*4*). Despite good sensitivity and negative predictive value of this approach (i.e. SNB) (*2*), its added value relative to ePLND on detecting LNI remains a subject of discussion. As a consequence, SNB in prostate cancer is still considered an experimental procedure (*2*). One concern herein is that the safety profile in terms of complications of adding SNB to ePLND has never been tested. Last but not least, to date, evidence supporting a potential role of SNB and ePLND in PCa in terms of oncological benefit are still limited and often controversial (*1*,*5*–*7*).

Based on this premise and to overcome these limitations, we relied on the largest available case series of patients who underwent robot-assisted radical prostatectomy (RARP) and ePLND with or without SNB (N = 1680). We aimed to define the effect of SNB and different SNB tracer modalities on LNI staging accuracy, complications rates and mid-term oncological outcomes.

Materials and Methods

Data source and patient selection

From January 2006 to December 2019, prospectively collected data were retrospectively analyzed from a single institutional (Antoni van Leeuwenhoek Hospital, The Netherlands Cancer Institute, Amsterdam) database regarding PCa patients treated with RARP and ePLND with or without additional use of SNB. SNB was performed in addition to the standard ePLND and was performed either using the hybrid fluorescent and radioactive tracer indocyanine green (ICG)–^{99m}Tc-nanocolloid (ICG-^{99m}Tc-nanocolloid) or free ICG (*8–10*). For the purpose of the current analysis, we focused on patients with a risk of LNI >5% according to the 2012 Briganti nomogram (*11*). The latter has been demonstrated to be one of the most accurate predictive model for LNI in external validation studies (*12*), particularly for the time span of our analysis. All surgeries were performed by robotic approach. All patients with complete data on follow- pathological data and recurrence were included. Overall, 1680 patients were included in the final analysis. 1,168 (69.5%) were offered ePLND only (^{non}SNB-group), 161 (9.6%) received ePLND complemented with SNB based on free ICG (^{ICG}SNB-group), and 351 (20.9%) patients received ePLND complemented with SNB using the ICG-^{99m}Tc-nanocolloid (^{Hybrid}SNB-group). Patients receiving ePLND without SNB were treated between 2006 and 2019, those receiving ePLND and hybrid tracer between 2010 and 2019 and those receiving ^{ICG}SNB between 2016 and 2019.

The study protocol was approved by the institutions' medical ethics committees (NL28143.031.09, NL41285.031.12, NL46580.031.13). Thereafter, a waiver from the institutional review board was received for the data collection/analysis

SNB and ePLND technique

The ePLND, SNB technique, and pathologic examination were previously described (*13*). Patients first underwent SNB, followed by ePLND and RARP. SNs were identified via lymphatic mapping with ICG-^{99m}Tc-nanocolloid (0.5mg albumin, 0.25 mg ICG, 240 MBq ^{99m}Tc in 2mL saline) or "free" ICG (5mg in 2ml sterile water).

ICG-^{99m}Tc-nanocolloid (2mL) was transrectally injected in the morning of surgery into the peripheral zone of each quadrant of the prostate, under ultrasound guidance, as previously described (*14*,*15*). Early and late dynamic lymphoscintigraphy were performed respectively 15 min and 2 hours post-injection. In the ^{Hybrid}SNB-group, preoperative SN mapping was performed with lymphoscintigraphy and single-photon emission computed tomography supplemented with low dose computed tomography (SPECT/CT). The nuclear medicine physician assessed all acquired images and reported the anatomical localization of the individual SNs. Surgery was planned to start from 4 h after ICG-^{99m}Tc-nanocolloid injection. All SNs were pursued with radio- and fluorescence guidance. The radioguidance was provided by the Europrobe laparoscopic 0^{o} gamma probe (Eurorad S.A.; Eckbolsheim, France; used in combination with a sterile cover). The fluorescence guidance was provided by the integrated FireFly^{TM} camera of the DaVinci Si robotic system.

In the ^{ICG}SNB-group, 2mL ICG was transrectally injected in the operating room under ultrasound guidance, before starting the surgery. In this group, all SNs were pursued with Firefly fluorescence guidance (*15*), followed by an ePLND template, which was defined as the region encompassed by the ureteric crossing and including the bifurcation of the common iliac artery, along the external iliac (the distal limit being the deep

circumflex vein and femoral canal), the internal iliac vessels and the obturator fossa. The lateral border was the genitofemoral nerve and the medial border the peri-vesical fat. Overall, 13 surgeons were involved in the current large RARP cohort, but SNB procedures were performed exclusively by 3 surgeons.

Outcomes

The primary endpoint of our study was to assess the added value of SNB to ePLND in the identification of nodal metastases. Additionally, we tested the lymph node detection rate according to the preoperative LNI risk, based on the 2012 version of the Briganti nomogram (*11*). Secondary endpoints were the safety profile of SNB by reporting rates of postoperative complications and mid-term oncological outcomes, namely biochemical recurrence (BCR) and clinical recurrence (CR). BCR was defined as two consecutive PSA measures ≥ 0.2 ng/ml (*2*). CR consisted of any radiological confirmed loco-regional or distant tumor recurrence. Postoperative complications were graded according to the Clavien-Dindo classification (*16*).

Variable definition

Clinical covariates included were age at surgery, neoadjuvant androgen deprivation therapy (ADT) use, clinical T stage (T1c, T2, T3), clinical N stage (Nx, N0, N1), biopsy Gleason score (bGS) and preoperative iPSA. Pathological and postoperative covariates consisted of pathological T stage (≤pT2, pT3a, ≥pT3b), pathological N stage (pN0, pN1), pathological GS (6, 7, 8-10), number of lymph nodes removed, presence of positive surgical margins and use of salvage radiation therapy.

Statistical analysis

Statistical analyses as well as reporting and interpretation of the results were conducted according to established guidelines (*17*) and consisted of four analytical steps. First, medians and interquartile ranges, as well as frequencies and proportions were reported for continuous and categorical variables, respectively. The Mann-Whitney and chi-square tests were applied to compare the statistical significance of differences in the distribution of continuous or categorical variables, respectively.

Second, multivariable logistic regression models were fitted to assess the impact of SNB (^{non}SNB-group vs. ^{Hybrid}SNB-group vs. ^{ICG}SNB-group) on LNI rate at final pathology, after adjusting for several clinical confounders. Models were adjusted using prespecified clinical covariates. Thereafter, multivariable-derived probability of LNI detection according to different SNB methods were plotted against preoperative Briganti score using locally weighted scatter-plot smoother function (*18*,*19*), after accounting for the aforementioned confounders.

