Radiolabelled antibodies and PET-CT: A potentially novel approach to screen for pancreatic ductal adenocarcinoma

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Pancreatic ductal adenocarcinoma is a dangerous malignancy, particularly due to a lack of accuracy in detecting it until it reaches later stages. This study outlines a proposed method to screen for PDAC with a high degree of accuracy in high-risk populations. It does this by evaluating the specificity, sensitivity, and accuracy of existing methods of PDAC screening and comparing it to the same proposed values in screening using the proposed modality. The proposed methodology of carrying out screening involves conjugating 99m-Tch to antibodies that bind to the MUC-1, MUC-4 and Mesothelin and injecting the resulting mixture into tissue surrounding the pancreas and using a PET-CT scan. The estimated specificity (84.6%), sensitivity (100%) and accuracy (84.6%) of this method were similar to existing modalities. This method has also shown indications of having greater potential in screening for early-stage PDAC and precursor lesions allowing for a possible diagnosis of future malignancy. However, this proposed modality has limitations e.g. the broad range of high-risk factors for PDAC and how they interact with each other. This impacts the prevalence of PDAC and makes determining the high-risk population difficult. In summation, this method represents a possible, effective, new avenue in screening for PDAC.

Keywords: Pancreatic Ductal Adenocarcinoma, PET-CT, Mucins, Mesothelin, Radiolabelled Antibodies

Introduction

Pancreatic cancer is the 10th most common type of cancer in the United Kingdom with approximately 10,500 people diagnosed with pancreatic cancer each year. Furthermore, pancreatic cancer is the 5th most common cause of cancer death accounting for 6% of all cancer deaths. Projections suggest that by 2040 there could be 16,000 pancreatic cancer cases yearly.[1] There are several familial and non-familial factors that may raise an individual's risk of developing pancreatic cancer, familial factors include Peutz-Jeughers Syndrome and hereditary pancreatitis, while non-familial risk factors include smoking, obesity, alcohol consumption, and diet.[2,3]

Pancreatic cancer occurs when healthy pancreatic cells accrue mutations in their DNA. These mutations cause the cells to grow uncontrollably and continue to live after normal cells die. These cells form a sheet or mass of cells called a tumour.[4] In order to prevent such cases, tumour suppressor and DNA repair genes are supposed to activate, slow cell division, trigger apoptosis, and restore damaged DNA. However, if these genes become damaged, they can cease to function properly allowing for cells to divide uncontrollably and accrue additional mutations. Proto-oncogenes function to aid in cell division but if they become damaged, mutated, or overproduced it can cause permanent activation accelerating cell division, which causes cells to grow out of control leading to cancer.[5] Pancreatic cancer is difficult to diagnose at an early age with the majority of pancreatic cancers having metastasised (expansion of the cancer to a secondary location within the body) by the time of initial diagnosis and only 9.7% of cancers restricted to a local level. One of the reasons for this late-stage diagnosis is that many patients are asymptomatic until further progression of the disease leading to a lack of early warning symptoms.[6]

Pancreatic Ductal Adenocarcinoma (PDAC) is a highly aggressive malignancy and the most common subtype of pancreatic cancer accounting for more than 90% of all cases.[7] The frequency of this cancer subtype makes it a good candidate for testing the efficacy of new screening and diagnostic methods.[8] Recently a new screening method has been developed for prostate cancer which uses a PET-CT scan and radioisotope conjugated antibodies which attach to cancer antigens and enhance contrast with surrounding tissue.[9] In order to counter the high mortality posed by PDAC, there is a need for a screening modality able to detect early-stage PDAC. This paper aims to investigate if the principal underlying this screening method can be applied in the detection of PDAC.

Research Question

Evaluating the effectiveness of a radio-labelled antibody PET-CT (Positron Emission Tomography with Computed Tomography) screening method in screening for PDAC (Pancreatic

Ductal Adenocarcinoma) in high-risk populations compared to existing screening tools in relation to factors of specificity, sensitivity, diagnostic accuracy and early screening of PDAC.

