Novel Volumetric and Morphological Parameters Derived from Three-dimensional Virtual Modeling to Improve Comprehension of Tumor's Anatomy in Patients with Renal Cancer

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Novel volumetric and morphologic parameters derived from 3D virtual modelling to improve comprehension of tumour's anatomy in patients with renal cancer.

Running head: 3D parameters and renal anatomy

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ABSTRACT

Background: 3D models improve the comprehension of renal anatomy.

Objective: to evaluate the impact of novel 3D-derived parameters, to predict surgical outcomes after Robot Assisted Partial Nephrectomy (RAPN).

Design, Setting, and Participants: 69 patients with cT1-T2 renal mass scheduled for RAPN were included. 3D virtual modeling was achieved from computed tomography. Following volumetric and morphological 3D parameters were calculated: V_T (volume of the tumor); V_T/V_K (ratio between tumor volume and kidney volume); CSA_{3D} (i.e. Contact Surface Area); UCS_{3D} (contact to the Urinary Collecting System); **Tumor-*Artery*** $_{3D}$: tumor's blood supply by tertiary segmental arteries (*score*=1), secondary segmentary artery (*score*=2) or primary segmentary/main renal artery (*score*=3); S_T (tumor's sphericity); $Conv_T$: (tumor's convexity); $Endophyticity_{3D}$ (ratio between the CSA_{3D} and the global tumor surface).

Intervention: RAPN with 3D model

Outcome Measurements and Statistical Analysis: 3D parameters were compared between patients with and without complications. Univariate logistic regression was used to predict overall complications and type of clamping; linear regression was used to predict operative time, warm ischemia time and estimated blood loss.

Results and limitations: Overall, 11 (15%) individuals experienced overall complications (7.2% had Clavien≥3 complications). Patients with UCS involvement at 3D model (UCS_{3D}=2), tumor with primary or secondary segmental arteries supply (Tumor-$Artery_{3D}$=1 and 2) and high $Endophyticity_{3D}$ values had significantly higher rates of overall complications (all $p \leq 0.03$). At univariate analysis, UCS_{3D}, Tumor-$Artery_{3D}$ and $Endophyticity_{3D}$ are significantly associated to overall complications; CSA_{3D} and $Endophyticity_{3D}$ were associated to warm ischemia time; CSA_{3D} was associated to selective clamping (all $p \leq 0.03$). Sample size and the lack of interobserver variability are the main limits.

Conclusion: 3D modeling provides novel volumetric and morphological parameters to predict surgical outcomes after RAPN.

Patient Summary: Novel morphologic and volumetric parameters can be derived from 3D model to describe surgical complexity of renal mass and to predict surgical outcomes after RAPN.

INTRODUCTION

Nephron sparing surgery (NSS) represents the treatment of choice for T1 Renal Cell Carcinoma (RCC) regardless of the surgical approach[1,2]. A critical and detailed comprehension of renal anatomy and tumour's complexity is essential to achieve optimal success of NSS. In the current era of precision surgery, the introduction of 3D modeling technologies has brought significant improvements for comprehension of renal anatomy, allowing a patient-tailored approach for NSS. Several nephrometry systems[3,4,5,6,7,8] have been proposed to objectively quantify the complexity of renal tumours and to predict surgical complications. However, the current nephrometry scoring systems were assigned mainly by visualization of two-dimensional (2D) imaging[9,10] which is suboptimal for a complete understanding of the morphological and anatomical features of renal mass and for planning partial nephrectomy (PN). Of note, 3D models are navigable and enable to facilitate the understanding of the size, location and depth of renal tumours, as well as the vascular and collecting systems anatomy[11,12]. Moreover, 3D models are more accurate to define the surgical complexity of renal masses by nephrometry score than conventional 2D imaging[12]. Thus, 3D models allow to better plan the surgical approach to NSS and to increase the rate of selective clamping[11,13,14]. However, the potential applications of 3D modeling are not totally investigated, and several information that can be derived from 3D virtual models and their elaboration are still unexplored.

The aim of the present study was to identify and to define novel volumetric and morphologic parameters derived from anatomical 3D modeling, and to evaluate the impact of these features to predict surgical outcomes after Robot Assisted PN (RAPN).