Third, two sets of logistic regression models were fitted to test the impact of SNB use and type on postoperative complications, after adjusting for age at surgery, neoadjuvant ADT, cT stage, cN stage, preoperative PSA and biopsy GG. Logistic regression models were repeated for Clavien-Dindo grade ≥ II and grade ≥ III. Additionally, to test the hypothesis that refinements in SN technique may have impacted the complication rate, an interaction term between type of SN (^{non}SNB-group vs. ^{Hybrid}SNB-group vs. ^{ICG}SNB-group) and year of surgery was used.

Fourth, Kaplan-Meier plots were used to depict BCR- and CR-free survival after stratification according to ^{non}SNB-group vs. ^{Hybrid}SNB-group vs. ^{ICG}SNB-group. Finally, multivariable Cox-regression models tested for predictors of BCR, as well as of CR. Previously defined pathological covariates were included as predictors in Cox regression models. Moreover, models predicting CR were further adjusted for the use of salvage radiation therapy. Analyses were performed using the R software v.3.6.3 and all tests were two-sided with significance level set at $p < 0.05$.

Results

Patient clinical characteristics

Table 1 and Figure 1 depict clinical characteristics of our cohort. Patients in the ^{ICG}SNB-group were older (67 vs 65 years old, p<0.001), had more GS 8-10 at biopsy (41.6 vs 29.4%, p<0.001) and had more cN1 at preoperative imaging (15.5 vs 5.7%, <0.001) compared to ^{non}SNB-group. No statistically significant differences in cT stage and PSA at surgery were recorded between the ^{ICG}SNB and ^{non}SNB-group. On the other hand, patients in the ^{Hybrid}SNB-group had more GS 7 at biopsy (65.2 vs 54%, p<0.001) and had less cN1 at preoperative imaging (0.9 vs 5.7%, <0.001) compared to the ^{non}SNB-group. When compared to the ^{ICG}SNB group, patients in the ^{Hybrid}SNB-group had less cN1 at preoperative imaging (0.9 vs 15.5%, p<0.001) and lower median preoperative LNI risk score (12.4 vs 20.5, p<0.001). Regarding operative time, the ^{ICG}SNB group was characterized by the shortest surgical median duration (111 min) when compared to both the ^{Hybrid}SNB (121 min) and ^{non}SNB (115 min) groups (p values 0.001 and 0.01, respectively). Lastly, the rate of administration of salvage radiation therapy did not differ between ^{Hybrid}SNB (27.1%) and ^{non}SNB (27.8%) groups (p=0.8), while it was lower in ^{ICG}SNB group (17.4%) when compared to both ^{Hybrid}SNB (p=0.02) and ^{non}SNB (p=0.006) groups.

Pathological report and nodal staging

Pathological findings are reported in Table 1. Overall, patients from the ^{ICG}SNB-group were less frequently organ-confined (≤ pT2c 34 vs 50.8%, p<0.001) and had less GS 8-10 (16.8 vs 24.4%, p<0.001) compare to those in the ^{non}SNB-group. Notably, the rate of pN1 in the first group was double than of the second (36 vs 18.9%, p <0.001). On the same

line, the nodal yield increased for the ^{ICG}SNB-group (median 20 vs 11, p<0.001), yielding higher rate of > 2 positive nodes at pathology (11.8 vs 5.8%, p<0.001). Similarly, pN1 rate (28.2 vs 18.9%, p<0.001), number of removed LNs (median 17 vs 11, p<0.001) and rate of > 2 positive nodes (9.7 vs 5.8, p<0.001) were remarkably higher in patients from the ^{Hybrid}SNB- vs the ^{non}SNB group. Compared to the ^{ICG}SNB group, patients in the ^{Hybrid}SNB-group had lower pN1 rate (28 vs 36%, p<0.001) and lower number of lymph nodes removed (median 17 vs 20, p<0.001).

At multivariable models predicting pN1, ^{Hybrid}SNB-group (OR 1.61, 95%CI 1.18-2.20, p=0.002) was an independent predictor of LNI detection at final pathology compared to ^{non}SNB group, after accounting for all preoperative covariates including number of removed nodes. On the other hand, ^{ICG}SNB-group did not reach the independent predictor status when compared to ^{non}SNB group (OR 1.35, 95%CI 0.89-2.03, p=0.1; Table 2). Compared to the ^{ICG}SNB-group, the ^{Hybrid}SNB-group (OR 1.19, 95%CI 0.76-1.86, p=0.4) was not associated with a significant increase in LNI detection at final pathology.

Subsequently, we graphically represented the variation of pN1 detection rate for hybrid tracer technique vs ^{non}SNB across different preoperative LNI risk calculated according to the 2012 Briganti nomogram (Figure 2). The use of hybrid tracer SNB approach was associated with higher pN1 detection rate across all the predicted preoperative LNI risk.

Postoperative complications

Overall, 572 (34%) patients experienced postoperative complications (Table 3). According to Clavien-Dindo classification, 78 patients (4.6%) experienced grade I, 237

(14.1%) patients grade II, 128 (7.6%) patients grade IIIa, 72 (4.3%) patients grade IIIB and 3 (0.2%) patients grade IV complications. The overall rate of Clavien-Dindo ≥ II was 25.1, 25.5 and 30.2% in the ^{non}SNB, ^{ICG}SNB and ^{hybrid}SNB groups, respectively. Similarly, Clavien-Dindo ≥ IIIa rate was 11.8, 11.2 and 13.4% in the respective groups.

At multivariable models, the ^{ICG}SNB-group was not associated with higher rate of Clavien-Dindo ≥ II (OR 1.22, 95%CI 0.80-1.85, p=0.3; Table 4) or ≥ IIIa (OR 1.02, 95%CI 0.56-1.77, p=0.9; Table 4), while the ^{Hybrid}SNB had a tendency to higher risk of Clavien-Dindo ≥ II complications (OR 1.30, 95%CI 0.98-1.70, p=0.059; Table 4) but not of Clavien-Dindo ≥ IIIa (OR 1.16, 95%CI 0.79-1.67, p=0.4; Table 4). Of note, year of surgery was associated with a reduced risk of Clavien-Dindo ≥ II complications (OR: 0.927, 95%CI 0.889-0.967, p<0.001), as well as of Clavien-Dindo ≥ IIIa (OR 0.922, 95%CI 0.872-0.974, p=0.004), demonstrating reduction of complication rates over time (Table 4). Particularly, the interaction test for the hypothesis that refinements in SNB technique in more recent years reduced postoperative Clavien-Dindo ≥ II complications was statistically significant for the ^{Hybrid}SNB-group (OR 0.90, CI 0.81-0.99, p=0.041). Specifically, the risk of experiencing a Clavien-Dindo ≥ II complication decreased approximately 10% every year when compared to the risk of experiencing a Clavien-Dindo ≥ II complication rate with standard LND. On the other hand, no significant interaction with year of surgery was recorded for ^{ICG}SNB-group (Table 4).

