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TOPIC PAPER

Outcomes after salvage radical prostatectomy and first-line radiation therapy or HIFU for recurrent localized prostate cancer: results from a multicenter study

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Abstract

Introduction Despite no consensus on the optimal management of recurrent prostate cancer after primary radiation or HIFU therapy, salvage prostatectomy (sRP) is reserved for only 3% of patients because of technical challenges and frequent post-operative complications. We assessed outcomes after sRP in a series of patients with localized PCa and that had received radiation therapy or HIFU as a first-line treatment.

Materials and methods Data from nine French referral centers on patients treated with sRP between 2005 and 2017 were collected. Pre- and post-operative data, including oncological and functional outcomes after first treatment and sRP, were analyzed to determine the predictors for biochemical recurrence (BCR) and cancer-specific survival (CSS) after sRP.

Results First-line treatments were external beam-radiation therapy (EBRT) for 30 (55%), brachytherapy (BT) for 10 (18%), and high-intensity focused ultrasound (HIFU) for 15 (27%). Median (IQR) PSA at diagnosis was 6.4 (4.9–9.5) ng/mL, median PSA at nadir was 1.9 (0.7–3.0) ng/mL, and median (IQR) to first BCR was 13 (6–20) months. Of the 55 patients, 44 (80%) received robot-assisted salvage radical prostatectomy and 11 (20%) received salvage retropubic radical prostatectomy. Restoration of continence was achieved in 90% of preoperatively continent patients; 24% that had received nerve-sparing (NS) procedures were potent after surgery. Prolonged catheterization due to anastomotic leakage was the most common complication. Age, preoperative clinical stage, NS procedure, and a pathological Gleason score were predictors for BCR.

Conclusions sRP was safe, feasible, and effective using either an open or robot-assisted approach, in experienced hands. Age, preoperative clinical stage, NS procedure, and pathological GS were linked with BCR after sRP.

Keywords Prostate neoplasm · Salvage · Recurrence: radiation therapy · Radical prostatectomy · Survival

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Introduction

Prostate cancer (PCa) is the most frequent neoplasm in the French male population with an estimated incidence of about 50,000 new cases reported each year [1]. In the USA, prostate cancer caused 164,690 new cases and 29,430 deaths in 2017. After lung cancer, it is the second most common cause of death from cancer in France and the USA [2]. In most cases, due to screening programs developed over the last two decades, PCa is diagnosed when it is still organ-confined, making it possible to treat with a curative intent. Besides radical prostatectomy (RP), which is still the most performed treatment, the Cancer of the Prostate Strategic Urologic Research Endeavour (CaPSURE) database suggests that 24.0% of men undergo external beam radiotherapy (EBRT) or brachytherapy (BT) as a primary treatment for prostate cancer [3], whereas a limited number should undergo high-intensity focused ultrasound (HIFU) [4]. After primary non-surgical treatment, with or without short-term hormonal manipulation, the RTOG-ASTRO Phoenix Consensus Conference defines PSA failure (with an accuracy of > 80% for clinical failure) as a PSA increase of ≥ 2 ng/mL higher than the PSA nadir value, regardless of the nadir serum concentration [5]. Although effective, these treatments have a 10-year recurrence rate of up to 50%.

Despite being an effective treatment, salvage radical prostatectomy (sRP) is performed in less than 3% of patients that have a biochemical recurrence (BCR) of PCa [4]. This may be because of a suspected increase in postoperative complications from a radiation-induced risk of fibrosis and poor wound healing [4].

Increasing numbers of studies now use a robotic approach in this setting [6–9]. In contrast, open sRP has been largely underutilized because of the risk of iatrogenic morbidity. In a recent open sRP series, a 15% rate of rectal injury, urinary extravasations in 5.0%, bladder-neck contracture in 10.0%, and persistent post-prostatectomy incontinence were reported in 20.0% [10–12]. Despite the widespread use of robotic surgery to perform radical prostatectomy [13], at present, only a small number of sRP series have been published.

The aim of our study was to assess the oncological and functional outcomes after sRP in men with localized PCa that recurred after first-line radiation therapy or HIFU.

