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Original Article

Risk factors for RNA integrity in fresh-frozen renal cancer samples from routine practice (UroCCR 9)

Facteurs de risque de l'intégrité de l'ARN dans les échantillons de cancer du rein congelés issus de la pratique courante (UroCCR 9)

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ABSTRACT

Introduction: High-quality biospecimens are essential for transcriptomic analyses in renal cell carcinoma (RCC), yet real-world determinants of RNA integrity in routine surgical settings remain insufficiently documented. This study aimed to evaluate RNA quantity and quality from cryopreserved RCC tissues and identify factors associated with RNA degradation.

Material and methods: We conducted a retrospective analysis of 160 patients who underwent surgery for clear cell RCC and included in the UroCCR network (2005–2012). Tumor and matched normal kidney tissues were prospectively collected during partial or radical nephrectomy and snap-frozen. RNA was extracted using an automated protocol. RNA concentration was measured by NanoDrop spectrophotometry, and RNA quality was assessed using the RNA Quality Score (RQS). Multivariate linear regression models with random intercepts were used to identify factors associated with RNA degradation.

Results: RNA extraction was successful in 302 of 310 samples. RNA concentration exceeded 25 ng/μL in 93% of samples, and 78.4% met both quantitative and qualitative criteria (RQS ≥ 6). Mean RNA concentration was 128.8 ± 104.4 ng/μL, and mean RQS was 7.52 ± 1.40. Tumor tissue showed higher RNA quality than matched healthy tissue (mean RQS: 8.33 ± 1.02 vs. 6.66 ± 1.30; $P < 0.001$). Preoperative embolization was independently associated with lower RNA quality ($P < 0.001$). Freezing delay (mean 30 ± 25 min) and duration of storage were not associated with RNA degradation.

Conclusion: High-quality RNA can be extracted from fresh-frozen RCC tissues under routine clinical conditions. RNA integrity is mainly influenced by tumour biology rather than procedural delays, supporting biologically informed biobanking strategies.

Level of evidence: 4.

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RÉSUMÉ

Introduction : La disponibilité de biospécimens de haute qualité est un prérequis essentiel aux analyses transcriptomiques dans le carcinome à cellules rénales (CCR). Cependant, en conditions réelles de pratique chirurgicale, les déterminants de l'intégrité de l'ARN demeurent insuffisamment caractérisés. Cette étude avait pour objectif d'évaluer la quantité et la qualité de l'ARN extrait de tissus de CCR cryoconservés, et d'identifier les facteurs associés à sa dégradation.

Matériels et méthodes : Nous avons réalisé une analyse rétrospective de 160 patients atteints de CCR à cellules claires inclus dans le réseau UroCCR entre 2005 et 2012. Des échantillons tumoraux et de parenchyme rénal sain appariés ont été prospectivement collectés lors de néphrectomies partielles ou totales, puis rapidement congelés. L'extraction de l'ARN a été réalisée à l'aide d'un protocole automatisé. La concentration en ARN a été mesurée par spectrophotométrie NanoDrop, et sa qualité évaluée à l'aide du RNA Quality Score (RQS). Des modèles de régression linéaire multivariée à intercept aléatoire ont été utilisés pour identifier les facteurs associés à l'intégrité de l'ARN.

Résultats : L'extraction d'ARN a été réussie pour 302 des 310 échantillons analysés. Une concentration supérieure à 25 ng/μL a été obtenue dans 93 % des cas, et 78,4 % des échantillons répondaient simultanément aux critères quantitatifs et qualitatifs (RQS ≥ 6). La concentration moyenne en ARN était de 128,8 ± 104,4 ng/μL, avec un RQS moyen de 7,52 ± 1,40. Les tissus tumoraux présentaient une qualité d'ARN significativement supérieure à celle des tissus sains appariés (RQS moyen : 8,33 ± 1,02 vs 6,66 ± 1,30 ; $p < 0{,}001$). L'embolisation préopératoire était indépendamment associée à une diminution de la qualité de l'ARN ($p < 0{,}001$). Le délai de congélation (moyenne 30 ± 25 minutes) et la durée de stockage n'étaient pas significativement associés à une altération de l'ARN.