Finally, no statistically significant interaction between the year of surgery and Clavien-Dindo ≥ IIIa complications could be determined, meaning that technical refinement for SNB over time did not affect severe complications (all p>0.05).

Oncologic outcomes

At 5 year of follow-up, unadjusted Kaplan-Meier plots depicted BCR-free survival rates of 54.9% for the ^{non}SNB-group, 38.4% for the ^{ICG}SNB-group and 57.7% for the ^{Hybrid}SNB-group (p=0.39; Supplementary Figure 1a). Similarly, 5-year CR-free survival rates were 67, 73 and 67.4% (p=0.9) for the respective groups (Supplementary Figure 1b). At multivariable Cox models, the ^{ICG}SNB-group was not an independent predictor of BCR (HR 0.84, 95%CI 0.61-1.15, p=0.2) and CR (HR 0.73, 95%CI 0.49-1.15, p=0.1) compared to ^{non}SNB-group. Conversely, ^{Hybrid}SNB-group was associated with lower risk of BCR (HR 0.79, 95%CI 0.63-0.98, p=0.037) and of CR (HR 0.76, 95%CI 0.58-0.98, p=0.035) compared to the ^{non}SNB-group (Table 5). As further confirmation on these results, when ^{Hybrid}SNB-group was considered as reference, no difference in BCR (HR 1.06, 95%CI 0.75-1.50, p=0.7) and CR (HR 0.97, 95%CI 0.63-1.49, p=0.9) was reported compared to the ^{ICG}SNB-groups, while the non-SNB was confirmed to have higher risk of BCR (HR 1.26, 95%CI 1.01-1.57, p=0.037) and CR (HR 1.32, 95%CI 1.02-1.71, p=0.035). Graphical representations of the multivariable adjusted Cox-derived BCR- and CR-free survival using Kaplan Meier plots were reported in Figure 3a-b.

Discussion

In this largest retrospective series of PCa patients treated with RARP and ePLND with or without SNB, we tested the impact of SNB on different outcomes, namely LNI staging accuracy, complications rates and mid-term oncological outcomes. These aims are based on recent literature suggesting a potential beneficial effect of SNB for detecting nodal metastases outside standard the ePLND template (*20*). Additionally, other evidences suggested that SNB addition is associated with potential decrease in BCR rate compared to standard ePLND (*5*). Our analyses highlighted several important findings.

First and foremost, with the findings in the ^{non}SNB-group we underlined that meticulous ePLND does not ensure complete accuracy with regard to nodal status. Adding SNB to standard ePLND improves LNI detection rate in univariable analysis. Specifically, ICG-^{99m}Tc-nanocolloid allows to detect 10% more LNI compared to ePLND without SNB. Similarly, ICG was associated with 18% absolute increase in LNI detection rate relative to standard ePLND (Table 1). Our results reinforce previous findings reported by a recent systematic review that assessed the diagnostic accuracy of SNB procedure in PCa (*4*). In this review the SN(s) were the only metastatic site(s) in 73% of LN-positive patients and in 1 out of 20 patients who underwent ePLND, positive LNs would have been missed without SNB (*4*). Our findings confirm that SNB should always be combined with ePLND, as supported by a recent SN consensus panel (*21*). Despite being in line with previous series based on tertiary care referral centers (*6*,*22*) or population-based (*23*) data repositories, it may be argued that the lower number of lymph nodal yield in the ^{non}SNB group (median 11 nodes) compared to ^{hybrid}SNB or ^{ICG}SNB group might have affected the reported differences in LNI. However, it is of note to underline that for the first time ever, we

demonstrated that at a multivariable model, which accounted for multiple confounders including number of nodes removed, the diagnostic added value remained operational exclusively for ^{hybrid}SNB groups (OR 1.65) but not for ^{ICG}SNB-group (OR 1.35). These findings suggest that ICG basically extends the ePLND template further without specific guidance on aberrant lymphatic drainage pathways. On the other hand, the hybrid tracer really highlights aberrant drainage profiles, impacting the ePLND template. Because these aberrant profiles are seen at preoperative imaging, this impacts the ePLND template which is performed during surgery. Additionally, when we graphically explored the variation of the actual LNI rate for hybrid tracer technique vs. ^{non}SNB across different preoperative LNI risk, we confirmed that the ^{hybrid}SNB approach was associated with higher pN1 detection rate across all the predicted preoperative LNI risk, corroborating the accuracy of SNB in detecting pN1 both in low- and high-risk patients. For instance, for a preoperative predicted risk of LNI of 20%, the intraoperative guidance of the hybrid tracer can reduce the risk of false negative findings of approximately 10%, meaning that 1 out 10 patients who underwent would have been missed without using SNB with the hybrid tracer.

Second, when we assessed the safety profile of the SNB procedure, we observed that neither ^{ICG}SNB nor ^{Hybrid}SNB was associated with increased risk of postoperative complications Clavien-Dindo ≥ II. Thus, SNB appears to be safe and can be implemented in routine clinical practice without exposing patients to higher risk of complications. It is also of note that the interaction term between year of surgery and SNB showed a significant reduction of Clavien-Dindo ≥ II complications over time for the hybrid tracer, which was also the first to be applied historically (^{non}SNB 2006-2019, ^{ICG}SNB 2016-2019, ^{Hybrid}SNB 2010-2019). This suggests that the time wherein the hybrid tracer was used helped to refine

the procedure and surgical skills for SNB. This learning curve seems to have benefited the ^{ICG}SNB-group which was the last to be initiated. Regarding high grade complications (Clavien-Dindo ≥ III), we failed to observe any effect of year of surgery on SNB, suggesting that severe complications are not related to the SNB procedure. Lastly, regarding operative time, the addition of SNB with hybrid tracer was associated with longer operative time compared to ePLND alone and SNB with free ICG, probably due to the time needed for introducing and guiding the laparoscopic gamma probe towards the target tissue. However, such differences were small (median time: + 6 min and + 10 min, respectively; Table 1) and, in consequence, had very limited clinical impact.