Materials and methods

Data from patients undergoing sRP during a 12-year period (2005–2017) from eight referral centers across France and one referral center in Belgium were retrieved. All centers had a minimum caseload of 150 cases of RP per year and sRP was performed only by an experienced surgeon beyond their learning curve. All patients received radiation therapy or HIFU as the first-line treatment for PCa, and had suffered from BCR, as defined by the Phoenix criteria (PSA nadir + 2 ng/mL) [14].

BCR was biopsy-proven in all cases. Clinico-pathological data were prospectively collected. All patients gave their written informed consent to be included in the databank of the institution where they were treated. Collected data included age at time of the prostatectomy, ASA score, comorbidities, PSA, Gleason score (GS), initial treatment, hormone therapy, period between initial treatment and the prostatectomy, operative data, surgical margins, TNM, follow-up, postoperative complications as per the Clavien classification (within 90 days of surgery) [15], biochemical recurrence, urinary incontinence, and erectile dysfunction.

Post-surgery (sRP) BCR was defined as PSA > 0.2 ng/mL in two consecutive samplings. Post-operative continence was defined as the use of no pads per day; potency was defined as the ability to achieve and maintain erections firm enough for sexual intercourse, with or without the use of PDE5-I.

Surgical technique

All centers performed robot-assisted salvage radical prostatectomy (sRARP) except for one center, where ten patients were treated with salvage retropubic radical prostatectomy (sRRP). sRARP was performed according to a previously published technique [8], whereas sRRP was performed using the standard technique [16]. Lymph-node dissection (LND) was performed according to the surgeon's choice. Preservation of the neurovascular bundles was offered to patients that were preoperatively potent whenever it was oncologically feasible.

The surgeons were asked to report on a scale from 0 to 2, the difficulty of the intervention compared to a standard RP.

Statistical analyses

We performed descriptive statistics on the clinical and pathological characteristics of our population. Specifically, categorical and continuous variables were presented as frequencies with proportions, and medians with interquartile ranges, respectively. Kaplan–Meier curves were computed for biochemical recurrence-free and cancer-specific survival rates. Univariate Cox's regression analyses were used to calculate hazard ratios associated with biochemical recurrence-free and cancer-specific survival rates for each preoperative and postoperative covariate.

Due to the low number of cases of biochemical recurrences ($n = 17$) and cancer-related deaths ($n = 9$), we could not perform multivariate Cox's regression models. All

statistical analyses were performed using Stata v.0.14.0 (StataCorp, College Station, TX, USA). Two-sided statistical significance was defined as $p < 0.05$.

Results

Study population

A total of 55 patients were included in the study; median (IQR) age at time of prostatectomy was 64 (range 61–67) years. Fourteen patients were smokers (25%), five were receiving anticoagulant treatment (9%), and 11 were receiving a long-term platelet-aggregation inhibitor (20%).

First-line treatment was EBRT in 30 (55%), BT in 10 (18%), and HIFU in 15 (27%) cases. Median (IQR) PSA at diagnosis was 6.4 (4.9–0.5) ng/mL, median PSA at nadir was 1.9 (0.7–3.0) ng/mL, and median (IQR) to first BCR was 13 (6–20) months. The median (IQR) number of prostate biopsies performed after first recurrence was 12 (range 12–13) and the median number of positive biopsies was 3 (range 2–4). At post-recurrence biopsy, GS was impossible to clearly determinate in 12 patients (22%), whereas 11 (20%) had a GS of 6, 24 (44%) a GS of 7, and 8 (14%) a GS of ≥ 8. At the time of the initial diagnosis, PCa clinical stage was T1c in 36% ($n = 20$), T2 in 45.5% ($n = 25$) and T3 in 4% ($n = 2$).

Recurrence was visible in MRIs in 18 (32%) cases and extracapsular extension (ECE) of the disease was found in only two patients. Eight (14%) patients received androgen-deprivation therapy after the first-line treatment.

Oncological outcomes

Final pathological analysis showed PCa stage T2 in 22 (40%) patients, T3 in 29 (52.7%), and T4 in 2 cases (3.6%).

Among the 55 patients included in the study, 17 (31%) showed BCR and 6 (11%) patients died of PCa during the follow-up.

The 2- and 5-year BCR-FS rates were 87% and 55%, respectively; the 2- and 5-year CSS rates were 93% and 80%, respectively. The curves in Figs. 1 and 2 describe BCR-free survival and CSS within the cohort.