Conclusion : Un ARN de haute qualité peut être obtenu à partir de tissus de CCR cryoconservés en conditions réelles de pratique clinique. L'intégrité de l'ARN semble principalement influencée par des facteurs biologiques tumoraux plutôt que par les délais procéduraux, soulignant l'importance de stratégies de biobanque intégrant les spécificités biologiques des tumeurs.

Niveau de preuve : 4.

Introduction

Advances in molecular biology and increased access to patient-derived tissue have led to new insights into oncogenesis and the development of targeted therapies. Renal cell carcinoma (RCC), a tumour type marked by profound biological heterogeneity and increasing therapeutic complexity [1], exemplifies the need for high-fidelity biospecimens. Despite progress in systemic therapies, particularly VEGF inhibitors and immune checkpoint blockade, clinically useful biomarkers in RCC remain lacking. The challenge is twofold: firstly, identifying prognostic biomarkers to guide follow-up and select patients for adjuvant treatment [2–4]; and secondly, establishing predictive biomarkers to anticipate therapeutic responses [5]. Both are central to personalised medicine. In this context, the availability of high-quality biological samples, including tumour tissue, has become essential for biomarkers characterisation [6]. Ensuring the quality of these samples often requires prompt cryopreservation of fresh tissues to minimise the rapid degradation of RNA [7]. This requirement imposes several logistical constraints on surgical and pathological teams, which must be integrated into routine clinical workflows. Moreover, several factors can affect sample quality, including the patient's disease status, tumour heterogeneity [8], and physiological variables [9], as well as critical pre-analytical conditions such as warm ischaemia time [10], delays in freezing [11–13], methods of tissue handling and preservation, and storage duration [14,15]. These variables can significantly influence molecular stability, and if not properly controlled, may compromise the reliability and reproducibility of research outcomes [16]. While guidelines for optimal cryopreservation have been published [17–19], more systematic controlled studies are needed to quantify the effects of these variables and define acceptable thresholds for different molecular assays. Since 2005, as part of a national initiative funded by the French National Cancer Institute (INCa), we have developed a dedicated renal cancer biobank within the French Kidney Cancer Research Network (UroCCR). This study aims to evaluate our biobanking protocols for fresh renal tumours, assess the quality of cryopreserved tissue samples, and identify practical, real-world risk factors associated with tissue degradation.

Material and methods

Tissue collection, ethics statement and patient consent

Tumour and matched normal kidney tissue were prospectively collected from patients undergoing partial or radical nephrectomy for a renal mass at the Department of Urology, University Hospital of Bordeaux. Prior to the surgery, all patients received both oral and written information regarding the objectives and methodology of the UroCCR project, and written informed consent was obtained. The UroCCR project (NCT03293563) received approval from the appropriate institutional review board (Comité de Protection des Personnes Sud-Ouest et Outre-mer III, approval No. DC 2012/108), authorisation from the CNIL (No. DR-2013-206), and a favourable opinion from the CCTIRS. All procedures were conducted in accordance with the Declaration of Helsinki. A retrospective cohort of 160 patients diagnosed with clear cell RCC (ccRCC) between January 2005 and January 2012 was subsequently selected.

Tissue management and storage procedure

The handling and cryopreservation of our samples were carried out in accordance with the guidelines set out by the Haute Autorité de santé for the cryopreservation of tissues, cells, and biological fluids derived from clinical care [19]. Immediately after resection, surgical specimens were transported fresh, without formaldehyde fixation, at room temperature by courier to the pathology laboratory, where equal amounts of tumour and adjacent normal kidney tissue were sampled. Each sample was placed in a labelled tube, snap-frozen in liquid nitrogen, and transferred to the tumour bank for storage at −80 °C. The delay between specimen extraction and snap-freezing, referred to as "freezing delay", was recorded (Fig. 1).