Third, when we explored the effect of SNB on oncologic outcomes, we provided evidence that the ^{Hybrid}SNB-group was associated with a significantly lower risk of BCR relative to ^{non}SNB group; there was a 20% lower risk of harbouring BCR. We failed to observe this benefit for the ^{ICG}SNB-group. Our findings corroborate previous evidence that adding SNB to ePLND improves BCR-free survival (*5*), while adding a sub-analysis according to type of SNB tracers used. This protective effect of the hybrid tracer on BCR may be explained by the identification of aberrant lymphatic drainage pathways which are not usually included in standard LND templates, thus optimizing nodal staging and improving patient management. Moreover, after adjusting for use of salvage radiation therapy, we confirmed the added value of the hybrid tracer when CR was assessed. Specifically, the implementation of the hybrid tracer was associated with a significant 24% reduction risk of experiencing CR. These findings are of note and, to the best of our knowledge, we are the first to demonstrate a potential benefit of the addition of SNB, using hybrid tracer, to ePLND on the risk of loco-regional or distant recurrence. However,

considering the relatively short follow-up and the limited number of events of our cohort, further studies are needed to confirm our results.

Recently, a new gamma-probe for image-guided robotic surgery was developed (i.e. DROP-IN probe) and implanted into clinical practice (*24–27*). Its increased manoeuvrability yielded higher in vivo SNs detection rate compared to laparoscopic rigid gamma probe (*25*), suggesting that the impact of ^{Hybrid}SNB might be further improved in future studies that rely on DROP-IN probe as radio guidance in the robotic setting. Interesting to note is also that the Firefly fluorescence guidance realized within the ^{Hybrid}SNB-group was achieved while injecting a 20-times lower amount of ICG than in the ^{ICG}SNB-group. Lastly, even though we did not perform a specific cost assessment of the SNB procedures in the current analysis, it is important to remark that the SNB is correlated with the use of additional technological resources (e.g., gamma probe, DROP-IN probes, SPECT/CT), as well as with extra scanning time (fees vary across the healthcare systems of different countries) and with longer operative time, which in turn increase the overall costs of the procedure. Therefore, this point should be taken into account when implementing SNB in a routine surgical practice. However, prices of gamma probes are expected to decrease in the near future due to its expanding use and novel (hybrid) camera systems (*28*).

Despite its strengths, our study is not devoid of limitations. First, our report is based on a retrospective analysis with all of its inherent limitations and bias of selecting patients for specific methods of ePLND cannot be excluded. Second, our data reflects a single tertiary care referral center with high-volume SN procedures and trained surgeons for radio-guided SN procedures. Based on the impact that imaging at nuclear medicine had on

the success of the ^{Hybrid}SNB-group the generalizability of our findings may be limited to centres with a nuclear medicine department. Third, the median follow-up was relatively short. Future randomized controlled trials are needed in order to confirm the findings reported here. Fourth, the fact that the ICG-SNB-group was considerably smaller than the hybrid-SNB group might have influenced our findings and need further validation in bigger sample size. Lastly, it is important to underline that the current study does not involve the use of hybrid tracers relying on PCa specific biomarkers such as ^{99m}Technetium-based prostate-specific membrane antigen (^{99m}Tc-PSMA). However, despite having lower specificity for prostatic tissue when compared to ^{99m}Tc-PSMA, the ICG-^{99m}Tc-nanocolloid tracer has important advantages which should be noted. Indeed, ICG-^{99m}Tc-nanocolloid tracer allows to intraoperatively delineate the lymphatic drainage profile of the prostate, which is not possible when using PSMA-based tracers which, conversely, allow to identify metastatic lesions, when present, but not to define lymphatic drainage profile. Moreover, the intraoperative use of PSMA-based tracers was mainly tested in the context of recurrent PCa in patients with positive lesion at preoperative PET/CT scan (*29*), therefore its utility and staging accuracy in the primary treatment of intermediate/high risk patients is still under evaluation.

Conclusions

SNB realized using the hybrid tracer ICG-^{99m}Tc-nanocolloid improves LNI detection rate in prostate cancer patients, reducing the risk of false negative findings at final pathology. This can be realized without compromising patient safety in terms of postoperative complications. Moreover, we find that this method may have a potential benefit in terms of biochemical and clinical recurrence.

Author contributions

Elio Mazzone 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.

Financial disclosures

Elio Mazzone 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: partial support by an NWO-TTW-VICI grant (TTW 16141).

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Compliance with ethical standards

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Conflict of interest

None to declare.

KEY POINTS

Question: Is the implementation of sentinel node biopsy for prostate cancer able to improve nodal staging and, consequently, oncological outcomes in patients receiving radical prostatectomy and lymph node dissection?

Pertinent findings: In our study, the use of ICG-99mTc-nanocolloid tracer was an independent predictor of nodal involvement and lower biochemical and clinical recurrence rates, while using free ICG did not reach the independent predictor status when compared to non-sentinel node group.

Conclusions: The implementation of hybrid sentinel node biopsy technique in prostate cancer improves detection of positive nodes with subsequent optimization of patient management, without harming patient safety.

