

# A Review: Molecular Imaging Techniques to Monitor NK Cells in Vivo in a Preclinical and Clinical Scenario

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Available online at: <http://www.ijcert.org>

Received: 3/08/2019,

Revised: 17/08/2019,

Accepted: 28/08/2019,

Published: 30/08/2019

**Abstract:** In recent years, the use of natural killer (NK) -based immunotherapy has shown promising measures against various cancers. The therapeutic efficacy of NK cell immunotherapy depends to some extent on the migration of NK cells and subsequent infiltration into tumours in animal models or in humans. The continuous improvement of the healing and therapeutic properties of NK cells stimulates the performance and use of immunotherapy based on NK cells. In this review, we summarize the molecular imaging techniques used to monitor NK cell migration and infiltration in vivo, both preclinical and clinically. The advantages and disadvantages of each molecular imaging modality are considered. Finally, we present our understanding of the use of molecular imaging techniques to monitor NK cells in vivo in a preclinical and clinical scenario.

**Key Words:** photoacoustic imaging; optoacoustic imaging; breast imaging; breast cancer detection; breast phantom imaging; animal breast imaging; in vivo breast imaging; breast cancer screening; breast cancer diagnosis, bioluminescent; RI; SPECT; PET

## 1. Introduction

Prostate carcinoma (PCA) is the most common cancer and the third leading cause of male death in men in the United States. The main challenge for PCA management is the lack of non-invasive tools that can distinguish between aggressive and non-invasive cancers. This limitation results in a higher prognosis and higher treatment, demonstrating that 48 patients treated with PCA avoid one death. This over diagnosis and over-treatment can lead to unnecessary biopsies, surgeries, radiation therapy, chemotherapy and anxiety. Good diagnostic techniques can reduce these unnecessary procedures. To meet this need for more efficient screening, metric multi-computer magnetic resonance imaging (pMRI) can be used to examine the entire prostate.

In recent years, prostate PRI has been increasingly used to determine CAp. The current advantage of MpMRI in

screening comes from its high prognostic value for negative prostate cancer. However, the full potential of IRMPm has not yet been reached. Over diagnosis of PCA can be reduced by MRI scanning, which allows better detection of lesions, classification of lesions (benign or malignant) and the magnitude of the lesion.

Accurate assessment of prostate dissection and volume provides valuable information for the diagnosis and clinical management of benign prostatic hyperplasia (BPH) and PCA. It improves BPH treatment, surgical planning, and prognosis of PCa prognosis. Transrectal ultrasound fusion (TRUS) biopsy with magnetic resonance imaging (MRI) requires resection of the prostate gland, which is most commonly used to diagnose PCA. The performance of an MRI / TRUS fusion biopsy depends on the precise segmentation of the prostate onto magnetic resonance imaging, as the edges of the prostate form reference frames for fusion with ultrasound data. Consequently, any

inaccuracy in the identification of prostate boundaries can lead to biopsy errors. In addition to segmentation, prostate volume assessment is also a useful measure, especially for BPH treatment, surgical planning, and PCA prognosis. BPH is one of the most common diseases affecting the elderly, with a prevalence of 90% in the 1980s. Higher prostate counts in men with BPH are associated with more severe lower urinary tract symptoms and greater urinary retention. In addition, studies have shown that patients have different responses to BPH medications depending on prostate size. In addition, the choice of surgery takes into account prostate volume and each intervention has its own risk profile. In addition to guiding BPH treatment, prostate volume is also used to predict PCA. Prostate size alone is a valuable marker for predicting PCA; PCA has been more accurately detected in the prostate less than 50 cm<sup>3</sup> than in those less than 50 cm<sup>3</sup>. Prostate volume can also be used to calculate prostate-specific antigen concentrations, which can be used to differentiate BPH from PCA and which could be used to evaluate the results of radical prostatectomy.

Accuracy in the detection, segmentation, and quantification of prostate damage is important at different stages of CPA management. Lesion detection identifies biopsy areas. Accurate segmentation is important to improve the performance of fusion biopsy. In addition, segmentation improves the delivery of radiotherapy. Volume estimation predicts prognosis after prostatectomy. Detection of prostate damage is important because effective treatment of PCA depends directly on early detection of cancer. Although the CPA often chooses an unforeseen course, it can sometimes progress quickly. In these cases, wound detection by pMRI is crucial because it provides an area with hypersensitivity and a high target biopsy yield. Without detecting MPMRI damage, randomized 12-core TRUS biopsies are performed, which may result in small or anterior PCa loss.

Early detection of prostate damage improves timely treatment of PCA, but accurate wound resection improves radiotherapy. Prostate damage is a major source of contouring error when administering radiation therapy. This incorrect division leads to a lower dose of the tumour as well as a higher dose of normal cells. Although radiation therapy is an effective method of treating cancer, its use is hampered by vague descriptions. A more specific type of life-threatening injury is to improve the target of the injury and the relative dose of radiotherapy, resulting in a lower recurrence rate.