Molecular analyses on frozen specimen

RNA was extracted retrospectively, in parallel from tumour and matched normal tissue, using a standardised procedure. Briefly, tissue

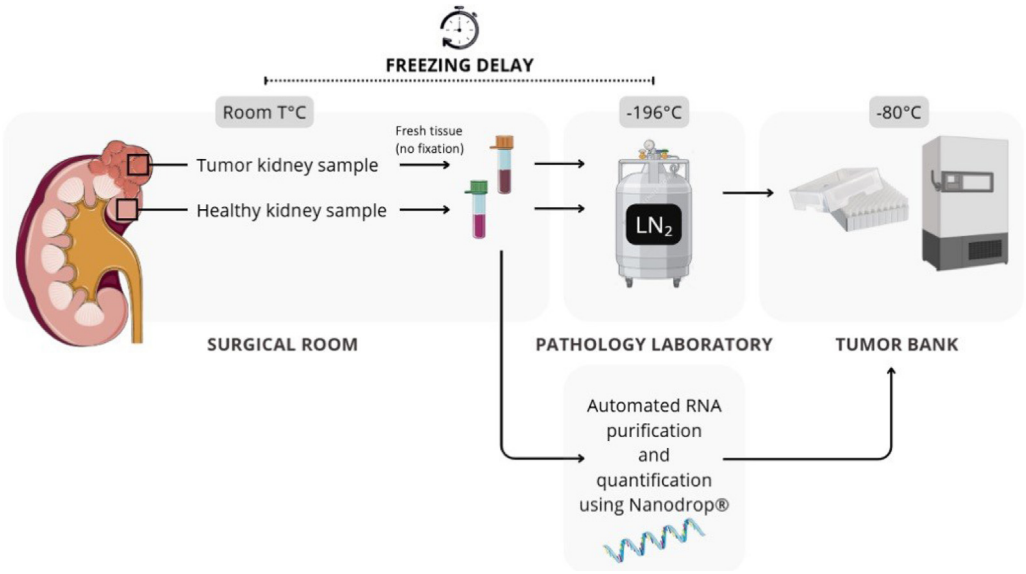

Fig. 1. Workflow and temperature conditions for kidney tissue biobanking and RNA processing. Tumour and healthy kidney samples are collected at room temperature, cryopreserved in liquid nitrogen, and stored at −80 °C. RNA is simultaneously purified using an automated protocol and subsequently quantified with Nanodrop®.

sections of 20 μm – obtained from a tissue block of approximately 40 mg – were homogenised and processed on the QIAcube® using the RNeasy® Plus Mini Kit (QIAGEN, Germany), following the manufacturer's protocol. The quantity of extracted RNA was measured using a NanoDrop® spectrophotometer, and RNA quality was assessed using the RNA Quality Score (RQS), determined by electrophoretic migration on the LabChip GX II Automated System (Caliper Life Sciences, USA), following the manufacturer's protocol. RNA quality assessment was carried out only for samples with a minimum RNA concentration of 25 ng/μL, which is the threshold required for RQS calculation and subsequent RT-qPCR analysis. All measurements were performed in duplicate.

Kidney cancer database

For each patient, the following data were recorded and stored in the UroCCR database: (a) Patient-related data: age, sex, S-classification, and preoperative haemoglobin level; (b) Tumour-related data: tumour size, pTNM classification, location, Fuhrman grade, presence of thrombus in the renal vein, and presence of sarcomatoid or necrotic components; (c) Surgical characteristics: type of procedure (partial or radical nephrectomy), surgical approach (open or laparoscopic), previous embolisation, operative time, and estimated blood loss; (d) Cryopreservation parameters: freezing delay and year of freezing; and (e) RNA characteristics: concentration (ng/μL) and quality (RQS) from both healthy and tumour samples tumour.