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Figures

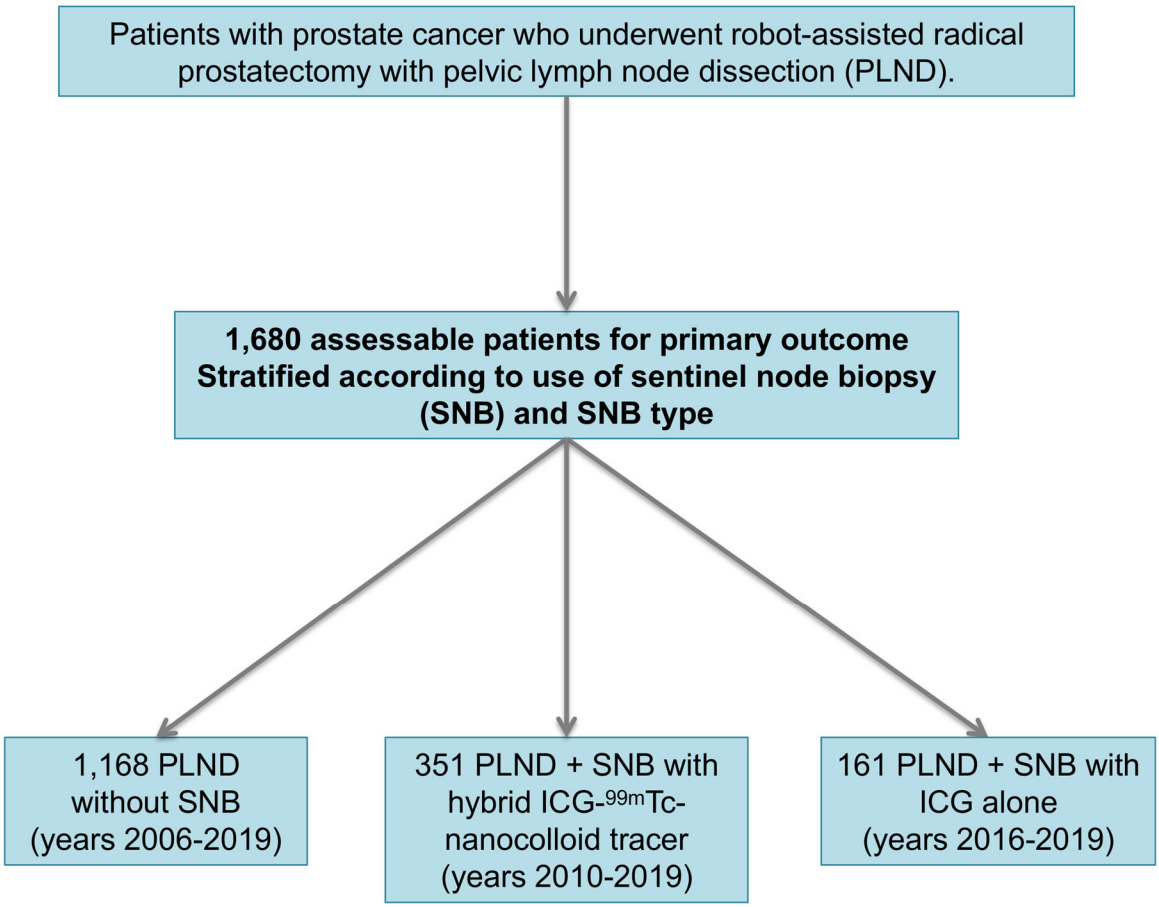


Figure 1 – Flow-chart describing the final patient population included in the study and the implementation of different tracers for sentinel node biopsy over time.

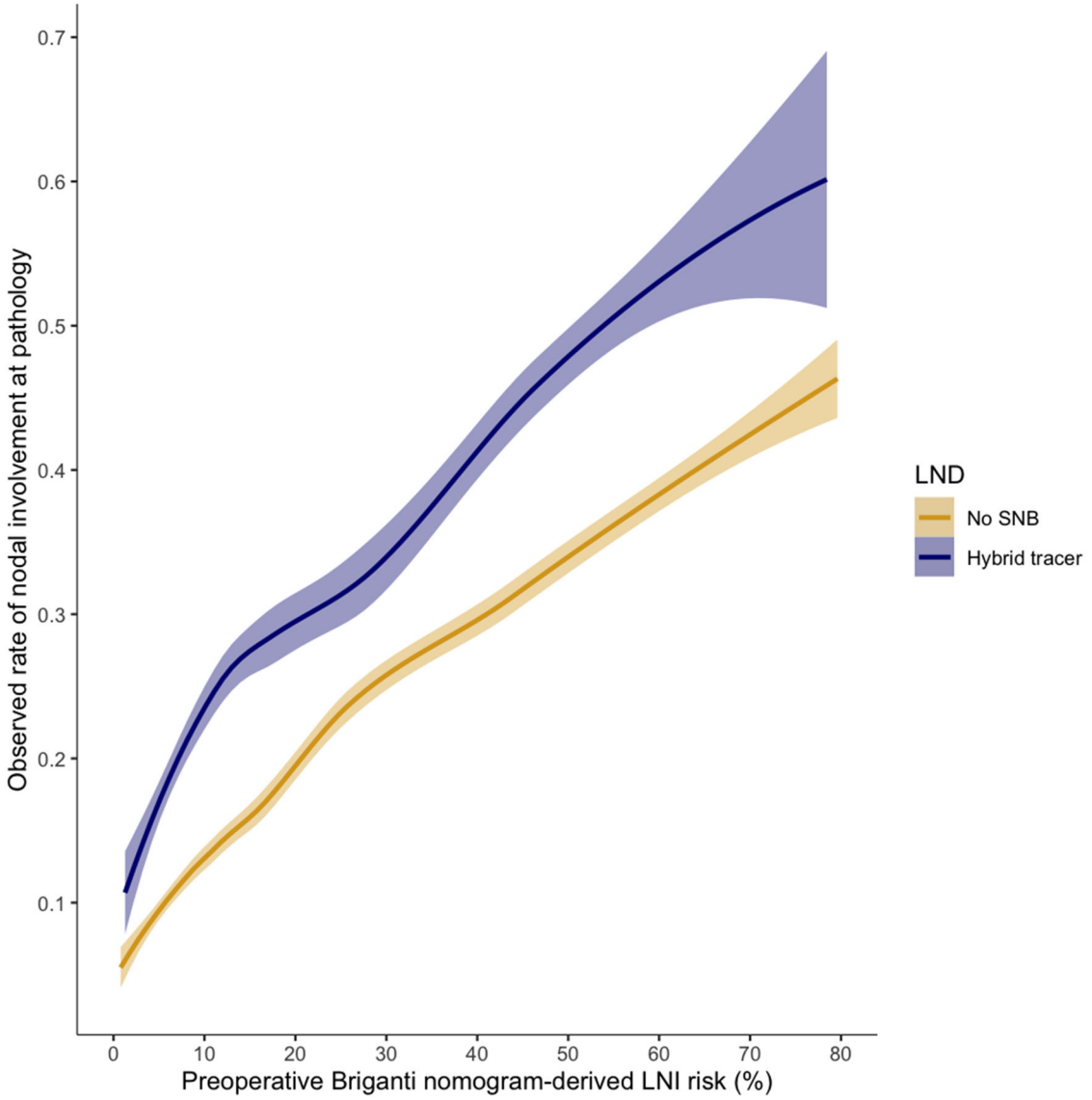


Figure 2 – LOWESS plot representing the observed lymph node invasion rate at final pathology plotted against the preoperative predicted risk of nodal involvement calculated according to the Briganti 2012 nomogram, stratified according to use of ^{hybrid}SNB or no SNB.