MATERIALS AND METHODS

Study design and participants

We prospectively enrolled 69 consecutive patients with organ-confined (cT1-T2) renal mass, referred to RAPN at our Institution between January 2019 and March 2020. Participants signed a written informed consent document. The study was approved by our Institutional Ethics Committee (IRB approval 3386/2018). Before surgery, patients were addressed to undergo 3D virtual modelling from preoperative computed tomography (CT) scan. The surgeon reviewed both the 2D CT imaging and the 3D virtual models before and during RAPN to guide the surgical planning and to improve anatomic knowledges during surgery.

3D modeling

To obviate bias due to inaccurate 2D preoperative imaging, before surgery all patients underwent high quality chest and abdominal contrast-enhanced CT at our Institution (slice thickness: 1.25 ÷ 2.5 mm, step interval: 0.8÷ 2.0 mm). All 3D virtual model reconstructions based on preoperative high-CT scan, were carried out by engineers at eDIMES Lab of the University of Bologna (IRCCS, Azienda Ospedaliero-Universitaria, S. Orsola-Malpighi Hospital), as previously described[11,15,16].

Briefly, multiple imaging series with different contrast levels were used for the selective identification of each anatomical structure of interest (healthy renal parenchyma, renal tumour, arterial tree, renal veins, urinary collecting system [UCS]) in the image segmentation process. Segmentation, i.e. the labelling of each structure of interest in CT images was achieved using D2P™ software (‘DICOM to PRINT’; 3D Systems Inc., Rock Hill, SC). The segmented anatomical structures arising from the multiple imaging series were then combined into one file using alignment of common regions, such as the healthy renal parenchyma that was segmented in all the series. The segmentation process, which is a semiautomatic procedure requiring both good knowledge of the anatomy and deep expertise in medical image processing, was performed by engineers, who worked in close interaction with surgeons and radiologists for reviewing the segmentation results and the anatomical correctness of the reconstructed 3D virtual models[14]

Surgical technique

PNs were performed with robot-assisted approach by a single expert surgeon (RS). DaVinci Xi platform with four arms, as previously described[11,14]. In case of clamping approach to the renal hilum we adopted warm ischemia: a selective (first segmental branch) or super-selective (second and tertiary segmental branch) clamping approach was preferred whenever feasible according to preoperative imaging and intraoperative patients-specific surgical anatomy[11,15].

3D-derived parameters

Three expert bioengineers (EM, LC and BB) and three urologists (LB, AM and SB) with experience with nephrometry, calculated the following volumetric and morphological 3D parameters of the renal mass on the basis of the obtained 3D virtual models, using Meshmixer (Autodesk Inc, San Rafael, CA) and Excel (Microsoft Corp., Redmond, Washington, US) software: $\boldsymbol{V_T}$ [cm^3] (i.e. volume of the tumor);$\boldsymbol{V_T/V_K}$ (i.e. ratio between the tumor volume and the ipsilateral kidney volume); ***Tumor-Artery$_{3D}$***: cortical tumor with blood supply by tertiary segmental arteries (*score*=1), medullary tumor with blood supply by secondary segmentary artery (*score*=2) and hilar tumor with blood supply by primary segmentary or main renal artery (*score*=3) based on univariate logistic regression analysis to predict overall complications; $\boldsymbol{S_T}$ (i.e. sphericity of the tumor): continuous parameter to quantify how closely the shape of the tumor approaches that of a mathematically perfect sphere (S_T=1); ***Conv$_T$***: (i.e. convexity of the tumor): continuous parameter to quantify the regularity of tumor 3D morphology, obtained as ratio between the tumor volume and the smallest volume that fully encloses it, and that is convex at all points; ***CSA_{3D}*** (i.e. Contact Surface Area [cm^2]); ***UCS_{3D}*** (i.e. contact of the tumor to the UCS; no contact with UCS [score=1], contact/dislocation/invasion of UCS [score=2] based on univariate logistic regression analysis to predict overall complications); ***$Endophyticity_{3D}$***: ratio between the CSA_{3D} and the global tumor surface: it is an index of the tumor endophyticity, as evaluated from the 3D model.