Literature Review

Existing Indicators for Developing PDAC

At present, there are a range of familial and non-familial factors that influence the probability of developing PDAC. For the purposes of the screening method proposed in this paper, current guidelines regarding screening for pancreatic cancer are to be adopted. Therefore, a genetically high-risk population is made up of those individuals with the following characteristics: individuals who have Peutz-Jeghers Syndrome, an inherited condition which raises the risk of developing certain gastrointestinal tract cancers or the following germline gene mutations: CDKN2A, BRCA1, BRCA2, PALB2ATM, MLH1, MSH2, or have a first-degree family member with pancreatic cancer who in turn has a first-degree family member with pancreatic cancer.[2] Screening for PDAC among this population should start between 40 and 50 years of age or 10 years before the youngest affected blood relative at the time of their diagnosis.[10]

An environmentally high-risk population is made up of those individuals who have been subjected to the following external factors: cigarette smoking which accounts for approximately 11-32% of pancreatic cancer cases, obesity with a sedentary lifestyle, having an uneven diet with a lack of fibre, vegetables, and fruit with an excess of saturated fat and processed meat intake, a Heliobacter Pylori infection, or a Hepatitis B or C infection.[3]

Current Screening Methods for Pancreatic Cancer & Shortcomings

Present detection methods for pancreatic cancer rely on various screening modalities involving the use of fine needle biopsy advised by ultrasonography, magnetic resonance imaging, positron emission tomography, and various blood tests comparing against specific antigens.

Endoscopic Ultrasonography

Endoscopic ultrasound (EUS) has become the gold standard for the detection of pancreatic cancer and has been shown to have a higher specificity and sensitivity than other modalities as well as a low rate of complications.[11] EUS is a minimally invasive imaging technique that involves inserting an endoscope into the GI tract which is used alongside high-frequency sound waves to detect lesions and irregularities.[12] Studies have shown high specificity (89-100%), sensitivity (92-100%) and accuracy (86-99%) in the detection of pancreatic malignancies using EUS. Typically used in conjunction with fine needle aspiration, the visualization of the pancreatic lesion by ultrasonography is used to obtain a tissue sample for cytological evaluation. In the case that a fine needle aspiration does not provide sufficient tissue for the molecular and histological evaluation of a malignancy, a fine needle biopsy may be carried out in order to differentiate a malignancy from other pancreatic disorders and lesions.[13] An advantage of EUS is that instead of requiring a separate biopsy procedure a sample of tissue can be taken through the needle attached to the endoscope thereby reducing the potential for further complications. However, fine needle aspiration (FNA) and fine needle biopsy (FNB) poses the risk of a serious complication called Fine Needle Seeding (FNS) in which there is an iatrogenic tumour cell implantation along the puncture route. In FNS, tumour cells are spread outside the original site of the malignancy, this risk ranges up to 1.4% for FNA and up to 7.8% for FNB.[14] Thus the need for EUS-FNA and EUS-FNB must be carefully measured against the possible benefits and risks involved particularly due to the low specificity, sensitivity and accuracy of EUS-FNA in identifying tumours less than 10mm compared to the severity of possible side effects.[15]

Magnetic Resonance Cholangiopancreatography

Magnetic Resonance Cholangiopancreatography (MRCP) is a specialized form of Magnetic Resonance Imaging (MRI), in which computer software is used to generate images of the pancreatic and bile duct regions where tumours often form.[16] MRCP has increased in popularity since its invention with improvements in all areas of application. As of today, the specificity, sensitivity, and accuracy of MRCP in detecting Pancreatic Cancer stand at 88%, 100% and 98% respectively.[17] A possible advantage of MRCP is that it has shown positive indications and potential application in the early detection of pancreatic cancer. However, PDAC cannot be diagnosed by imaging alone, thus a biopsy would be needed to verify the diagnosis. Nonetheless, MRCP is one of the foremost methods of detecting pancreatic cancer globally.[18] Further MRCP has extremely low risks of complications which makes it ideal for an initial assessment of the lesion prior to any clinical procedure.