Statistical analysis

For each variable, an initial bivariate analysis was conducted to compare healthy and tumour tissue, using either a *t*-test or a Wilcoxon test depending on the normality of the data. Subsequently, both univariate and multivariate analyses were performed. A linear regression model with a random intercept was used to account for intra-patient correlations. A stepwise modelling strategy was applied, whereby all variables associated with each outcome at a significance level of $P < 0.20$ were initially included. The final model selection also took into account the Akaike Information Criterion (AIC). For each variable retained in the final model, estimated effects are presented as relative differences in RNA concentration (ΔC_{RNA}, %) or absolute differences in RNA quality scores (Δ_{RQS}), along with their standard errors and corresponding *P*-values. A significance threshold of 5% was used for all analyses. All statistical analyses were conducted by the Institut de Santé Publique, d'Épidémiologie et de Développement (ISPED, Bordeaux, France) during the initial study. The study adhered to the International Society for Biological and Environmental Repositories (ISBER) Best Practices, Fourth Edition.

Results

Cohort description

Clinical data, surgical procedure characteristics, histological findings and storage conditions are shown in Supplementary Supplementary table 1. This study included 160 patients with a median age of 61 years (IQR: 29–87) and a male-to-female ratio of 1.76. At the time of diagnosis, half of the patients were asymptomatic. Surgical specimens were obtained in 28% of cases during partial nephrectomy and 72% during radical nephrectomy, with 82 procedures (51%) performed laparoscopically. The mean operative time was 141 ± 41 minutes. In nine cases (6%), arterial embolisation was performed prior to surgery due to the presence of venous extension. The mean tumour size was 7.07 ± 6.95 cm, with pT1a (32%) and pT1b (23%) being the most common stages. Lymph node and distant metastases were present in 18% and 24% of patients, respectively. Tumours were predominantly located in the lower (31%) or upper (30%) poles. Fuhrman grade 3 was most frequent (44%), with sarcomatoid and necrotic components observed in 8% and 41% of cases, respectively.

Quantitative and qualitative assessment of extracted RNA

Assessment per sample

Of the 160 patients, 310 samples were available, and RNA was successfully extracted from 302 of them. Ten healthy tissue samples were unavailable due to the minimal margin of the tumorectomy specimens, and eight samples (comprising six healthy tissue samples and two tumour samples) were damaged, resulting in an extraction failure. Based on the RNA concentration threshold of 25 ng/μL, quality assessment was performed on 291 samples (Supplementary table 2). Therefore, our dataset includes 291 samples with a mean

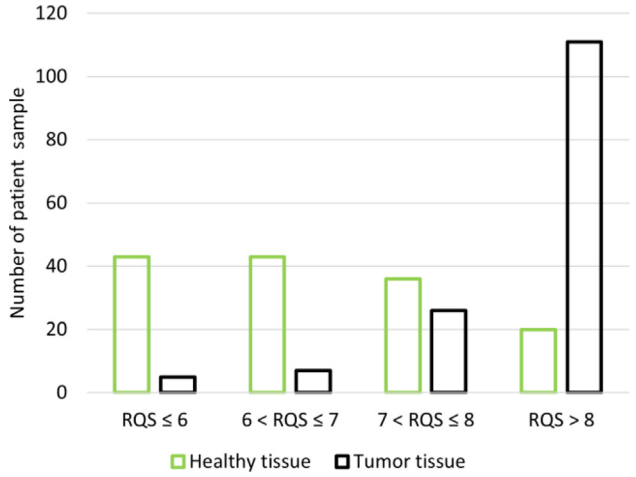

Fig. 2. RNA Quality Score (RQS) distribution in tumour and matched healthy tissue samples.

freezing delay of 30 ±25 minutes. The majority of samples were frozen between 2007 and 2009, with 34% processed in 2008 and 31% in 2009. RNA concentration was comparable between tumour samples (142.43 ± 114.62 ng/μL) and healthy samples (115.06 ± 91.27 ng/μL, $P = 0.11$), with an overall mean concentration of 128.75 ± 104.35 ng/μL. The mean RQS was 7.52 ± 1.40. However, RQS were higher in tumour samples (8.33 ± 1.02) compared to healthy samples (6.66 ± 1.30, $P < 0.0001$). Fig. 2 illustrates the distribution of samples by tissue type and RNA quality.