The 3D-derived parameters are described in detail in Table 1 and depicted in Figures 1-2.

Covariates

Intraoperative data including overall operative time, type of resection (simple enucleation vs. standard PN), level of arterial clamping (totally clampless vs. non-selective [i.e., clamping of main renal artery] vs. selective clamping [i.e., clamping of primary, secondary or tertiary segmental arteries]), time of defatting, time of hilar dissection, time of ischemia, time of resection and intraoperative complications were recorded. Postoperative data included length of hospital stay, haemoglobin, serum creatinine and eGFR at discharge, and 30- and 90-day postoperative complications, defined as any postoperative event altering the normal post procedural course and/or delaying discharge and/or caused readmission, and were classified according to the Dindo modification of the Clavien system[17] and Comprehensive Complication Index (CCI)[18].

Outcomes

The primary outcome of the study was to investigate whenever the proposed novel volumetric and morphologic parameters derived from anatomical 3D modeling may predict surgical outcomes in patients underwent RAPN (including, overall complications, operative time, warm ischemia time and estimated blood loss).

Statistical analyses

First, Chi-squared test, T-student test and Mann-Whitney U-test were used to compare proportions, means and medians of volumetric and morphological 3D parameters between patients with and without postoperative complications after RAPN. Second, to evaluate the association between the proposed volumetric and morphological 3D parameters (namely, ***V_T,*** ***V_T/V_K*****,** ***CSA_{3D}***, ***UCS_{3D},*** **Tumor-*$Artery_{3D}$*,** ***S_T,*** ***$Conv_T$*** and ***$Endophyticity_{3D}$***) and the occurrence of overall complications and clamping approach we performed univariate logistic regression analysis, while linear regressions were used to test the association with operative time, warm ischemia time and estimated blood loss.

Finally, to produce curve representing the probability to experience overall complications over ***$Endophyticity_{3D}$***, LOESS plots were produced using mean value of ***$Endophyticity_{3D}$*** to estimate overall complications predicted by linear regression analysis. All statistical tests were performed using the Statistical Package for Social Sciences software, v.26.0 (SPSS Inc., Chicago, IL, USA) with a 2-sided significance level set at $p<0.05$.

RESULTS

Overall, 55 (79.7%), 13 (18.8%) and 1 (1.5%) patients had cT1a, cT1b, cT2a renal cancer, respectively (Table 2). The intraoperative adopted clamping approach was clampless, non-selective (main artery), selective (first segmental artery) and super-selective (second or third segmental artery) in 23 (33.3%), 19 (27.5%), 24 (34.8%) and 3 (4.3%) cases, respectively (Table 3). During surgery, two (2.9%) intraoperative complications were observed. Overall, 10 (14.4%) patients experienced postoperative complications (all Clavien grade ≤3) with mean CCI of 6.9. Supplementary Table 1 shows the type and grade of any overall complication. Patients with high PADUA score risk (p=0.03), UCS involvement at 3D model (***UCS***$_{3D}$=2, p=0.02), tumor with primary or secondary segmental arteries supply (***Tumor-Artery***$_{3D}$=2 and 3, respectively, p=0.02) and high ***Endophyticity***$_{3D}$ values (p=0.03) had significantly higher rates of overall complications (Table 4). At univariate logistic regression, ***UCS***$_{3D}$ (OR: 4.59), ***Tumor-Artery***$_{3D}$ (OR: 3.50) and ***Endophyticity***$_{3D}$ (OR: 1.04) are significantly related to any overall complications; ***CSA***$_{3D}$ (OR: 0.49) and ***Endophyticity***$_{3D}$ (OR: 0.12) were associated to warm ischemia time; ***CSA***$_{3D}$ (OR: 0.92) was associated to selective clamping (all p ≤ 0.03; Supplementary Table 2); Supplementary Figure 1 depicts the linearity of the association of ***Endophyticity***$_{3D}$ with complications (p=0.03).