Miscellaneous Pancreatic Cancer Detection Methods

Endoscopic Retrograde Cholangiopancreatography (ERCP) is a procedure used to detect and diagnose problems of the lower GI tract and associated glands in which dye is injected into the affected tissue to aid with detection on an X-Ray.[19] In many places today, MRCP has replaced ERCP since MRCP is non-invasive and has minimal associated complications. Certain

studies indicate that ERCP and associated serial pancreatic juice aspiration cytological examination (SPACE) obtained by endoscopic nasopancreatic drainage (ENDP) might be useful in the detection of very early-stage pancreatic cancer.[20]

Presently PET-CT scans are used in the detection of pancreatic cancer through the use of 18-Fluorodeoxyglucose to map glucose metabolism.[21] As cancers grow, they use a series of signalling pathways to rapidly increase their glucose uptake. Therefore PET-CT scans are given a high sensitivity and accuracy for the detection of pancreatic cancer with ranges of 85%-97% and 85%-% respectively.[21,22] However, due to interference by other non-cancer based pancreatic lesions, there is a considerably wider and lower range of specificity for the detection of pancreatic cancer, from 50%-87%.[21]

Potential of a PSMA based screening method for Pancreatic Cancer

While there are several methods of targeted pancreatic cancer screening currently undergoing review, immunoassays, liquid biopsies, and volatile organic compound detection, the PET-CT in conjunction with radiolabelled antibodies shows the greatest promise.[23]

Recently, a novel technique combining biomarkers with imaging for the detection of prostate cancer has been developed. However, there are few imaging agents that have been approved by the national regulatory institutions of various nations. This technique has provided higher specificity and sensitivity in the detection of prostate cancer compared to existing therapies. It also provides the ability to detect cancerous lesions between 3-10mm smaller than those that can be accurately detected by other pancreatic detection methods. This is vital to the early detection, resectability and treatment of pancreatic cancer.[24]

This technique would work by a series of high frequency, overexpressed and neo-expressed antigens being identified, and the most effective complementary monoclonal antibodies (mAb) being found. Multiple antigens would be used to increase contrast with surrounding tissue which expresses these antigens at low levels. Second, these mAbs would be conjugated with a radiometal ion. Next, these mAbs would be injected into a solution in the area around the pancreas to increase the speed and uptake of antibodies by the antigens. Finally, a PET-CT scan would be carried out and the scan would be evaluated for irregular levels of radioisotope uptake. If this is detected a biopsy would be carried out in order to confirm the diagnosis. In short, this screening modality would target lesions at a cellular level leading to detection in earlier stages of pancreatic cancer and a lower risk of the tumour metastasising prior to detection. These steps are outlined in Figure 1 using the components specific to this paper.

Possible Components of a PSMA Based PET-CT scan in Pancreatic Cancer Screening

In light of the above application of radiolabelled mAbs and binding antigens, a theoretical combination of antigens and complementary radio-labelled antibodies can be proposed. This could allow for the detection of early-stage pancreatic cancer, possibly even allowing for the detection of stage 0 pancreatic cancer more commonly known as stage 3 Pancreatic Intraepithelial lesions, (PanIn) a precursor lesion to PDAC, due to a shared expression of antigens between PanIn lesions and PDAC.[25]

From the outset, the biggest hurdle is picking the correct target antigens in developing an imaging agent for a Pancreatic PET-CT scan. The first potential target would involve choosing membrane bound and transmembrane antigens that are either over or neo-expressed in PDAC in a high frequency of cases.

When looking at PDAC, the most common antigens in decreasing order are, Mesothelin ($\sim 100\%$), MUC-1 (90%) and MUC-4 ($>80\%$).[26–28] To make the best use of these antigens, it is vital to find and use complementary antibodies with the highest possible blend of specificity and sensitivity in order to ensure that the majority of cases are detected with accuracy. With that in mind this paper uses the antibodies with the highest specificity and sensitivity that could be found at present.

A mesothelin mAb has a high specificity of 94% and an intermediate sensitivity of 62% in an Elisa test for serum testing for mesothelin.[29] The high frequency of mesothelin and the high specificity of the antibody, contribute to low rates of false positives and an excellent use as a diagnostic tool in the evaluation of PDAC. The low sensitivity can be rectified by using the combination of antigens outlined above as they bring a unique combination of highly expressed antigens allowing for more easily detected PDAC tissue. Further, the higher sensitivity of the complementary antibodies again raises sensitivity. The sensitivity of MUC-1 antibody PAM-4 ranges between 86% and 94% in the detection of early stage PanIn lesions and PDAC along with a high specificity.[30] The high sensitivity in the detection of precursor lesions of PDAC leads to better patient outcomes in screening as patient's can be informed and treated before the onset of malignancy. Moreover, the high frequency of expression of MUC-1 helps distinguish it from outliers in mesothelin expression. Finally, the MUC-4 mAb has a sensitivity and specificity of 100% and 90% respectively, both of which will contribute to a higher overall accuracy due to values being higher than both other complementary antigens.[31] In order to determine the most effective radioisotope for diagnostic application it's important to consider type of radiation released, half-life and penetrating power. The best antibody for the labelling of antibodies for a diagnostic application is 99m-Tch due to the fact that it emits low levels of