Evaluation of the extent of preoperative prostate damage to assess positive surgical boundaries, recurrence of biochemical prostate-specific antigen (PSA), and cancer-specific survival after prostatectomy. This volume is a better indicator of the surgical limit than other factors such as

Gleason value and extracapsular elongation. The extent of damage also serves as an independent PSA recurrence variable, which is an early sign of recurrent disease that may require life-saving radiotherapy. In addition, wound size predicts cancer-specific survival more than variables such as lymphadenopathy, seminal vesicle invasion, and Gleason score.

When prostate lesions are detected by MPMRI, the nature of the lesions is important in selecting appropriate treatment options. Accurate classification of prostate damage IRMMP can prevent biopsies in men with low-grade tumours, reduce the number of biopsy nuclei, and reduce the incidence of high-diagnosis and false-negative biopsies. Reduction of unnecessary biopsies is important because potential complications of TRUS biopsies include haematuria, lower urinary tract symptoms, and transient erectile dysfunction. In addition, the number of biopsy nuclei obtained increases the risk of complications, including rectal bleeding, hematospermia, haemorrhagic complications, and severe urinary retention. In addition, excessive detection of PCA can cause serious psychological damage to quality of life and increase the risk of over-treatment. Excessive treatment side effects following radical prostatectomy and radiotherapy include urinary incontinence, bleeding, and fistulae, as well as erectile dysfunction.

Artificial intelligence (AI) is a good tool to improve the detection of prostate damage, the characterization of damage, and the quantification of damage. AI can systematically evaluate pMRI images. Machine learning (ML), AI sector and its sub-discipline, deep education (DL) One of the attractive methods of medical imaging is the ability to interpret large amounts of data. Applying ML to prostate pMRI data can improve imaging-based clinical decisions. The purpose of this review is to summarize (1) prostate organ division, (2) prostate lesion detection and segmentation, and (3) obtaining ML applications for prostate pMRI that relate to prostate lesion characterization

## 2. Related Works:

There are certain widely available medical imaging techniques, such as X-ray mammography, ultrasound imaging (US), and magnetic resonance imaging (MRI), that are used alone or in combination for cancer screening. breast. The most commonly used diagnostic imaging protocol for an asymptomatic patient consists of referring the patient to a biopsy procedure to confirm the diagnosis of breast cancer if the patient presents with a suspicious X-ray mammogram and a U.S. image. X-ray mammography, which is associated with the risk of ionization, is of limited sensitivity in women under 50 years of age. Although the American Cancer Society recommends regular breast cancer screening with X-ray mammograms in older women, it also recommends the use of X-ray mammograms for breast cancer. breast. X-ray mammography is not used for the imaging of dense breast

tissue, which is usually observed in younger women. Another imaging technique used for breast cancer imaging is American imaging. When X-ray mammography raises a suspicion that contradicts American images, an MRI is performed before the patient is referred for a biopsy procedure. Due to the low contrast of soft tissues and the high dependence of the operator, American imaging is not the most effective means of detecting breast cancer. American imaging and X-ray mammography provide morphological information about the breast. As in the early stages, breast cancer does not cause significant morphological changes, and X-ray mammograms and American imaging are not suitable for early detection of breast cancer.

MRI is a non-invasive imaging technique that does not involve ionizing radiation. It may offer better sensitivity than X-ray mammography or American imaging for breast cancer. Imaging of dense breast tissue and breast implants can be successfully achieved using MRI, but they cannot be performed using an X-ray mammogram. MRI plays an important role in the diagnosis of primary occult breast cancer in patients with axillary lymph node metastases, as well as in the monitoring and repeat of neoadjuvant chemotherapy. It offers good spatial resolution and is also useful for indicating whether breast cancer has spread to the breast wall. The quality of MRI depends on the patient's hormonal status, so contrast agents are needed. It is an expensive method of identification and therefore has the disadvantage of being unavailable. It takes longer than mammography. In addition to high costs and high imaging time, MRI has other limitations, such as low specificity and high false positives. Prior to surgery, this low specificity of MRI can lead to pathological confusion, allowing surgeons to perform more extensive breast cancer surgeries. It does not improve the overall survival rate, nor does it reduce the local recurrence rate. Although MRI is generally considered more accurate than X-ray mammograms, it can sometimes prevent breast cancer, especially if a particular patient has calcium deposits that can be detected by X-ray mammography. X. Due to low specificity, high cost, need for contrast agents, acceptability for pregnant women and patients with metal implants, MRI is not the best imaging modality for early detection of breast cancer.