Functional outcomes

After the initial treatment, nine (16%) patients developed urinary complications and four (7%) developed rectal complications. Among the patients with urinary complications, four showed complicated prostatitis with acute urinary retention, four showed irritation of the bladder associated with pollakiuria, and one showed post-radiation pre-sphincter stricture. Among the patients with rectal complications, four showed rectal syndromes associated with diarrhea and rectal bleeding.

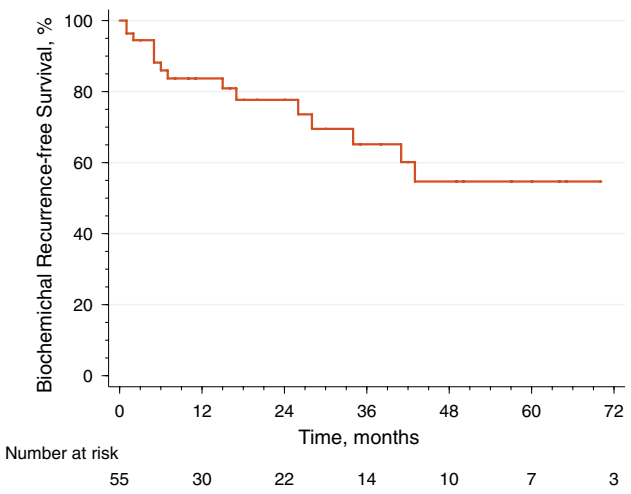

Fig. 1 Biochemical recurrence-free survival

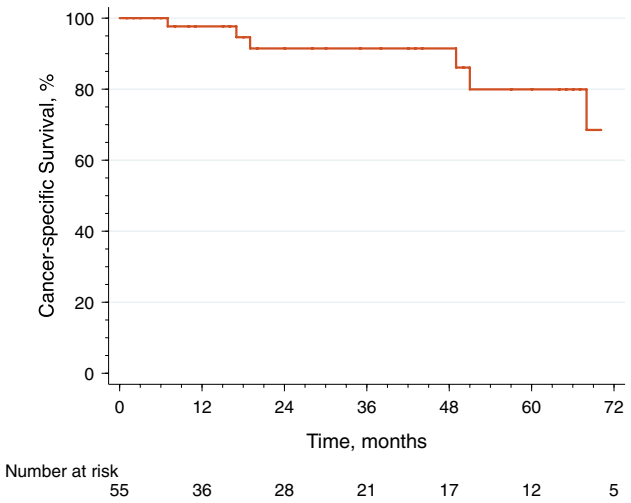

Fig. 2 Cancer-specific survival

In addition, eight (14%) patients received complementary (salvage) hormone therapy (Table 1).

Intraoperative outcomes and intra- and post-operative complications

Forty-four patients (80%) had sRARP and 11 patients (20%) had sRRP. The median surgical difficulty was rated as 1 on a scale of 0–2 (0 = common difficulties, 1 = more difficult, 2 = very difficult).

The median operating time was 150 min (IQR 131–187) with a median blood loss of 300 (150–500) mL. The median (IQR) length of hospitalization was 4 (range 4–6) days. The median (IQR) time of urinary catheterization was 7

Table 1 Cohort preoperative characteristics

	Overall ($n=55$)
Age, years, median (IQR)	64 (61–67)
ASA score, *n*, median (IQR)	2 (1–2)
Tobacco smokers	14 (25.5)
Initial PSA, ng/mL, median (IQR)	6.4 (4.9–9.5)
Nadir PSA, ng/mL, median (IQR)	1.9 (0.7–3.0)
Preoperative PSA, ng/mL, median (IQR)	4.96 (2.41–8.80)
Clinical T stage, *n* (%)	
1c	20 (36)
2	25 (45.5)
3	2 (4)
NA	8 (14.5)
Preoperative Gleason score, *n* (%)	
≤6	32 (58.2)
7	19 (34.5)
≥8	3 (5.5)
NA	1 (1.8)
First-line treatment, *n* (%)	
Radiotherapy	30 (54,5)
Brachytherapy	10 (18.2)
HIFU	15 (27.3)
Positive Scores at post-recurrence biopsy, *n*, median (IQR)	3 (2–4)
Time to first BCR, months, median (IQR)	13 (6–20)
Gleason Score at 1st recurrence, *n* (%)	
≤6	11 (20)
7	24 (44)
≥8	8 (14)
NA	12 (22)
Preoperative ADT, *n* (%)	8 (14.5)
Preoperative continent, *n* (%)	30 (54.5)
Preoperative potent, n (%)	25 (45.5)
Preoperative urinary tract complications[a], *n* (%)	9 (16)
Preoperative rectal complications[b], *n* (%)	4 (7)
PCa recurrence at MRI, *n* (%)	18 (32.7)