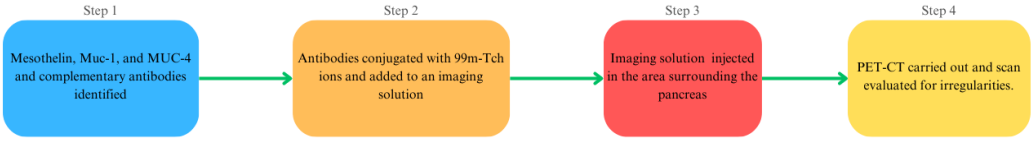

Fig. 1 Potential steps in usage of novel screening modality

gamma radiation which causes minimal damage to surrounding tissue while providing a high degree of penetrating power for easy detection while using PET-CT scans.[32] Illustrated below is a diagram of the cell membrane of a cell exposed to these antibodies.

Results

PET-CT imaging agent for pancreatic cancer has the highest sensitivity of any screening modality save for MRCP. It can also be seen that this modality has a lowered specificity and accuracy due to the variety of antigens that can be picked up by the combination of antibody conjugates. However, since the specificities of the antibodies are measured in immunoassays it is possible for them to be higher in vivo as a range of factors can influence the specificity of an antibody when in sera.[33] Therefore, in Figure 3, there is potential for the specificity and accuracy values to vary from what is stated. Evaluating the differences between the various screening modalities in the receiver operating characteristic curve (ROC), we can clearly see that all modalities are a distance from the random chance line indicating high diagnostic predictive value. We can further see that EUS-FNA has the lowest efficiency of the three screening modalities for pancreatic cancer as it sits furthest from the top left-hand corner. Next, we can see that the proposed PET-CT method and MRCP both have near identical efficiencies in screening for PDAC with MRCP holding a slight advantage. Further, we can clearly see that the proposed PET-CT technique has a high Area Under Curve (AUC) and therefore a high diagnostic accuracy which combined with the high accuracy displayed by the PSMA PET-CT scan indicates more clearly the true accuracy of the proposed method in screening for PDAC, which may approach that of MRCP when discriminating between affected individuals in a sample in a clinical environment. It is clear that the gradient of the ROC curve for EUS-FNA is less steep than the other two modalities, this indicates a higher false positive rate. Moreover, the high AUC values displayed by MRCP and the proposed modality, indicate a higher true positive rate compared to EUS-FNA despite the higher specificity values seen in Figure 3. This is further supported by the higher accuracy shown by MRCP in Figure 3 which directly corresponds to the greater AUC compared to EUS-FNA. Finally, comparing the estimated specificity, sensitivity and accuracy of the proposed modality compared to that of existing modalities in Figure 3, we can see that the specificity of this methodology falls short of that shown by the two major modalities, however, the sensitivity remains higher than EUS-FNA and on par with MRCP due to the array of antibodies and antigens chosen. The accuracy of the proposed modality remains lower than that of the two major modalities due to its lower specificity. Further, considering the efficacy of the PSMA screening modality, this method may should be able to screen for lesions between 3 and 10mm with higher sensitivity and specificity than EUS-FNA.[15,24]

Potential Limitations of Screening Modality

As with many screening modalities, this method also has challenges, disadvantages and limitations associated with its use. As with all antigens, the degree to which they are overexpressed can vary from patient to patient and cancer to cancer. This makes it difficult to create a baseline of overexpression and antibody uptake which should justify a biopsy and histology report to confirm a diagnosis. Furthermore, due to the broad definition of risk factors for high-risk populations for pancreatic cancer, there is a limited understanding of how these factors interact with one another and how they impact the prevalence of pancreatic cancer. This impacts the calculations that go into determining the accuracy of this pancreatic cancer detection method as well as making it difficult to determine the frequency of screening a patient needs to undergo in order to maximise the efficacy of PDAC screening. The primary limitation of this detection method is that although the greater variety of antibodies gives rise to greater sensitivity to the antigens, it also increases the rate of false positives giving rise to potentially unnecessary medical procedures and placing unnecessary stress on patients. Likewise, if the chosen antigens are expressed in other pancreatic lesions this may complicate the diagnostic procedure and lead to other unnecessary tests. Moreover, due to the nature of radioisotopes, the use of these imaging agents poses a burden on kidneys which must be con-