Angiogenesis, that is, the formation of new blood vessels, is a key feature in the detection of malignancies. This characteristic can be determined by examining the breast with optical radiation in the NIR (near infrared) region. However, pure optical imaging supports spatial resolution with increasing soft tissue depth, while photoacoustic imaging (PA) can maintain good spatial resolution in tissues. PA imaging is a hybrid imaging technique developed based on PA effect. PA effect, after a short absorption of laser light (nanoseconds), the light-absorbing material (soft tissue) produces American waves.

The absorbed light energy results in localized heating in the light-absorbing material, which increases the pressure, and this pressure is released in the form of broadband American waves. Because light is used for PA imaging, PA imaging can determine functional information regarding the optical properties of tissues, which change with the distribution of blood vessels, as well as other chromophores (light-absorbing tissue elements). ) Cloth. At the same time, PA images are not a problem of poor spatial resolution in deep soft tissues because they reveal more undisturbed American waves in the soft tissues. The low-intensity ionizing laser light used in PA imaging is not harmful to health, unlike the ionizing radiation associated with X-ray screening mammography. Another advantage of PA imaging is that the capture technology is similar to PA imaging and the United States, so that a commercially available American imaging system can be modified to produce a dual-mode PA and US imaging system. This dual-mode system is used to obtain simultaneously recorded PA and US breast images that can be used for early detection of breast cancer. Using the morphological indicators provided by the American images, it is possible to identify at an early stage the malignancy that the PA image has already detected. Photoacoustic imaging (PA) systems are generally divided into two categories: PA tomography and PA microscopy. In PA tomography, a large-diameter pulsed laser beam is used to irradiate the tissue surface, and American different transducer networks (flat, linear, spherical, hemispherical, circular, cylindrical) are used for tissue / organ scanning. Erected roads. PA signals generated by tissues. 2D grayscale images (scan B, scan C) are generated using PA reconstruction algorithms with the obtained PA data. The scheme of the PA tomography (PAT) system for the detection of breast cancer is shown in Figure 1, which describes the process of generating the PA signal from the breast and the process of generating PA images at the levels of grey from the received PA signals.

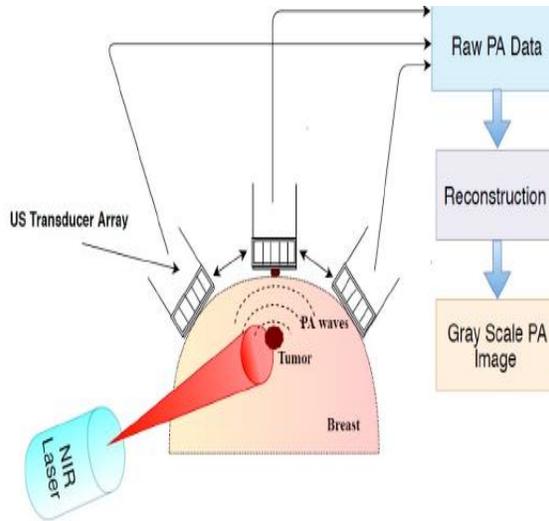


Figure 1. Schematic of the PAT system for breast cancer detection.

American cylindrical, circular, spherical, and hemispherical grids should represent major parts of the region, so these ranges are not suitable for in vivo imaging, with the exception of some animal images or breast cancer. On the other hand, American flat and linear networks can be widely used for in vivo imaging because they can operate with limited access. In the case of in vivo breast imaging, it is not possible to use American spherical networks because the entire area around the organ must be imaged. In such cases, if access is limited, American flat and linear tables can be used. However, some researchers have used hemispherical sequences in breast imaging in the United States. Reconstruction algorithms are mainly variants of posterior projection algorithms used to recover spatially differentiated PA signals generated at each site in tissues. In PA microscopy, tissues / organs are illuminated using a tightly focused beam, and the PA signal is usually detected using a single-element-focused American sensor. Tissues / organs are scanned by an American sensor, as well as certain pathways through a laser beam, and the PA signals received by the PA sensor can be used directly to generate 2D PA images. Using contrast media, PA imaging can significantly improve contrast and imaging depth. In cancer detection, there are two strategies for targeting contrast agents: a passive and an active targeting strategy. The physical properties of the tumour, such as improved permeability and retention (EPR) effect, are used for the passive target. This setting is more important in xenograft tumour models than in human patients. An active targeting strategy uses molecules that can be selected for a specific target. These binding molecules or target fragments co-exist with contrast agents prior to administration. The researchers used animal studies to detect breast cancer using neocyanine green nanoparticles

(ICG), methylene blue, Evans blue and separation, and checkpoints (SLN).