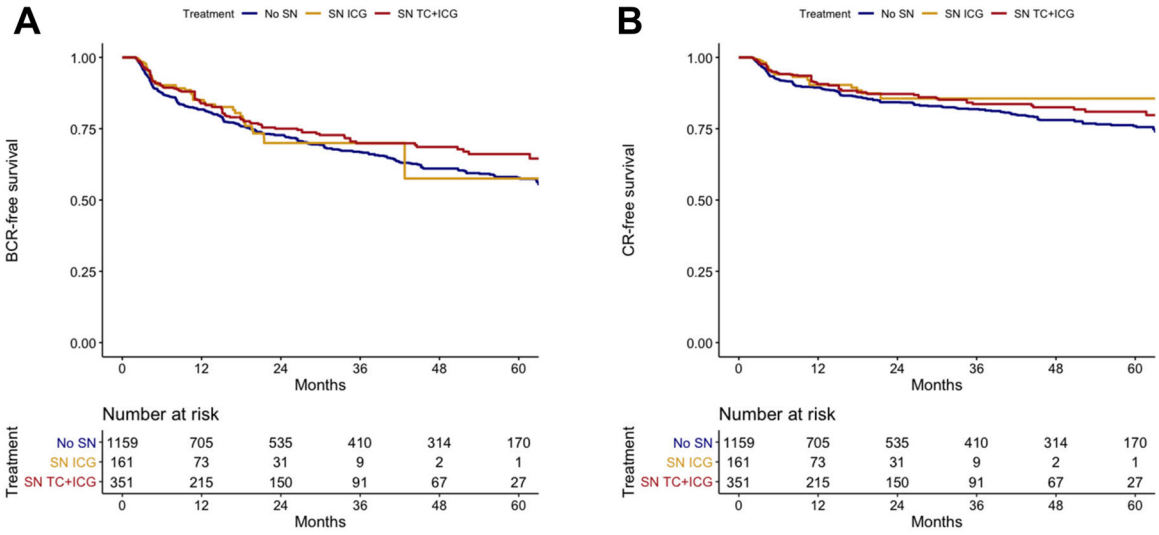


Figure 3 – Kaplan-Meier plots depicting multivariable Cox-derived biochemical recurrence-free (A) and clinical recurrence-free (B) survival time after RARP and ePLND with or without use of additional sentinel node biopsy (either hybrid tracer or free-ICG)

Graphical Abstract

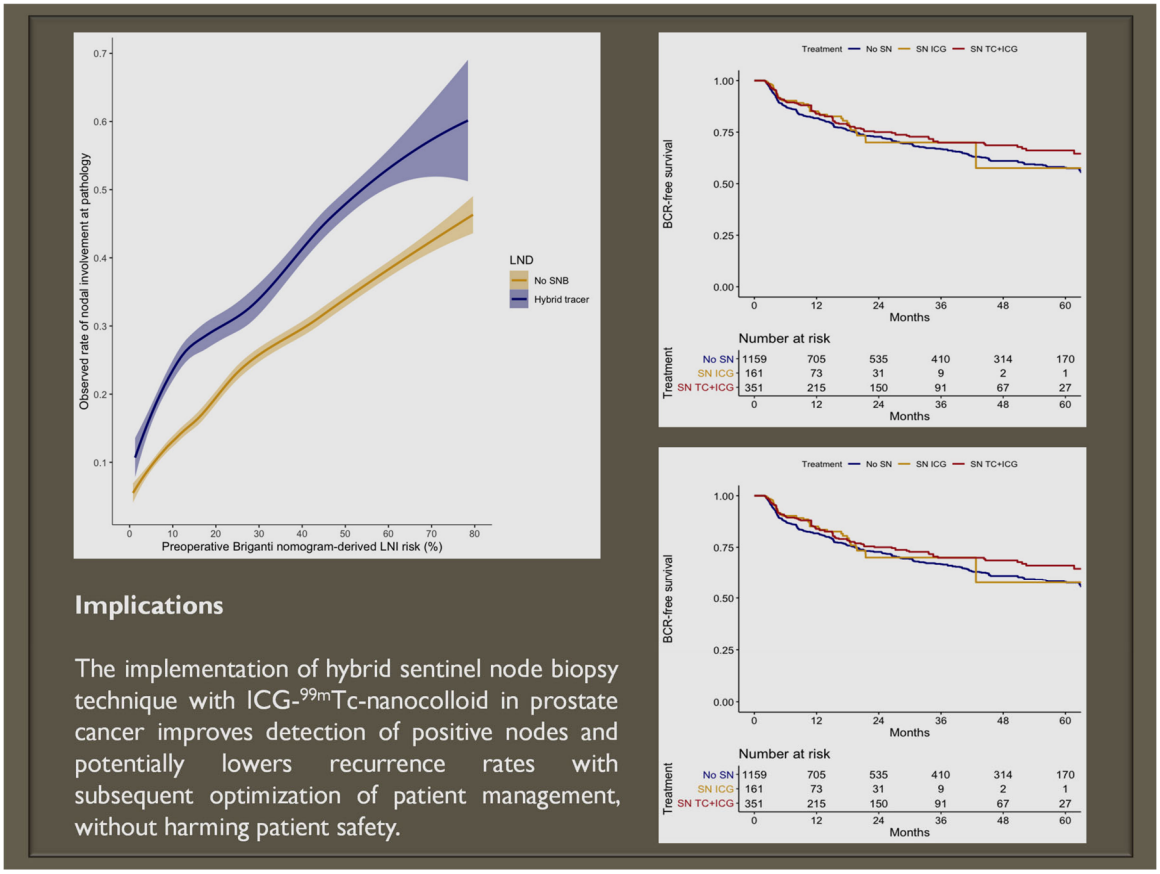


Table 1. Clinical and pathological characteristics of 1,680 patients with prostate cancer treated with robot-assisted radical prostatectomy and pelvic lymph node dissection with (^{ICG}SNB-group or ^{Hybrid}SNB-group) or without sentinel node biopsy (^{non}SNB-group) at a single high-volume institution