DISCUSSION

Beside tumor's size[19], different characteristics, including location, renal sinus involvement, relationship with UCS, contact with renal surface and vascular anatomy, should be carefully evaluated before planning PN to predict surgical complexity and the effectiveness of PN rather than radical nephrectomy. As consequence, different renal nephrometry scores[5,6,7,20,21] have been introduced to better standardize tumor's characteristics. Which nephrometry system is the most accurate to predict surgical complexity and better outcomes of PN[22], is still matter of debate. Of note, RENAL and PADUA score, which are easy to calculate by using 2D CT scan images and have a good association with most outcomes, are the most popular in literature[23]. Of note, CT scan images are easily available, however, 2D imaging could be inaccurate to precisely define the relationship of renal mass with nearby kidney's structures. Indeed, 2D images are unable to identify the exact intrarenal vascular anatomy and to predict the real tumour blood supply from segmental branches[13]. Thus, the adoption of 3D virtual model can be used as additional tools to improve the understanding of renal anatomy before PN[11,24]. As consequence, the high-fidelity 3D reconstruction of renal vasculature allows to increase the adoption of selective clamping[11,24].

Moreover, previous authors[12] stated that 3D-based PADUA and RENAL scores better define the complexity of renal mass and had higher predictive accuracy for postoperative complications compared to nephrometry scoring system based on 2D imaging.

However, the potential applications of 3D modelling are not totally investigated, and several information that can be derived from 3D virtual models and their elaboration are still unexplored. Indeed, we identified novel morphologic and volumetric parameters derived from 3D models.

Several results are remarkable. First, we report for the first-time novel 3D features to define the complexity of renal mass in standard manner, and we provide a comprehensive evaluation of the impact of the proposed 3D-derived parameters to predict surgical outcomes after RAPN. Second, ***V_T***, ***V_T/V_K***, ***S_T***, ***$Conv_T$***, ***CSA_{3D} and $Endophyticity_{3D}$*** are numeric parameters based on 3D features with objective description and lower potential reporting error compared to visual parameters based on 2D imaging; ***UCS_{3D} and $Tumor\text{-}Artery_{3D}$*** are visual parameters, but the assessment based on 3D models increases the precision to define relationship between the tumor and the collecting system and arterial branches compared to conventional 2D imaging.

Moreover, they can be easily calculated using Meshmixer software and Excel calculator spreadsheet, out of additional costs, and they are generalizable and standardize for scientific report thus allowing effective comparison with different cases.

Third, among all novel proposed 3D parameters to characterize renal mass and to evaluate complication after NSS, the volume of the tumor, the ratio between the tumor volume and the ipsilateral kidney volume, the sphericity of the tumor, the convexity of the tumor and the CSA, all based on 3D model, were comparable between patients who experienced complications and those who did not. However, patient with UCS involvement (p=0.02), tumor with primary or secondary segmental arteries supply (p=0.02) and higher Endophyticity (p=0.03) calculated on the 3D model, had significantly higher rates of overall complications. Similarly, ***UCS_{3D}***, ***$Tumor\text{-}Artery_{3D}$*** and ***$Endophyticity_{3D}$*** are significantly associated to any complications at univariate logistic regression.

These data confirmed that UCS involvement is a crucial characteristic in predicting overall complications after PN since urinary leakage represents one of most diffuse complications (4.3% in our cohort) in case of close relationship between the tumor and the collecting systems. The segmental arteries supply, based on 3D rendering of arterial branches evaluated on 3D model, is useful tools to plan effective clamping PN. Moreover, tumors with blood supply from main artery or first segmental arteries are more suitable for complications due to centrally located mass, at higher risk of renal bleeding (6.2% in the overall population) or urinary leakage. The ***$Endophyticity_{3D}$*** aims to replace the categorized endophytic rate (namely, ≥ 50%, <50% and endophytic) as depicted in RENAL[6] and PADUA[5] score that suffer from inaccurate evaluation by 2D imaging and difficult evaluation of border-line cases: the objective numeric expression from 3D evaluation as continuous variable suggests that 20-points increase in $\boldsymbol{Endophyticity_{3D}}$ has a significant impact to predict complication after RAPN (Supplementary Figure 1).

The 3D derived features provide additional volumetric and morphological parameters, that could not be evaluated in 2D images, and may be useful to objectively characterize, to report and to understand the complexity of renal tumors and to predict complications, thus helping surgeons during planning of the surgical approach. However, the quality of CT scan used for 3D model reconstruction should be high-quality with slice thickness ≤2.5 mm, otherwise the precision of 3D model is inadequate to be reliable for surgical navigation.