IQR interquartile range, *PSA* prostate-specific antigen, *HIFU* high-intensity focused ultrasound, *ADT* androgen deprivation therapy, *MRI* magnetic resonance, *PCa* prostate cancer

[a]Patients reporting urinary-tract injury/complications after primary PCa treatment

[b]Patients reporting rectal injury or sequelae after primary PCa treatment

(7–10) days. The median follow-up was 24 months (range 7–51).

Most patients ($n=45$) developed Clavien I–II complications in the early post-operative days, whereas only two had Clavien III (both caused by post-operative urethral stricture). Only one patient had a rectal injury intra-operatively, but this did not result in further post-operative complications. sRP was complicated by post-operative urethral stricture in only four cases (7.3%).

Even though a lymph-node dissection was performed in 49.09% of cases ($n=27/55$), no lymphocele was reported. To be noted, one patient had a cysto-prostatectomy because of an associated infiltrating bladder tumor and another had an abdominoperineal amputation because of an associated tumor of the rectum.

Further post-operative outcomes are reported in Table 2.

Univariate analysis

Univariate analyses showed that age at prostatectomy ($p=0.01$) and cT stage before first treatment ($p=0.03$) (among the preoperative variables) and a nerve-sparing approach ($p=0.02$) and a pathological GS ($p<0.001$) (among the post-operative variables) had a negative impact

Table 2 Perioperative results

	Overall ($n=55$)
Surgical approach	
Robot-assisted (sRARP)	44 (80)
Open (sRRP)	11 (20)
Operative time, min, median (IQR)	150 (131–187)
Hospitalization, days, median (IQR)	4 (4–6)
EBL, ml, median (IQR)	300 (150–500)
Catheterization, days, median (IQR)	7 (7–10)
Attempted PLND, *n* (%)	27 (49.1)
Attempted nerve-sparing, *n* (%)	25 (45.5)
Pathological T stage, *n* (%)	
2	22 (40.0)
3	29 (52.7)
4	2 (3.6)
N/A	2 (3.6)
Pathological N+, *n* (%)	6 (10.9)
Pathological Gleason Score, *n* (%)	
≤6	6 (10.9)
7	26 (47.3)
≥8	15 (27.3)
N/A	8 (14.5)
Complications[a], *n* (%)	
I	44 (80)
II	1 (1.8)
III	2 (2.3)
PSM, *n* (%)	4 (7.3)
BCR, *n* (%)	17 (30.9)
Anastomotic stricture, *n* (%)	4 (7.3)
Post-op continence[b], *n* (%)	27 (49.1)
Post-op potency[c], *n* (%)	6 (10.9)
Intraoperative rectal injury, *n* (%)	1 (1.8)
Needing transfusion, *n* (%)	4 (7.3)
PCa-related deaths	9 (16.4)
Time to BCR, months median (IQR)	15 (5–38)
Follow-up, months median (IQR)	24 (7–51)

EBL estimated blood loss, *PLND* pelvic lymph node dissection, *BCR* biochemical recurrence

[a]According to Clavien–Dindo classification

[b]Use of 0 pads per day at 12-month follow-up visit

on BCR-FS after sRP. Concerning CSS, age at prostatectomy ($p=0.02$) was the only pre-operative factor, and a pathological GS ($p<0.001$) was the only post-operative factor that affected survival (Tables 3 and 4).

Post-operative urinary continence (at 12-month follow-up) was achieved by 27 patients (49% of the entire cohort and 90% of those that were preoperatively continent [$n=30$]); erectile function (with or without PDE5-I) was restored in 8/25 (32%) preoperatively potent patients that received a nerve-sparing radical prostatectomy.