This review article attempts to show an in-depth analysis of previous research on the development of HSP imaging technology for breast cancer detection. Some previous research papers show a comparative analysis of PA different imaging system parameters. In the review paper, Menke] focused on clinical trials in human patients using prototypes developed by the Deterrent study groups until 2014 and provided a comparative analysis of the configuration. Determination of system and their function parameters for D\_Erent prototypes for breast cancer imaging. In another review article on the clinical application of PA imaging, Jakrisson et al. summarizes the latest advances in PA imaging for the treatment of breast cancer based on the results of clinical trials in various study groups. Vallur and others participated. Presented a review article presenting complex PA imaging modalities, highlighting the clinical application of PA imaging modalities in new cancers. Summarizing various previous studies on brain, breast, lung, and prostate, thyroid, and skin cancers, Gargiulo et al. describes previous applications of PA imaging for cancer detection using endogenous and exogenous contrast agents. Steinberga et al, presented various clinical studies performed using PA images. Some recent reviews of articles have reported advanced PA imaging systems as well as clinical trials for the diagnosis of breast cancer using PA imaging.

The transformation of any medical imaging system into clinical practice is based on its gradual development, beginning with the proof-of-concept stage, when the system is tested on digital phantoms. Following successful conception studies, the system is tested in vivo in animals using ghosts that mimic human tissues. In the final stage, the system is evaluated in carefully designed clinical trials involving human patients. At each stage, based on the results of research studies, the system is modified and perfectly adapted to its end-use requirements in the clinical environment. Our review provides a complete picture of the development of photoacoustic imaging (PA) for the treatment of breast cancer based on preclinical and clinical studies conducted by several research groups. Especially in deep tissue applications, PA imaging systems are not sufficient to detect endogenous contrast malignancies. To see the effectiveness of PA imaging in deep breast imaging applications, its performance must be evaluated using exogenous contrast agents. Animal studies have been performed using a variety of contrast agents, such as dyes and nanoparticles, to detect breast cancer. Our review presents the results of these animal studies using contrast agents to detect breast cancer and the control layer lymph nodes (SLN). To understand the imaging potential of PA for the use of contrast agents such as dyes and nanoparticles in the detection of SLT, a summary of various studies

describing the benefits of PA imaging with contrast agents for the detection of SLN is present. It gives readers a complete picture of the development of PA imaging systems for the treatment of breast cancer. Recent peer-reviewed articles focus on clinical imaging studies of PA, including ghost studies, animal studies using endogenous and exogenous contrast agents (dyes and nanoparticles) for liver cancer. Breast as well as SLN detection and ex vivo studies in human breast tissue.

To understand the effectiveness of PA imaging, its function should be compared to conventional imaging techniques for breast cancer. This report provides a detailed comparative analysis of PA imaging systems with conventional imaging systems used to detect breast cancer, based on clinical results reported by various study groups. PA spectroscopic imaging can be used to measure the density of dye-absorbing elements such as oxyhemoglobin, deoxyhaemoglobin, melanin, and lipids in soft tissues. This allows us to assess the degree of oxygen saturation, total haemoglobin level, lipid content, and so on. Between D\_Event breast pathologies (normal, hyperplasia, DCIS and IBC). To explore the potential of HSP spectroscopic imaging systems, this report provides a summary of HSP spectroscopic imaging studies conducted by various research groups. It has been found in the literature that PA images can be used to monitor the e-efficacy of anti-cancer therapies, such as chemotherapy or molecular targeted therapy, by altering associated vascular PA images. on tumours. Only a few studies have reported the potential of PA imaging in the monitoring of breast cancer treatment, and the results of this review are summarized in this review. In addition to a detailed comparative analysis of the parameters of different PA imaging systems used by deferent study groups until 2019, this review attempts to present clinical evidence to support the use of PA imaging in breast cancer detection. The main points of this report are summarized in Table 1.

Table 1. Highlights of the presented review.

Based on the study results reported by various research groups beginning from 1997 to 2019, this review provides:

- A complete picture of the evolution of photoacoustic (PA) imaging for breast cancer management.
- A detailed comparative analysis of PA imaging with other conventional imaging techniques used for breast cancer detection.
- Answers to the issues related to the role and utility of PA imaging technology for the detection and diagnosis of breast cancer.
- The utility of spectroscopic PA imaging studies to differentiate between different breast pathologies.
- The potential of PA imaging technology for breast cancer treatment monitoring.

This summary document is organized as follows: "Methods" describes the list of different documentary research databases, search keywords and search period. Summarizes the results of the results listed in the Outcomes Methods section and provides a comprehensive overview of the research work done by the Deferent research teams to use PA imaging technology in breast cancer management. It is divided into four subgroups with detailed information on phantom studies, animal studies, ex vivo and

in vivo studies in humans, and animal studies are divided into groups with endogenous and exogenous contrast results (including SLN imaging). The configuration parameters of PA different imaging systems are discussed, as well as the configuration information developed by different research groups. It provides a detailed discussion of the potential use of HSP imaging technology in the detection of breast cancer compared to traditional imaging techniques such as American imaging, X-ray mammography, and MRI. based on the results of in vivo studies performed. The last section, " " " " " " ", highlights further research needed to translate technology from the laboratory environment into clinical practice.