Finally, the proposed innovative 3D derived parameters may be useful to create further 3D-based nephrometry scores to predict outcomes of PN.

Despite several strength, our study is not avoided from limitations. First the sample size is limited, however the prospective nature of the study may mitigate this limitation.

Second, the inclusion of 3 urologists and 3 bioengineers for the evaluation of these parameters could be biased by interobserver variability.

Third, most nephrometry scores and parameters were ideated to predict outcomes and complications of open PN; all cases included in our cohort underwent RAPN, so the adoption of robotic approach could have reduced the occurrence of postoperative complications.

Fourth, in our experience 3D models are not routinely used in every cases due to several issue: engineers should have experience in using certified software for medical image segmentation and they need strict collaboration with radiologists and urologist for reviewing the images and validating the model, 3D reconstruction may take from 2 to 3 hours and it costs approximately 100 euros per single reconstruction, considering the software licence fee and costs for human resources. However, increasing evidence suggest the importance of 3D models for several utilities during PN, giving the chance to even more diffusion in the future and to improve automated segmentation algorithms, thus reducing costs and increasing accuracy related to this technology.

Further perspective may include the proposed 3D-derived anatomic and morphologic parameters in a novel 3D-specific nephrometry score to standardize the surgical complexity of renal mass and to better predict surgical outcomes of NSS.

CONCLUSION

The use of computerized software for processing 3D models can be used to extrapolate objective and standardized features to describe surgical complexity of renal tumour: volume of the tumor, ratio between the tumor volume and the ipsilateral kidney volume, sphericity of the tumor, convexity of the tumor, *CSA*, UCS involvement, arterial tumor's supply and Endophyticity. Of note, UCS_{3D} involvement, arterial tumor's $supply_{3D}$ and $Endophyticity_{3D}$ are significantly associated ~~correlated~~ with overall complications after RAPN, while only CSA_{3D} and $Endophyticity_{3D}$ were associated to warm ischemia time and CSA_{3D} was associated to selective clamping.

Disclosure of potential conflicts of interest

The authors declare that they have no conflict of interest.

Research involving Human Participants and/or Animals

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional research committee (Comitato Etico di Area Vasta Emilia Centro, Policlinico Sant’Orsola-Malpighi, Bologna, Prot. N. 323) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Figure legend

Figure 1. a) Tumour Volume (V_T), in green, and kidney volume (V_K), in grey, as derived from the 3D models. b) UCS_{3D} index calculated from the 3D models: it categorizes the contact of the tumour with the urinary collecting system (UCS). In this example, two different scores of UCS_{3D} index are shown. c) Tumor-$Artery_{3D}$ index calculated from the 3D models: it categorizes how the tumour is in close proximity to the arterial vessels. In this example, three different scores of Tumor-$Artery_{3D}$ index are shown (Score 1: blood supply by tertiary segmental arteries; Score 2: blood supply by secondary segmentary artery; Score 3: supply by primary segmentary or main renal artery)

Figure 2. a) Tumour sphericity index (S_T) calculated from the 3D model: it quantifies how closely the shape of the tumour approaches that of a perfect sphere. In this example, two different values of S_T index are shown. b) Tumour convexity index ($Conv_T$) calculated from the 3D model: it quantifies the regularity of tumour 3D morphology, i.e. how it approaches to a convex (i.e. with no concavities) shape. In this example, two different values of the $Conv_T$ index are shown. c) CSA index calculated from 3D model (CSA_{3D}): it corresponds to the surface of the endophytic part of the tumour (orange part in the figure); d) $Endophyticity_{3D}$ index calculated from the 3D model: it corresponds to the ratio between the CSA_{3D} and the global surface area of the tumour (SA_T) represented in blue in the figure. In this example, two different values of the tumour $Endophyticity_{3D}$ index are shown.

Supplementary Figure 1. Predicted probability of overall complications (solid graph) and 95% confidence intervals (dotted graphs) is plotted against $\text{Endophyticity}_{3D}$ by linear regression analysis of mean value of $\text{Endophyticity}_{3D}$ value.

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