Assessment per patient

The quantity and quality of RNA were also assessed on a per patient basis. This analysis allowed for the evaluation, within individual patients, of the average RNA concentration and quality variability according to tissue type. Ultimately, successful RNA extraction was achieved from both healthy and tumour tissues in 142 out of 160 patients. Among these, 133 patients had RNA concentrations above 25 ng/μL and met the qualitative criteria. The results, including statistical comparison by tissue type, are presented in the Supplementary table 3. Compared to healthy tissue, RNA extracted from tumour tissue showed significantly higher concentrations ($P = 0.029$) and higher RNA quality ($P < 0.001$).

Risk factors for alteration of RNA extraction efficiency

An exploratory analysis was performed to evaluate potential associations between the relevant variables outlined in Supplementary table 1 and Supplementary table 2 and the total RNA concentration. Total RNA concentration differed according to clinical presentation, tumour characteristics, and year of sample collection (Fig. 3). Patients with general symptoms at diagnosis had higher RNA yields than asymptomatic patients ($P = 0.019$) or those with only loco-regional symptoms ($P = 0.012$). Similarly, samples from patients with metastases (M+) showed higher RNA concentrations than those without (M0; $P = 0.004$). RNA concentration was associated with Fuhrman grade, with higher-grade tumours yielding more RNA. RNA concentration was associated with Fuhrman grade, with higher concentrations observed in grade 4 tumours compared with grades 1–2 and 3 (−27.7%, $P = 0.009$; −26.5%, $P = 0.006$) (Table 1). Tumours with a sarcomatoid component ($P = 0.011$) or necrosis ($P = 0.021$) were associated with higher RNA concentrations. Additionally, RNA