### 3. Materials and Methods

Imaging plays a major role in CE patient management. Although the EC formally operates under the auspices of the International Federation of Gynaecologists and Obstetricians (FIGO), preoperative imaging studies guide primary surgery and are particularly useful for stratifying high-risk patients. Lymphadenectomy - the main clinical problem. Although the EC has guidelines for advanced pre-operative imaging, different imaging options and different local choices for access to advanced imaging equipment may lead to practices in changing centres. In humans, transvaginal ultrasound and / or magnetic resonance imaging (MRI) is usually performed preoperatively to assess the size of the local tumour. Computed tomography (CT) alone or in combination with CT positron emission tomography (PET-CT) can be used to assess both abdominal dilatation and pelvic and periarticular lymph nodes. MRI, PET-CT, CT and single photon computed tomography (SPECT) were used in EC animal models to describe and monitor tumour growth. In addition, these imaging techniques allow for non-invasive evaluation Quantification of treatment efficacy through new therapies and imaging markers that are closely related to response to treatment are described. Preclinical EC tumour growth monitoring by ultrasound is also a valuable adjunct to these imaging techniques; however, we do not know of any previous EC studies using this method. Optical imaging using fluorescence can be used.

Optical imaging using fluorescence and bioluminescence has been widely used as an adjunct in preclinical EC studies to determine control layer lymph nodes (SLN) EC with high accuracy.

**MRI:** MRI is a highly versatile modality with standard sequences yielding high soft-tissue resolution providing detailed information on anatomy, and advanced imaging techniques allow depiction of functional and microstructural properties of the tissue. Diffusion-weighted (DW)-MRI is a

functional imaging method depicting random diffusion of water molecules that reflects microstructural tissue characteristics. Typically, malignant tumours exhibit higher cellular density which putatively induces restricted water diffusion; thus, malignant tumours are often distinguished from normal tissue by its restricted diffusion. The DW images using different diffusion weighting (b-values) are used to generate apparent diffusion coefficient (ADC) maps on which the diffusion coefficient of the tissue can be measured. Interestingly, changes in tumour ADC value, with normalization towards non-restricted diffusion during treatment, have been linked to a favourable treatment response. Dynamic contrast-enhanced (DCE)-MRI is a different functional imaging method that depicts microvascular features and yields imaging parameters reflecting tissue perfusion and permeability. For EC diagnosis, conventional pelvic MRI is an excellent method to assess myometrial- and cervical stroma invasion, and both DW- and DCE-MRI are considered promising supplementary MR sequences in EC for the prediction of advanced stage and an aggressive clinical phenotype

To illustrate the anatomical MRI sequence (T1 and T2 weighted) to characterize tumour growth in uterine horns in mice, we have been able to visualize an orthotropic mouse EC model using MRI. Interestingly, the hyper intensive tumour signal in the T2-weighted series and the tumour in the T1-weighted series with enhanced contrast (EC) (relative to ambient myometrial) were similar to those observed in the human EC (Figure 1). In addition, DW excretion DW-MRI with limited B-intensity image intensity and low ADC value on the ADC map is limited in rat tumours, similar to that observed in humans (Figure, Table 1). To better understand the imaging results of conventional imaging and the promising new imaging techniques in the human EC, we read readers in our recent review .