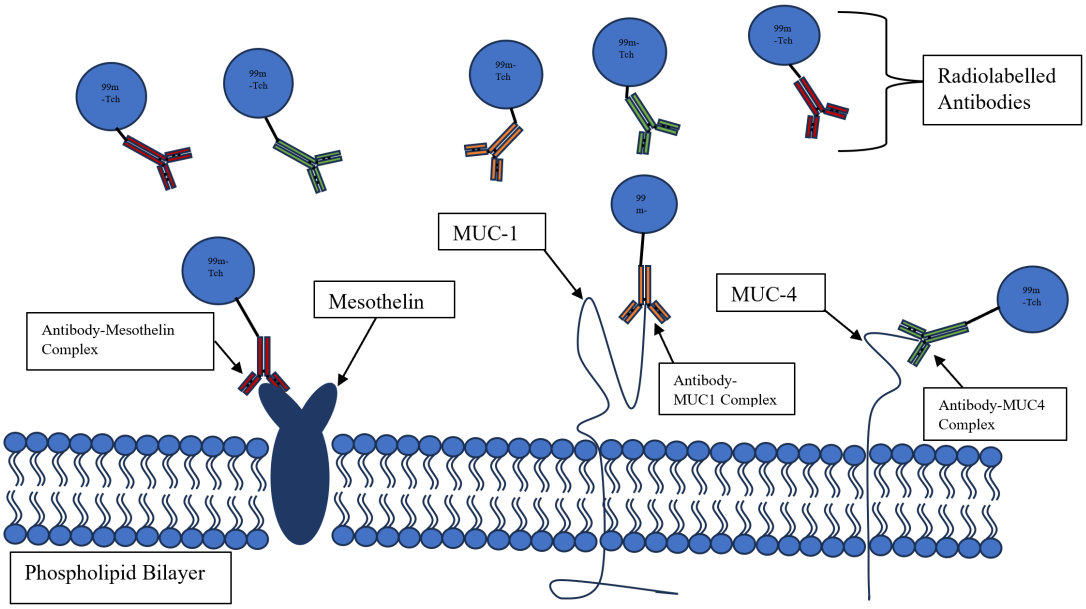

Fig. 2 Cell membrane of affected PDAC cell exposed to Radiolabelled antibodies

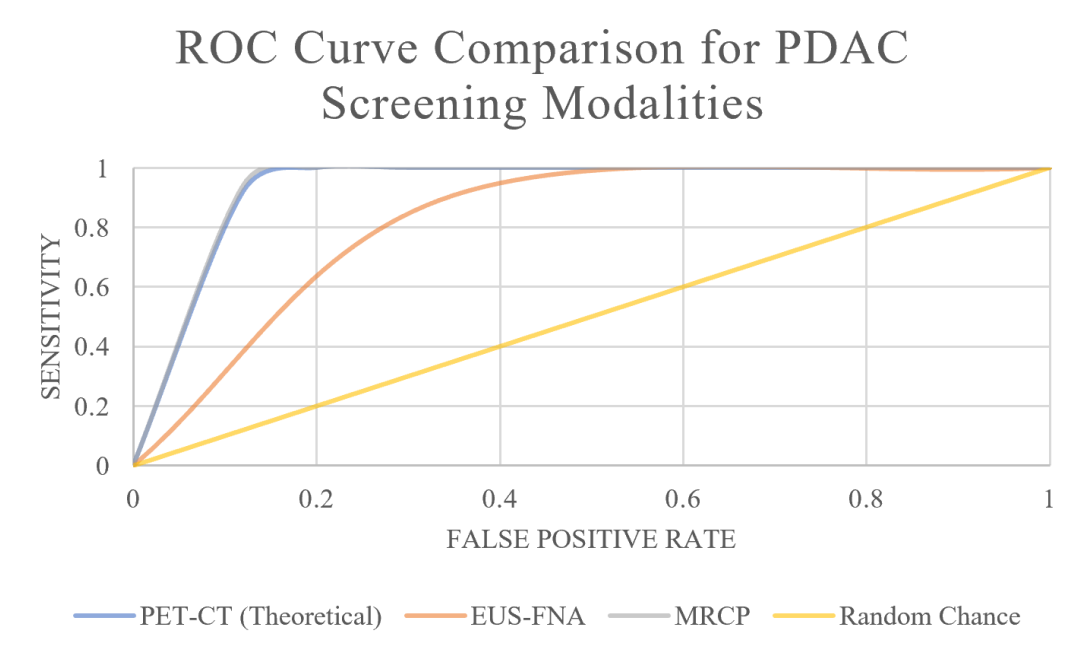

Fig. 3 ROC curve comparison for PDAC screening modalities [17,35–39]

Table 1 Sensitivity, specificity, and accuracy of PDAC screening modalities

Screening Method	Sensitivity	Specificity	Accuracy	References
PSMA Screening	85%	91%	92%	33[34]
EUS-FNA	90.8%	96.5%	91%	34[35]
MRCP	100%	88%	98%	17[17]
Pancreatic Cancer (Estimated)	100%	$> 84.6\%$	$> 84.6\%$	35, 36, 37, 3[3,36–38]

sidered prior to use and may preclude certain groups of individuals such as young children and the elderly from using this method due to the potential for kidney damage which limits the usefulness of this tool. In cases wherein antibodies bind to antigens present in blood circulation and/or common antigens expressed on the surface of other cells, it may impact the diagnostic interpretability of imaging. Thus, instead of contrast between pancreatic tissue, there may be levels of contrast between various regions of the body as the blood carried radioisotope travels throughout the body as well as contrast between the different regions of tissue in the body that regularly express common antigens. This may lead to a greater number of false positives and further, lead to incorrect diagnoses as precursor lesions or local cancers may be confused for metastases. Finally, as this is a theoretical modality there may be confounding factors present in the PSMA PET-CT scan that increase its accuracy which have not been considered and could limit the efficacy of this tool.

In order to deal with the issue of determining a baseline for overexpression of antigens, it may be best practice to establish and modal and mean average for the expression of each antigen in PDAC using clinical studies, then use this information to create an overall modal and mean average and then use these values in conjunction with further clinical studies to find the modal and mean average for overall antibody uptake in affected patients. These values can then be used for comparison when carrying out the test and determining the need for a biopsy and a histology report, they can also be further used to differentiate between cells with normal expression of antigens overexpressed in PDAC. To determine how risk factors for PDAC interact to impact the potential risk for developing PDAC, it would be necessary to carry out a meta-analysis of a large sample of individuals who have had various combinations of the different risk factors and compare it to the number of each