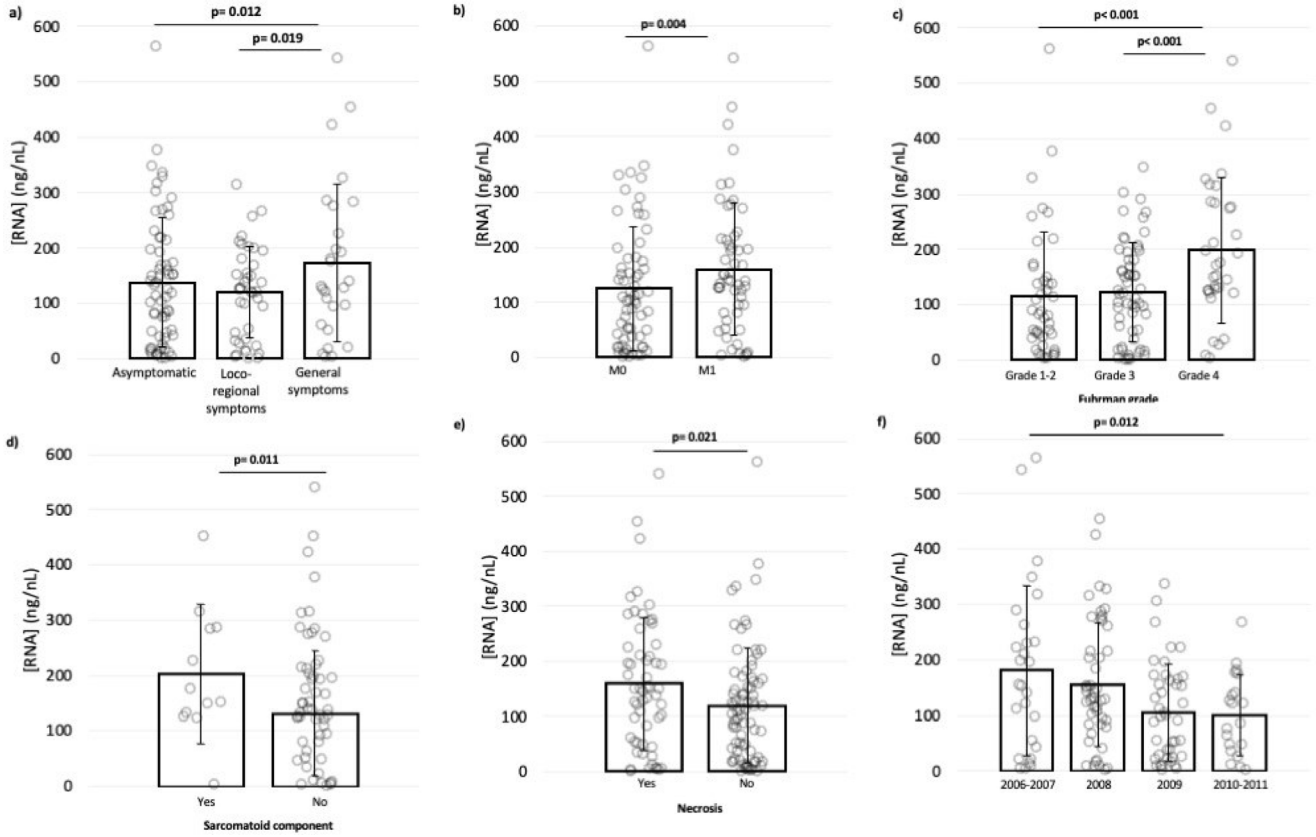

Fig. 3. Clinical and pathological correlates of RNA concentration in tumour samples. Mean RNA concentrations (ng/μL) in tumour samples stratified by clinical and pathological features: (a) clinical presentation, (b) metastatic status, (c) Fuhrman grade, (d) presence of sarcomatoid component, (e) presence of necrosis, and (f) year of surgery. Statistically significant differences ($P < 0.05$) are indicated.

Table 1
Multivariable analysis of factors associated with RNA concentration and quality.

Outcome	Parameter	Reference	Coefficient	ΔC_{RNA} (%)	*P*-value	Global *P*-value
RNA concentration	Fuhrman Grade	4				**0.010**
	1–2		−46.59	−27.7	0.009	
	3		−44.47	−26.5	0.006	
	Year of surgery	2010–2011				**0.001**
	2006–2007		+66.72	+39.7	0.001	
	2008		+37.96	+22.6	0.048	
	2009		+6.45	+3.8	0.736	
RNA quality	Tissue type	Tumour				< **0.001**
	Healthy		−1.689	−24.25	< 0.001	
	Preoperative embolization	Yes				< **0.001**
	No		1.444	+20.66	< 0.001	

Bold values indicate statistically significant global p-values ($P < 0.05$).