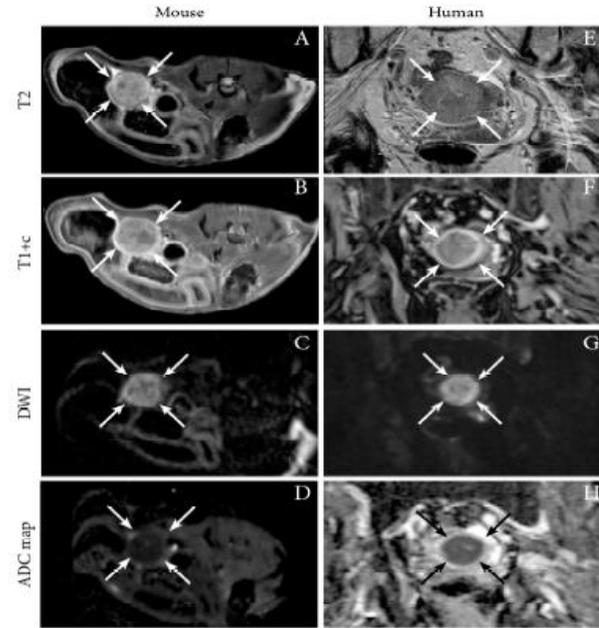
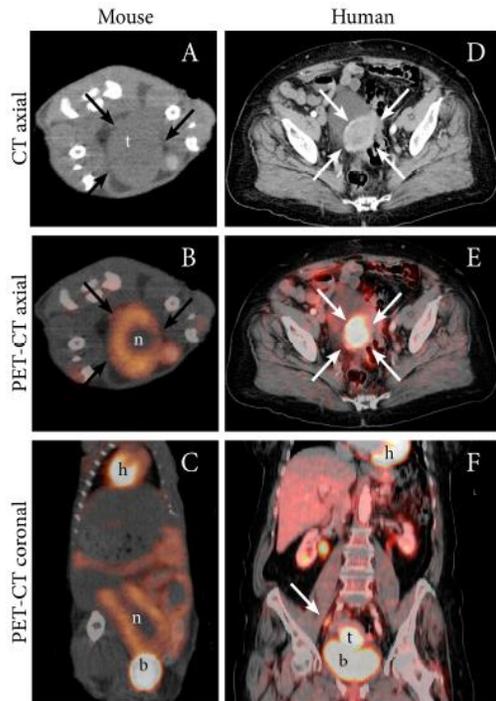


Figure 1. Axial magnetic resonance (MR) images depicting tumour (arrows) in an orthotropic endometrial cancer (EC) mouse model (Ishikawa cells) (A–D), and corresponding axial MRI images visualizing a uterine tumour (arrows) in an 87-year-old woman with EC (grade 2 endometria, FIGO stage IIIC1; same patient as in Figure 2) (E–H). (A, E) T2-weighted images depict hyper intensive tumours and (B, F) T1-weighted contrast-enhanced images (T1+c) depict moderately enhancing uterine tumours. (C, G) Both the preclinical- and human tumours exhibit restricted diffusion with hyper intensity on high b-value diffusion-weighted imaging (DWI) and (D, H) corresponding hypo intensity on the apparent diffusion coefficient (ADC) maps. Images A–D are reproduced under the open access CC BY license from a previous publication.

Loss of phosphatase and tensing homologue (PTEN) is a common genetic aberration in the EC, and loss of PTEN alters the oncogenic signalling pathway in PI3K and recovers by altered homologous recombination (HR). DNA breaks down. In therapeutic studies, T2-weighted MRI was used in a mouse genetic model with PT2 deficiency in the EC to show reduced tumour size due to a synergistic effect treated with PI3K- (BKM120) and poly (ADP-ribose) polymerase. (PARP) inhibitors (olaparibs) (Table 1). Similarly, T2-weighted MRI was used to show the dependence of rapamycin, a rapamycin inhibitor (mTOR) target tumour size, on the elimination of the mammalian target rat genome model, where EC was developed after hepatic kinase tumour suppressor 1B (Lkb1), an AMP-negative AMP regulator. ) -mTOR pathway (Table 1).



**Figure 2.** FDG PET-CT depicting an FDG-avid tumour in an orthotopic patient-derived xenograft (PDX) model of EC (grade 3 endometriosis) (A–C), and in an 87-year-old woman with EC (grade 2 endometria, FIGO stage IIIC1; same patient as in Figure 1) (D–F). (A) In the mouse model, axial non-contrast CT imaging depicts a large tumour (t) (arrows) in the abdomen whereas (B) axial (C) and coronal FDG PET-CT display increased FDG uptake in the periphery of the tumour (arrows) and a central necrotic core (n). (D) In the patient, diagnostic contrast-enhanced axial CT image depicts a slightly enhancing primary tumour (arrows) and (E) axial and (F) coronal FDG PET-CT depict an FDG-avid primary uterine tumour (arrow) and a metastatic par iliac lymph node (arrow). Physiologic FDG uptake in the heart (h), liver, kidneys, renal pelvis and intestines and urinary FDG excretion to the bladder (b) is visible.

**PET:** PET imaging in oncology is most commonly performed using glucose and fluorodeoxy-glucose (FDG) labelled  $^{18}\text{F}$ . Cancer cells are characterized by high metabolic energy expenditure and generally elevated glucose levels. As a result, cancer usually shows FDG formation in PET images. PET-CT can be used to detect lymph node metastases in the EC with high accuracy, so preoperative FDG-PET imaging is often recommended in high-risk ECs. In addition to increasing FDG in metastatic lymph nodes, the primary EC is generally also interested in FDG. Increased FDG absorption in orthotopic tumour samples from Ishikawa cells and human grade 3 endometriosis (PDX) was demonstrated by our team using PET in small animals (Table 1)., and representative images illustrating a similar PET-CT

PDX model and human EC. The results of grade 2 endometriosis (FIGO IIIC1) are shown in Figure 2.