Discussion

Since its first description in 1985 [16], sRP has been always reserved for a minority of BCR patients because of concerns about possible complications.

Accordingly, no more than 3% of PCa patients recurring from a previous ablative technique receive sRP, as acceptable results in terms of efficacy and safety were frequently difficult to achieve [7]. With the introduction of robotics, and thus improved vision and dexterity, an increased number of patients have been treated with sRP (although only in referral centers); this has resulted in slightly better results than for sRRP [9, 17–21]. Few studies on follow-ups after sRP have been published so far: indeed, our study is the first (to our knowledge) multicenter study to report the results from some of the most experienced centers in France and Belgium. In view of the limited population (i.e., $n=55$) and the number of centers involved, we may consider that sRP is not a popular option in France or Belgium amongst urologists.

In our cohort, most patients that had surgery were diagnosed with localized PCa; as in the previous studies, most patients had no or limited comorbidities, i.e., cT1-T2 N0 cancer and a GS of ≤7 at first diagnosis. Nonetheless, at final pathological analysis, 53% of these patients had locally advanced disease (at least pT3). Such a proportion of locally advanced cancers may explain our oncological results, which are slightly inferior to those of other recent studies, where 71% of patients had localized cancers [9, 16–21].

Functional outcomes in our series were among the best reported in the literature [17–21], as continence at 12 months was achieved by 27/30 (90%) of preoperatively continent patients, although this included younger patients and those with a limited disease. Although NS surgery was performed in 25 patients, only 6 (24%) could have an erection at 12-month follow-up.

Our multicenter setting makes post-operative care more difficult to assess between the centers, e.g., postoperative catheterization depended of different protocols at each center and not of a real need for a catheter for anastomotic leakage. However, it can be noted that no prostatectomy postoperative protocols were adapted for sRP in any of the involved centers.

In our series, the time until a first recurrence was slightly shorter than that reported in other published series. This shorter recurrence time, although it did not affect oncological outcomes, may have led to better surgical outcomes. Indeed, complications from irradiation are usually later complications [17–21]. The fact that salvage surgery was achieved quite soon after irradiation may be a criterion to avoid complications.

Table 3 Univariate analysis of preoperative characteristics as possible predictors for biochemical recurrence (BCR) and cancer-specific survival (CSS)

Variable	Univariate analysis for BCR		Univariate analysis for CSS	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age at sRP, years	1.13 (1.02–1.25)	**0.01**	1.23 (1.03–1.45)	**0.02**
ASA score	1.10 (0.79–1.53)	0.59	0.85 (0.48–1.51)	0.59
Cigarette smoking	1.20 (0.39–3.68)	0.756	1.19 (0.19–7.37)	0.84
Antiaggregant therapy	1.73 (0.55–5.52)	0.35	0.93 (0.18–4.84)	0.93
PSA at PCa diagnosis	1.04 (0.92–1.17)	0.58	1.12 (0.96–1.31)	0.13
Gleason score at diagnosis				
6	Reference		Reference	
7	2.33 (0.80–6.79)	0.12	0.88 (0.16–4.82)	0.88
> 7	–	–	–	–
Unknown	13.66 (1.45–127)	0.02	–	–
Pre-treatment cT stage				
T1c	Reference		Reference	
T2	2.89 (0.76–11.0)	0.12	2.91 (0.58–14.7)	0.19
T3	15.13	**0.03**	–	–
Unknown	4.27 (0.85–21.4)	0.08	–	–
PSA nadir	1.19 (0.85–1.67)	0.30	0.88 (0.43–1.82)	0.74
Extracapsular extension	1.85 (0.23–14.7)	0.56	–	–
First-line treatment				
Radiotherapy	Reference		Reference	
Brachytherapy	0.55 (0.15–2.02)	0.37	0.53 (0.11–2.67)	0.44
HIFU	0.48 (0.10–2.23)	0.35	3.18 (0)	1
Time to first recurrence	1.02 (0.98–1.06)	0.26	0.99 (0.94–1.05)	
Gleason at recurrence				
6	Reference		–	
7	3.12 (0.38–25.9)	0.29	–	–
> 7	7.96 (0.83–75.9)	0.07	–	–
Unknown	4.57 (0.48–43.6)	0.18	–	–
Recurrence visible at MRI	1.12 (0.13–9.77)	0.91	–	–
PSA at recurrence	1.04 (0.95–1.15)	0.35	1.15 (0.98–1.36)	0.08
Preoperative hormonotherapy	1.68 (0.49–5.87)	0.40	1.15 (0.15–8.48)	0.89