		Overall	**^{non}SNB-group n=1168 (69.5)**	**^{ICG}SNB-group n=161 (9.6)**	**p-value (^{non}SNB-group vs ^{ICG}SNB-group)**	**^{Hybrid}SNB-group n=351 (20.9)**	**p-value (^{non}SNB-group vs ^{Hybrid}SNB-group)**	**p-value (^{ICG}SNB-group vs ^{Hybrid}SNB-group**
PSA before treatment, ng/ml	Median	9.5	9.7	9.4	0.6	9	0.002	0.1
	IQR	6.8-16	6.9-16	6.7-18		6.4-14		
Age, years	Median	65	65	67	<0.001	65	0.1	<0.001
	IQR	60-69	60-68	64-71		60.5-69		
Briganti LNI risk, %	Median	12.6	11.9	20.5	<0.001	12.4	0.4	<0.001
	IQR	6.1-30.5	5.6-29.1	10.9-41.7		6.2-29.2		
Biopsy Gleason score, n (%)	6	212 (12.6)	187 (16)	7 (4.3)	<0.001	18 (5.1)	<0.001	0.03
	7	954 (56.8)	638 (54.6)	87 (54)		229 (65.2)		
	8-10	514 (30.6)	343 (29.4)	67 (41.6)		104 (29.6)		
cT, n (%)	cT1c	250 (14.9)	180 (15.4)	18 (11.2)	0.3	52 (14.8)	0.8	0.5
	cT2	941 (56)	655 (56.1)	94 (58.4)		192 (54.7)		
	≥cT3	489 (29.1)	333 (28.5)	49 (30.4)		107 (30.5)		
Percentage of positive cores, n (%)	< 33%	454 (27)	319 (27.3)	23 (14.3)	<0.001	112 (31.9)	0.2	<0.001
	33-66%	711 (42.3)	504 (43.2)	67 (41.6)		140 (39.9)		
	> 66%	515 (30.7)	345 (29.5)	71 (44.1)		99 (28.2)		
cN, n (%)	cNx	387 (23)	323 (27.7)	3 (1.9)	<0.001	61 (17.4)	<0.001	<0.001
	cN0	1198 (71.3)	778 (66.6)	133 (82.6)		287 (81.8)		
	cN1	95 (5.7)	67 (5.7)	25 (15.5)		3 (0.9)		
Follow-up, months	Median	38	46.5	15	<0.001	35	<0.001	<0.001
	IQR	14-66	17-70	7-25		14-58		
Operative time, min	Median	119	115	111	0.01	121	<0.001	<0.001
	IQR	100-126	99-128	97-121		113.5-131		
Number LN removed, n	Median	12	11	20	<0.001	17	<0.001	<0.001
	IQR	8-18	6-15	17-25		11-21		
pN stage, n (%)	pN0	1302 (77.5)	947 (81.1)	103 (64)	<0.001	252 (71.8)	<0.001	<0.001
	pN1	378 (22.5)	221 (18.9)	58 (36)		99 (28.2)		
Pathological GS, n (%)	6	158 (9.4)	129 (11)	3 (1.9)	<0.001	26 (7.4)	0.1	<0.001

	7	1116 (66.4)	754 (64.6)	131 (81.4)		231 (65.8)		
	8-10	406 (24.2)	285 (24.4)	27 (16.8)		94 (26.8)		
pT stage, n (%)	≤pT2c	851 (50.7)	593 (50.8)	55 (34.2)	<0.001	203 (57.8)	0.005	<0.001
	pT3a	411 (24.5)	260 (22.3)	68 (42.2)		83 (23.6)		
	≥pT3b	418 (24.9)	315 (27)	38 (23.6)		65 (18.5)		
Number of positive nodes, n (%)	>2	121 (7.2)	68 (5.8)	19 (11.8)	<0.001	34 (9.7)	<0.001	0.1
	0	1302 (77.5)	948 (81.2)	102 (63.4)		252 (71.8)		
	1-2	257 (15.3)	152 (13)	40 (24.8)		65 (18.5)		
Surgical margins, n (%)	neg	1054 (62.7)	712 (61)	102 (63.4)	0.6	240 (68.4)	0.01	0.3
	pos	626 (37.3)	456 (39)	59 (36.6)		111 (31.6)		
Salvage Radiotherapy	No	1232 (73.3)	843 (72.2)	133 (82.6)	0.006	256 (72.9)	0.8	0.02
	Yes	448 (26.7)	325 (27.8)	28 (17.4)		95 (27.1)		

LNI = lymph node invasion; SNB = sentinel node biopsy; GS = Gleason score; LN = lymph nodes; ICG = indocyanine green

Table 2. Multivariable logistic regression model predicting detection of positive nodes at final pathology

Variable		OR	95% CI		p-value
cT stage					
	cT1c	Ref			
	cT2	1.14	0.74	1.79	0.4
	≥cT3	3.25	2.11	5.14	<0.001
Biopsy GS					
	6	Ref			
	7	1.99	1.20	3.46	0.009
	8-10	3.00	1.79	5.27	<0.001
cN stage					
	cNx	Ref			
	cN0	0.85	0.58	1.23	0.4
	cN1	3.02	1.84	4.98	<0.001
Percentage of positive cores		1.633	1.371	1.94	<0.001
PSA at RP		1.010	1.002	1.018	0.01
Number of removed nodes		1.032	1.015	1.049	<0.001
SNB use					
	^{non}SNB-group	Ref			
	^{ICG}SNB-group	1.35	0.89	2.03	0.1
	^{Hybrid}SNB-group	1.61	1.18	2.20	0.002

GS = Gleason score; SNB = sentinel node biopsy; RP = radical prostatectomy; OR = odds ratio; CI = confidence interval; ICG = indocyanine green

Table 3. Complication rate and grading of 1,680 patients with prostate cancer treated with robot-assisted radical prostatectomy and pelvic lymph node dissection with (^{ICG}SNB-group or ^{Hybrid}SNB-group) or without sentinel node biopsy (^{non}SNB-group) at a single high-volume institution.

Variable		Overall	^{non}SNB-group n=1168 (69.5)	^{ICG}SNB-group n=161 (9.6)	^{Hybrid}SNB-group n=351 (20.9)
Any postoperative complication, n (%)	No	1108 (66)	777 (66.5)	115 (71.4)	216 (61.5)
	Yes	572 (34)	391 (33.5)	46 (28.6)	135 (38.5)
Clavien-Dindo grade*, n (%)	I	78 (4.6)	58 (5)	4 (2.5)	16 (4.6)
	II	237 (14.1)	155 (13.3)	23 (14.3)	59 (16.8)
	III a	128 (7.6)	80 (6.8)	16 (9.9)	32 (9.1)
	III b	72 (4.3)	56 (4.8)	2 (1.2)	14 (4)
	IV	3 (0.2)	2 (0.2)	0 (0)	1 (0.3)
	Unknown	54 (3.2)	40 (3.4)	1 (0.6)	13 (3.7)

SNB = sentinel node biopsy, ICG = indocyanine green

* Patients may have experienced more than one complication

Table 4. Multivariable logistic regression models predicting CD ≥ 2 and ≥ 3 before and after testing for interaction between type of SNB and year of surgery.