combination which have gone on to develop PDAC and finally compare those values with that of the general population to find the overall increase in the risk of developing PDAC. The greater sensitivity of the array of antibodies, and blood circulation of antigens with other cells could be dealt with by taking a number of overlapping images of the affected areas in order to discriminate between truly affected regions and areas with affected blood flowing through them.

Discussion

Only clinical studies can truly determine the efficacy of new screening methods for pancreatic cancer, which limits the amount that literature reviews and quantitative analyses can achieve in this regard. However, because antibody labelling is a novel approach, a lengthy ethical approval period would need to take place, followed by clinical trials leading to several years of delay. Therefore, for the purpose of this paper, quantitative analysis was carried out to estimate the potential efficacy of this novel screening modality.

Quantitative analysis bears great merit in estimating the efficacy of the specific modality as the specificity and sensitivity values of individual antibodies as well as the value for the prevalence of PDAC are readily available, allowing for the combination of the values of these antibodies using the formulae for parallel testing. These values and formulae allow for a reasonable estimate to be made regarding the true specificity, sensitivity and accuracy of the proposed modality. The sensitivity, specificity and accuracy values for this modality approach those of currently used modalities and furthermore, evaluation of PSMA PET-CT imaging indicates that it may be more effective for small lesions, these factors indicate that this could be a promising technology and thus warrants clinical study. There are both few antibody-based imaging agents for pancreatic cancer combined with the fact that PET-CT scans are not being presently used in conjunction with these agents limits the potential efficacy of existing screening modalities. However, the success of PSMA PET-CT scans in detecting prostate cancer in Europe, as well as in clinical trials in the US, signals a clear turning point in this technology. Despite this prostate and pancreatic cancers have distinctly different histopathologies which means that a direct comparison cannot be made between the potential success of PSMA PET-CT and the proposed modality and thus care must be taken when comparing the two malignancies. The possibility of a groundbreaking new screening modality here should not be denied.