Bold values indicate significant *p* values

BCR biochemical recurrence, *CSS* cancer-specific survival, *sRP* salvage radical prostatectomy, *ASA* American Society of Anesthesiology

The rate of anastomotic stricture in our set was 7.2%, which is significantly lower than that reported in previous major series on sRP (i.e., 11–41%) [7, 11, 22–24]. Only one rectal injury occurred intraoperatively, and this was during sRRP, confirming the findings of Kenney et al. [17]. Similarly, the kind of post-operative complications was similar to those in previous studies [9, 17–20]; however, when only Clavien III complications ($n = 2$) are considered, our series had one of the lowest rates. Of note, a surgical approach did not affect BCR and CSS; similarly, it did not affect post-operative complications and functional outcomes.

The retrospective nature of our study was associated with the number of complications, and may have underestimated them. The relatively short follow-up time, the limited number of patients, and the multicenter design may have also affected the analyses. Additionally, pre-operative treatment was not always carried on in the institute where the prostatectomy was performed, thus limiting the pre-operative data.

Conclusions

sRP was shown to be safe, feasible, and effective, using an open or robot-assisted approach, and when performed by experienced surgeons. It is clearly an option that can be discussed for young men with recurrent localized PCa.

Additionally, the age at prostatectomy, the clinical stage at diagnosis, the NS procedure, and a pathological GS seem to have a role in determining BCR after sRP and thus need to be considered when counseling the patient for sRP.

Table 4 Univariate analysis on the post-operative characteristics that were possible predictors for biochemical recurrence (BCR) and cancer-specific survival (CSS)

Variables	Univariate analysis for BCR		Univariate analysis for CSS	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Surgical approach	0.95 (0.30–3.06)	0.94	0.86 (0.19–3.83)	0.85
LND performed	1.76 (0.59–5.24)	0.31	0.47 (0.10–2.14)	0.33
Nerve-sparing procedure	0.17 (0.04–0.77)	**0.02**	1.87 (0.42–8.45)	0.41
Operation difficulty	1.54 (0.98–2.42)	0.06	1.49 (0.79–2.84)	0.22
Tumor pathology stage				
T2	Reference		Reference	
T3	10.71 (1.40–81.5)	**0.02**	0.74 (0.17–3.36)	0.70
T4	11.84(0.72–193)	0.08	–	–
Gleason Score				
6	Reference		Reference	
7	6.28 (7.28–5.34)	**< 0.001**	3.70 (2.80–4.87)	**< 0.001**
> 7	1.43 (1.77–1.16)	**< 0.001**	8.85 (8.47–9.25)	**< 0.001**
Nodal stage (pN+)	3.05 (0.81–11.47)	0.10	0.50 (0.50–5.09)	
Prostate volume, mL	0.99 (0.95–1.02)	0.67	1.03 (0.98–1.08)	0.25
PSM	1.28 (0.16–10.18)	0.81	1.17 (0.94–14.54)	0.90
EBL, mL	1.01 (0.99–1.01)	0.69	1.01 (1.00–1.01)	**0.01**

Bold values indicate significant *p* values

LND lymph node dissection, *PSM* positive surgical margin, *EBL* estimated blood loss

Author contributions MR, AT protocol/project development. RC, ID, JO, GR, TP, PL-C, HB, DP data collection or management. TS, PG data analysis. RC, PG, MR, TS, AT, AG, AV, J-CB, JBB, FB, DW, BG, AR manuscript writing/editing.

Compliance with ethical standards

Conflict of interest The authors have disclosed any potential conflicts of interests.

Informed consent All patients gave their written informed consent to be included in the prostate-cancer database at each center.

Ethical approval All patients' anonymity was preserved. All authors made significant contributions to the findings and methods in the paper, and have read and approved the final draft. The hospital's Ethics Committees approval was obtained and conformed to the provisions of the Declaration of Helsinki.

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