		CD ≥ 2				CD ≥ 3			
		OR	**2.5 %**	**97.5 %**	**P value**	**OR**	**2.5 %**	**97.5 %**	**P value**
Age		1.008	0.990	1.027	0.3	1.025	1.000	1.052	0.046
Year of surgery		0.927	0.889	0.967	<0.001	0.922	0.872	0.974	0.004
SNB type	**No SNB**								
	ICG only	1.22	0.80	1.85	0.3	1.02	0.56	1.77	0.9
	ICG+99mTc	1.30	0.98	1.70	0.059	1.16	0.79	1.67	0.4
cT stage	**cT1c**								
	cT2	0.87	0.64	1.20	0.4	1.01	0.66	1.56	0.9
	>=cT3	0.71	0.50	1.02	0.06	0.63	0.39	1.05	0.07
Biopsy GS	**≤ 6**								
	7	1.39	0.96	2.06	0.08	1.95	1.14	3.50	0.01
	8-10	1.62	1.09	2.44	0.01	1.66	0.94	3.07	0.08
cN stage	**cN0**								
	cNx	0.65	0.47	0.89	0.009	0.50	0.32	0.78	0.002
	cN1	0.90	0.52	1.49	0.7	1.35	0.68	2.46	0.3
PSA at surgery		0.989	0.978	0.998	0.038	0.998	0.986	1.008	0.8
Neo ADT	**No**								
	Yes	1.14	0.79	1.62	0.4	1.34	0.84	2.09	0.1
Interaction between SNB and year	**No SNB and year**	Ref							
	SNB and ICG	1.41	0.97	2.12	0.08	1.21	0.75	2.11	0.4
	SNB and ICG+99mTc	0.90	0.81	0.99	0.041	1.06	0.93	1.21	0.3

CD = Clavien-Dindo; GS = Gleason score; SNB = sentinel node biopsy; ICG = indocyanine green; ADT = androgen deprivation therapy

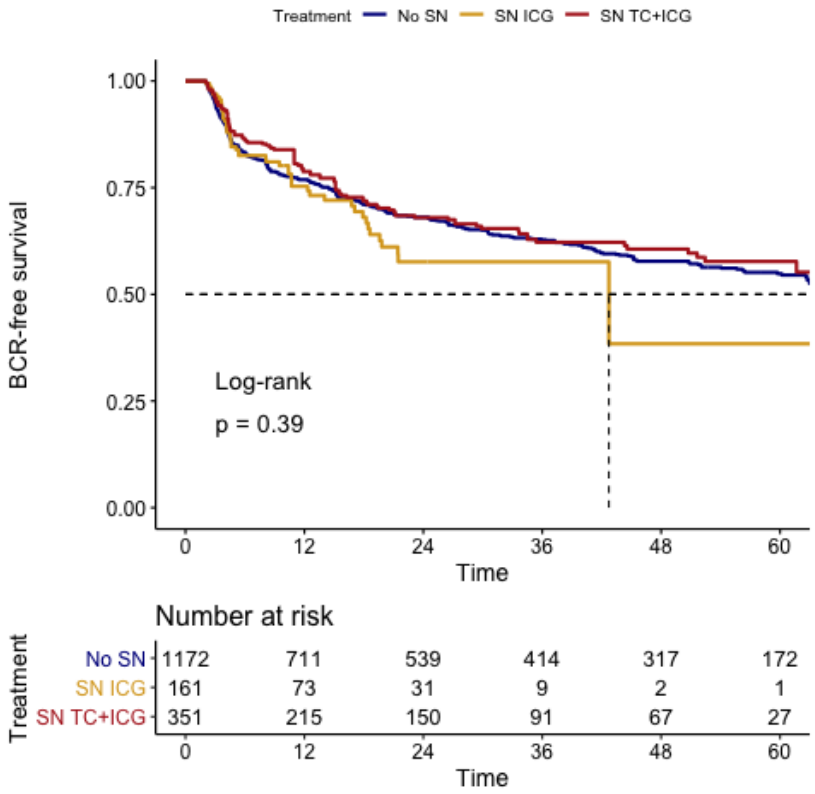
Table 5. Multivariable Cox regression models predicting biochemical and clinical recurrence in patients undergoing extended pelvic lymph node dissection with or without sentinel node biopsy.

Variable		Biochemical recurrence				Clinical recurrence			
		HR	95% CI		p value	HR	95% CI		p value
SNB technique	^{non}SNB-group	Ref							
	^{ICG}SNB-group	0.84	0.61	1.15	0.2	0.73	0.49	1.11	0.1
	^{Hybrid}SNB-group	0.79	0.63	0.98	0.037	0.76	0.58	0.98	0.035
pN stage	pN0								
	pN1	3.11	2.59	3.72	<0.001	3.40	2.74	4.23	<0.001
PSA at surgery		1.009	1.006	1.01	<0.001	1.010	1.006	1.014	<0.001
Pathological GS	6								
	7	1.91	1.17	3.10	0.009	3.77	1.53	9.26	0.003
	8-10	3.50	2.13	5.74	<0.001	8.84	3.59	21.7	<0.001
pT stage	≤ pT2c								
	pT3a	1.63	1.30	2.06	<0.001	1.99	1.50	2.64	<0.001
	≥ pT3b	2.17	1.74	2.71	<0.001	2.17	1.66	2.85	<0.001
PSM	No								
	Yes	1.23	1.04	1.46	0.01	0.93	0.76	1.14	0.5
Number of removed nodes		1.005	0.994	1.018	0.3	1.00	0.985	1.015	0.9
Salvage Radiation Therapy	No	--				Ref			
	Yes	--				1.29	0.92	1.58	0.1

SNB = Sentinel node biopsy; PSM = positive surgical margins; HR = hazard ratio; CI = confidence interval; ICG = indocyanine green

Supplementary Figure 1 – Kaplan-Meier plots depicting unadjusted biochemical recurrence-free (A) and clinical recurrence-free (B) survival time after RARP and ePLND with or without use of additional sentinel node biopsy (either hybrid tracer or free-ICG)

A.



B.