With the right combination of labelled antibodies and antigens, it is possible to unlock the potential within scans to detect early-stage pancreatic cancer as the underlying principle of screening using radiolabelled antibodies and PET-CT remains the same. If a proper combination of antibody imaging agents can be used alongside a PET-CT scan, the detection of

pancreatic cancer could end up being far more thorough and complete than if conducted by PET-CT alone or a combination of antibody imaging agents and a PET scan. The use of antigens that are overexpressed in PDAC precursor lesions means that high-risk individuals can be better advised on screening practices and possible needs for treatment prior to the development of a full PDAC. Furthermore, the use of the technology may allow for better detection of metastases to their secondary locations within the body.

The use of scans in this manner is a novel and exciting approach to tackling early-stage detection of cancers. With the existing technologies in this field, the application of this technique is not a far-flung fantasy but a promise that may be realized within the decade. Furthermore, the use of this technique in conjunction with existing screening modalities indicates a promising avenue for the development of novel and enhanced screening modalities.

Ethical Considerations and Clinical Trials

As with all procedures carried out on humans, the safety and security of patients must be guaranteed. Thus, before any modality is authorised for use on humans it must first undergo clinical trials progressing through the various stages and detecting possible faults and complications of the method. Further, it is important to address the potential ethical implications of using radiolabelled antibodies and on patients. Before clinical trials, the approximate safety of the imaging agent must be determined using a limited number(~ 10) of in-human studies to determine pharmacokinetic and metabolic data pertaining to the impacts of the antibodies on the body's organ systems. The first stage of clinical trials the imaging agent required for a PET-CT, would involve testing the agent on a small, handpicked sample (~ 30) comprising of individuals both with and without PDAC and testing for any potential complications and safety concerns, this will ensure that the antibodies and radioisotope don't have any unforeseen impacts on the body. The second stage would take place with a larger sample (50-80) group and would involve determining the quantity of the imaging agent that provides the best results in screening for PDAC out of a predetermined sample of PDAC-positive and negative individuals as well as defining the high-risk population that was mentioned in the limitations, this would involve determining how the various risk factors interact in giving rise to the heightened risk of developing PDAC.The third stage would involve creating a large sample (~ 500) comprised of several hundred individuals and would compare the accuracy of this imaging agent, in conjunction with PET-CT, to other existing screening modalities for PDAC or this modality could be used in testing centres using double-blind testing and investigators who would then compare the modality to other existing modalities such as EUS and MRCP. Further, this stage would involve determining the efficacy of the proposed modality. The final stage involves doing post-marketing research and analysing potential long-term side effects by following up with the patients over the span of several years after the use of the imaging agent such as potential permanent damage done to pancreatic function by antibodies and their radioisotope.[40] These stages are outlined in Figure 5 below. On occasion, at some stage in the course of clinical trials severe potential complications are discovered and the trial may be immediately terminated.

When considering the ethical implications of this imaging agent it is most important to consider the potential harm to patients that can be caused by the radioisotope attached to the antibodies as previously mentioned filtering these elements out of the bloodstream puts strain on the kidneys and thus if a patient has existing risk factors a doctor must consider if screening for PDAC is worth risking damage to the kidneys. Further, it is important to take patient-specific considerations into account such as patient autonomy and informed consent, especially when implementing a novel screening modality. It is essential to objectively inform patients of all pertinent information regarding the imaging agent such as potential complications discovered during clinical trials e.g. potential for kidney damage and allow them to make their own decision. Moreover, researchers have a responsibility to ensure patient well-being, this can be done through several means but first and foremost researchers during clinical trials have the obligation to carefully compile information on any unforeseen effects of the modality on trial patients whether positive or negative and provide this information to the relevant parties such as scientific journals to be disseminated at the end of the trial.