A recent EC preclinical treatment study showed that blocking the PI3K pathway using allergic acid (Table 1) reduced the maximum standard absorption values (SUVmax) in lung cell metastases as determined by EC KLA and AN3CA cell lines.

**CT:** Chest, abdomen, and pelvic CT are widely used to detect lymph node metastases and distant metastases in CE patients [16]. In preclinical studies, CT was used to detect local and advanced disease. In an EC estrogenic-regulated orthotopic model using enhanced contrast CT (EC-CT), the tumor volume obtained from the image during microscopy was positively related to the net tumour weight (Table 1). Computed tomography has also been used to detect lung metastases in a mouse model of the lung gene, where conditional inactivation of the target downstream of the transforming growth factor receptor  $\_$  (TGF $\_$ ), actin-like kinase 5 (Alk5), leads to CE (Table 1). In addition, regression of lung metastases after CT after ovarian surgery indicated that tumours were hormone-dependent.

**SPECT:** SPECT is a nuclear imaging technique based on the detection of gamma rays such as technetium-99m ( $^{99\text{m}}\text{Tc}$ ) and iodine-123 ( $^{123}\text{I}$ ). Clinically, SPECT-CT with  $^{99\text{m}}\text{Tc}$  nanocolloid / tin colloid was used to identify SLN stratification for lymphadenectomy in low-risk CE patients [19, 31]. In preclinical EC models, SPECT was used to monitor the treatment of two degenerative strains of oncolytic viruses (Copenhagen virus and Why the vaccinia) in subcutaneous xenografts of AN3CA and ARK-2 cell lines (Table 1).

**Optical Imaging:** Optical imaging, bioluminescence (BLI), or fluorescence (FLI) techniques can be an excellent tool for visualizing tumour growth, metastasis, and treatment effects in preclinical models. BLI requires transfection with reporter genes that express luciferase, and because normal cells do not express luciferase, BLI offers excellent sensitivity for tumour cell detection and a high signal-to-noise ratio. Unfortunately, this proves to be unsuitable for BLI imaging PDX models where cell mutation is not required. In preclinical CE, BLI imaging has long been used to monitor tumour growth and metastatic spread and to demonstrate the growth of estrogen-dependent tumours in orthotopic mouse models (Table 1). A representative BLI image of a rat implanted orthotopically with HEK1B tumour cells expressing luciferase is shown together with the corresponding neuroscopy results. In addition to visualizing tumour growth, BLI can use activity from specific signalling pathways. Identification of significantly reduced NF- $\kappa$ B pathway activity after treatment with the thermal shock protein inhibitor NVP-AUY922 (Table 1)

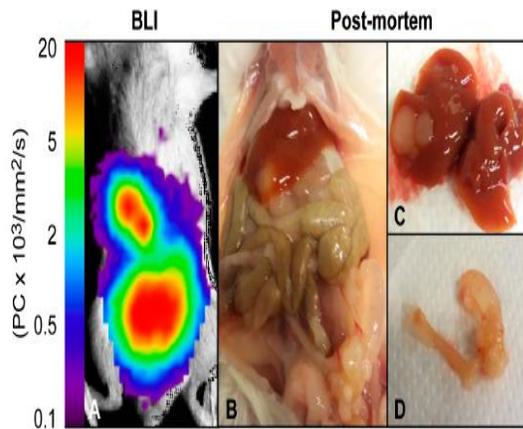


Figure 3. Bioluminescence imaging of an orthotopic EC mouse model. (A) Bioluminescence image and (B) post-mortem examination of a female NSG mouse ten weeks post orthotopic implantation with luciferase-expressing Hec1B cells. (D) Post-mortem examination revealed a primary uterine tumour and (C) liver metastases corresponding to the bioluminescence signal.

Fluorescent imaging (FLI) techniques are increasingly being used in preclinical studies. Microbiological and red fluorescence by ultrasound, recently produced in small doses of 5-aminolevulinic acid, has been shown to visualize EC xenografts after slaughter mediated by the enzyme ferrochelatase polyethylene mine. In addition, to study the anticancer effect of the mTOR inhibitor rapamycin, FLI using a green fluorescent protein was used in EC models with degenerative PTEN expression levels. Rapamycin has been shown to inhibit tumour growth in negative PTEN EC tumours compared to positive PTEN tumors. Similar to SLN mapping in humans with fluorescent dyes, fluorescence-guided resection of primary tumors and metastatic lymph nodes in an EC orthotopic rabbit model provided good sensitivity and specificity.