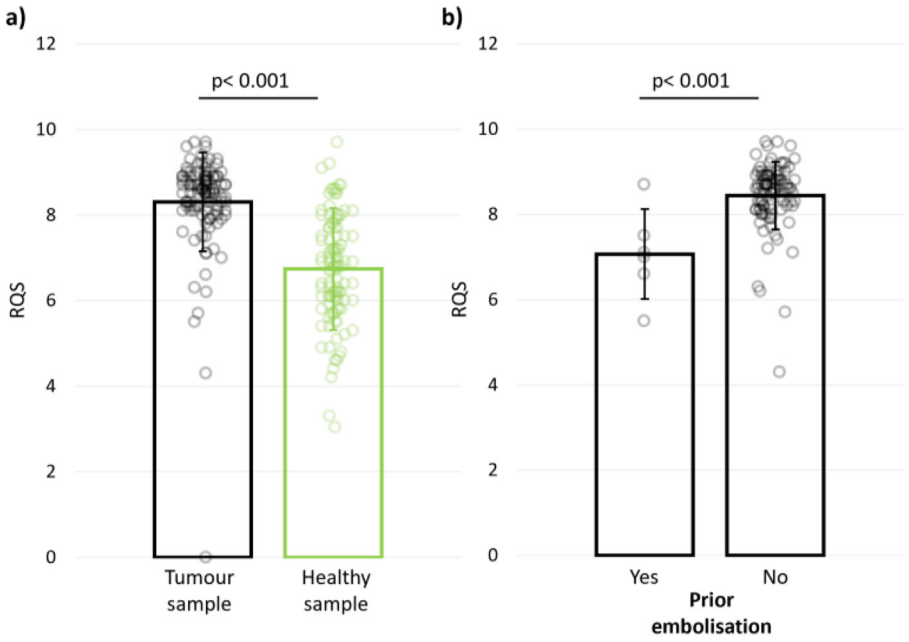

Fig. 4. Mean RNA Quality Score (RQS) by tissue type and prior embolisation status (univariate analysis).

concentration declined significantly over time (global $P < 0.001$), with the highest levels observed in samples from 2006–2007 (+39.7%, $P = 0.002$) and 2008 (+22.6%, $P = 0.048$), relative to the 2010–2011 reference period.

Risk factors for alteration of RNA quality

An association analysis was conducted between the variables of interest listed in Supplementary table 1 and Supplementary table 2, tissue type, and RQS. In univariate analysis, RQS was lower in healthy tissue compared to tumour tissue and in samples from patients who had undergone preoperative embolization (Fig. 4). In multivariate analysis, both tissue type and embolisation status remained independent risk factors for RNA quality (Table 1). Specifically, healthy tissue showed a 24.25% reduction in RQS compared to tumour tissue ($P < 0.001$), while embolisation was associated with a significantly lower RQS compared to non-embolised tumours ($P < 0.001$). Global *P*-values for both variables confirmed their strong association with RNA quality ($P < 0.001$).

Discussion

The accelerating shift toward personalised oncology has placed unprecedented demands on the quality and reliability of biospecimen collections [20]. In RCC, where robust prognostic and predictive biomarkers are still lacking, access to high-quality tumour-derived RNA is a prerequisite for meaningful transcriptomic analyses. In this context, our study provides a real-world evaluation of cryopreservation practices within a dedicated renal cancer biobank and identifies clinical and biological factors associated with RNA integrity.

A key objective was to evaluate the usability of cryopreserved tissue samples collected during routine nephrectomy procedures. Quantitatively, our results indicate that the vast majority of tumour and healthy tissue samples yielded RNA concentrations above commonly accepted thresholds [21] for downstream molecular analyses, including RT-qPCR. When considering paired tumour and healthy samples at the patient level, usability decreased modestly, reflecting the additional constraints associated with matched analyses. These findings are consistent with reports from other large biobanking initiatives relying on fresh-frozen tissues and support the robustness of standardised workflows implemented in routine clinical practice [21–24]. From a qualitative perspective, RNA integrity was generally high, with mean RQS values exceeding thresholds typically considered acceptable for transcriptomic applications [20]. Using a conservative cutoff, more than three quarters of samples fulfilled both quantitative and qualitative criteria. Notably, tumour tissue more frequently met RNA quality requirements than matched healthy parenchyma, a finding that has been reported previously [25] and was consistently observed across our analyses.

Our analyses identified several factors associated with RNA quality, highlighting that sample degradation cannot be attributed solely to technical aspects of tissue handling. Among these, preoperative embolisation was associated with reduced RNA integrity in our analysis. However, this observation should be considered exploratory, as embolisation was performed in a limited number of patients. The limited number of embolised tumours therefore represents an important limitation and precludes definitive conclusions regarding the impact of embolisation on RNA integrity. Although ischaemia is a recognised contributor to RNA degradation [11–13], this result underlines the impact of clinically indicated preoperative interventions on downstream molecular quality. Embolisation-induced devascularisation may expose tissues to prolonged hypoxic conditions prior to excision, which could affect RNA stability [26], and warrants confirmation in larger cohorts.