## 4. Conclusions

AI applications Prostate MRI are a better tool for more efficient and effective image interpretation that improves care. In pure imaging, ML has significantly improved prostate division and volume assessment. If better-stored data on prostate damage are available, ML may be more effective in detecting, quantifying, and characterizing the damage. As ML evolves, it will no doubt change the workflow of radiologists by doing very simple things in interpreting images. However, ML does not replace the key role of radiologists in solving complex clinical problems. AI is ready to improve radiologists' decisions. This helps radiologists take better care of their patients without overcoming the need for radiologists. Similarly, ML's ability

to evaluate complex data sets in a variety of domains suggests that this technique facilitates the combination of complex imaging, such as pMRI, with analysis of emerging biomarkers or tumour genetics. Thus, ML forms the basis of radio genomics, allowing the integration of imaging data, analysis of blood chemistry, and pathology in complex models that can predict a therapeutic response. Starting with large data sets and more sophisticated mathematical methods, the ML patient's prostate MP develops fully automated tools that receive MRI images, then outlines the range of desired functionality as well as the probability for a range of pathologies.

## References

1. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer statistics, 2017. *CA Cancer J. Clin.* 2017, 67, 7–30. [CrossRef] [PubMed]
2. Hugosson, J.; Carlsson, S. Overdetection in screening for prostate cancer. *Curr. Opin. Urol.* 2014, 24, 256–263. [CrossRef] [PubMed]
3. Schröder, F.H.; Hugosson, J.; Roobol, M.J.; Tammela, T.L.; Ciatto, S.; Nelen, V.; Kwiatkowski, M.; Lujan, M.; Lilja, H.; Zappa, M.; et al. Screening and prostate-cancer mortality in a randomized European study. *N. Engl. J. Med.* 2009, 360, 1320–1328. [CrossRef] [PubMed]
4. Oberlin, D.T.; Casalino, D.D.; Miller, F.H.; Meeks, J.J. Dramatic increase in the utilization of multiparametric magnetic resonance imaging for detection and management of prostate cancer. *Abdom. Radiol. (Ny)* 2017, 42, 1255–1258. [CrossRef] [PubMed]
5. Monni, F.; Fontanella, P.; Grasso, A.; Wiklund, P.; Ou, Y.C.; Randazzo, M.; Rocco, B.; Montanari, E.; Bianchi, G. Magnetic resonance imaging in prostate cancer detection and management: A systematic review. *Minerva. Urol. Nefrol.* 2017, 69, 567–578. [CrossRef] [PubMed]
6. Vitale, M.; Cantoni, C.; Pietra, G.; Mingari, M.C.; Moretta, L. Effect of tumour cells and tumour microenvironment on NK-cell function. *Eur. J. Immunol.* 2014, 44, 1582–1592. [CrossRef]
7. Vanherberghen, B.; Olofsson, P.E.; Forslund, E.; Sternberg-Simon, M.; Khorshidi, M.A.; Pacouret, S.; Guldevall, K.; Enqvist, M.; Malmberg, K.-J.; Mehr, R.; et al. Classification of human natural killer cells based on migration behaviour and cytotoxic response. *Blood* 2013, 121, 1326–1334. [CrossRef]
8. Gong, J.H.; Maki, G.; Klingemann, H.G. Characterization of a human cell line (NK-92) with phenotypical and functional characteristics of activated natural killer cells. *Leukemia* 1994, 8, 652–658.
9. Dahlberg, C.I.M.; Sarhan, D.; Chrobok, M.; Duru, A.D.; Alici, E. Natural Killer Cell-Based Therapies Targeting Cancer: Possible Strategies to Gain and Sustain Anti-Tumor Activity. *Front. Immunol.* 2015, 6. [CrossRef]

10. Rezvani, K.; Rouse, R.H. The Application of Natural Killer Cell Immunotherapy for the Treatment of Cancer. *Front. Immunol.* 2015, 6. [CrossRef]
11. Garrod, K.R.; Wei, S.H.; Parker, I.; Cahalan, M.D. Natural killer cells actively patrol peripheral lymph nodes forming stable conjugates to eliminate MHC-mismatched targets. *Proc. Natl. Acad. Sci. USA* 2007, 104, 12081–12086. [CrossRef]
12. Fang, F.; Xiao, W.; Tian, Z. NK cell-based immunotherapy for cancer. *Semin. Immunol.* 2017. [CrossRef] [PubMed]
13. Lee, B.J.; Mace, E.M. Acquisition of cell migration defines NK cell differentiation from hematopoietic stem cell precursors. *bioRxiv* 2017, 142380. [CrossRef]
14. Somersalo, K.; Saksela, E. Fibronectin facilitates the migration of human natural killer cells. *Eur. J. Immunol.* 1991, 21, 35–42. [CrossRef]
15. Taub, D.D.; Sayers, T.J.; Carter, C.R.; Ortaldo, J.R. Alpha and beta chemokines induce NK cell migration and enhance NK-mediated cytotoxicity. *J. Immunol.* 1995, 155, 3877–3888