In contrast, no significant association was observed between freezing delay and RNA quality within the timeframes encountered in our cohort. Most samples were cryopreserved within 30 minutes of excision, in line with current recommendations [27], and variability in this interval was limited. Freezing delay was defined as the interval between specimen excision and cryopreservation, while the time from tumour devascularisation to freezing could not be reliably assessed, representing a limitation of the present study. The relatively short and homogeneous post-excision freezing times may therefore have limited our ability to detect an association with RNA quality. Nevertheless, we cannot exclude the possibility that transcriptomic alterations may occur during this peri-excision interval [27], even in the absence of measurable RNA degradation. Future prospective studies should include systematic recording of devascularisation and ischaemia times, particularly in large or complex tumours and minimally invasive procedures.

A consistent and striking finding of this study was the lower RNA integrity observed in healthy kidney tissue compared with tumour tissue. On average, healthy samples exhibited substantially lower RQS values, confirming observations reported in previous studies [28,29]. This difference may reflect a reduced susceptibility to ischaemic or hypoxic stress and/or intrinsic biological differences between malignant and normal renal tissue, such as altered cellularity, metabolic reprogramming, and stress-response pathways, which may influence RNA stability [30]. In contrast, normal renal parenchyma may be more susceptible to acute ischaemic stress.

In addition, more aggressive tumour features, such as higher Fuhrman grade, metastatic disease, necrosis, or sarcomatoid differentiation, were associated with higher RNA yields. While this may facilitate tumour-focused biomarker studies, it poses challenges for analyses relying on matched normal tissue as a reference. Degraded control samples may introduce bias or reduce sensitivity in differential expression analyses, an issue that should be considered at both the design and interpretation stages of translational studies.

Contrary to concerns regarding long-term storage, sample age was not associated with reduced RNA quality in our cohort. Overall, RNA extractions were performed retrospectively after long-term cryogenic storage without evidence of substantial degradation in RNA quality, supporting the feasibility of ancillary molecular studies using archived biobank samples. Earlier samples even demonstrated higher average RNA concentrations, although this finding may reflect batch effects or unmeasured procedural differences rather than a true temporal trend.

Several limitations should be acknowledged. Although this analysis was conducted at a single center and should therefore be interpreted with caution, tissue collection and cryopreservation strictly followed standardized UroCCR recommendations designed to harmonize biological sample collection across participating institutions. This methodological framework supports the potential applicability of our findings within the UroCCR network, while multicenter confirmation remains warranted.

Taken together, these findings highlight that RNA integrity in biobanked renal tissues is influenced by a combination of biological, clinical, and procedural factors. While standardised cryopreservation protocols are essential, attention to tumour biology and preoperative interventions is equally important to ensure the quality and interpretability of molecular data derived from routine surgical specimens.

Conclusions

This study provides a pragmatic evaluation of cryopreservation practices in routine renal surgery. Standardised protocols allow reliable extraction of high-quality RNA suitable for transcriptomic analyses under real-world clinical conditions. RNA integrity is primarily influenced by biological and clinical factors, including tumour characteristics and preoperative embolisation, rather than procedural delays alone. These findings support biologically informed biobanking strategies integrated into routine clinical practice.

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Author contributions

Conceptualization: GM, JCB.
Methodology: GM, GC, JCB.
Formal analysis and investigation: BCN, LD, FS, SQ, JPM, LT, AD, MJP, GD, MGG, MY, AB.
Supervision: JCB.
Writing (original draft): GM.
Writing (review & editing): all authors.

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical approval

Approved by the Comité de Protection des Personnes Sud-Ouest et Outre-mer III (approval No. DC 2012/108).

Consent to participate

All patients provided written informed consent for participation in the UroCCR biobank.

Disclosure of interest

Jean-Christophe Bernhard reports financial support was provided by French National Cancer Institute. The other authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.fjurol.2026.103084.

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