Methodology

A systematic search was carried out of extant scientific literature using Embase, Pubmed and google scholar to obtain access to as many relevant articles as possible between inception to 2023, which reported on the diagnostic sensitivity, specificity and accuracy of all screening modalities for PDAC and for PSMA PET-CT as well as the frequency of antigen overexpression and neo-expression in PDAC and precursor lesions alongside the sensitivity, specificity and accuracy of their respective antibodies. Further, PSMA therapy was investigated as a basis upon which to structure this novel approach to detecting PDAC.

To ensure an effective search strategy key terms were used in order to get a broad range of relevant articles. The key terms used were " Pancreatic Ductal Adenocarcinoma", "staging", "diagnosis", screening", " EUS", "Endoscopic Ultrasound", "MRCP", "Magnetic Resonance Cholangiopancreatography", "MRCP", "overexpressed antigens", "neo-expressed antigens", "high-frequency antigens", "PSMA PET-

Fig. 4 Imaging Agent Trial Process

CT", "Prostate-specific membrane antigen", "PET", "Positron Emission Tomography", "CT", "Computed Tomgraphy", "prostate cancer", "radioisotope", "antibodies", mesothelin", "Muc-1", "Muc-4", "Mucins" "review", and "meta-analysis".

Inclusion Criteria:

1. Original and review articles on the role of Endoscopic Ultrasound/Magnetic Resonance Cholangiopancreatography/ Miscellaneous modalities in the screening and diagnosis of PDAC.
2. Original and review articles on the frequency of neo-expressed and overexpressed antigens in PDAC and precursor lesions.
3. Original articles comparing Endoscopic Ultrasound, Magnetic Resonance Cholangiopancreatography or miscellaneous modalities in the diagnosis or screening of PDAC.
4. Original and review articles outlining the diagnostic sensitivity, specificity and accuracy of antibodies which bind to Mesothlin, Muc-1, and Muc-4.
5. Review articles outlining the method to conjugate radioisotopes to antibodies.
6. Datasets from original and review articles on the role of Endoscopic Ultrasound/Magnetic Resonance Cholangiopancreatography in screening for PDAC.
7. Datasets from original and review articles on the role of PSMA PET-CT in screening for Prostate Cancer.

Exclusion Criteria:

1. Case reports
2. Articles on the imaging of tumours other than PDAC

The datasets in this study were used because they came from relatively recent studies and came from peer-reviewed studies which was not the case for several other studies that were considered for inclusion.

To develop an effective model, it was necessary to identify a select number of highly expressed antigens in PDAC with complementary antibodies with high sensitivity, specificity, and accuracy.

Selection Criteria:

1. Antigens overexpressed/neo-expressed in greater than 80% of PDAC cases.
2. Antigens whose complementary antibodies have a specificity greater than 90%.

After evaluating the antigens and antibodies which suited these criteria each individual antigen was evaluated for its potential to be used in the proposed modality. First, mesothelin was chosen as it has a nearly 100% neo-expression in PDACs, this lends the imaging agent a greater amount of reliability as the neo-expression and high frequency allow for greater ability to discriminate between affected and surrounding tissue.

Next, Muc-1 was chosen due to the high sensitivity (84%-94%) of its antibody which lends greater overall sensitivity to the test and the high frequency of overexpression of Muc-1 in affected tissue as it further allows for greater discriminating ability between affected and regular tissue and further allows to discriminate between outlier tissue examples in mesothelin expression. Finally, Muc-4 was chosen due to the high specificity (90%) and sensitivity (100%) of it's complementary antibody which contributes to an increase in the sensitivity, specificity and overall accuracy of the test. This combination of high-frequency PDAC antigens leads to an overall increase in the sensitivity due to the nature of parallel testing only requiring one factor to be positive to produce a positive result.

In order to carry out quantitative analysis the sensitivity, specificity, and accuracy of each of the complementary antibodies was reviewed and combined using the following formulae for parallel testing, $sensitivity : (A)sen + (B)sen - [(A)sen \times (B)sen], specificity : (A)spec \times (B)spec$ in order to accomodate the multiple factors (antigens), which require detection.[38] Once these values were calculated they were placed in a table with values from other screening modalities, they were then used together with the prevalence of PDAC to calculate the accuracy value of the proposed modality. The values from the previously determined datasets were later used to develop a ROC curve comparing the various modalities in order to perform a more in-depth analysis of the datasets.

Quantitative analysis was carried out in this manner due to the difficulty and delays in obtaining approval for carrying out the various clinical tests as well as the ease of access to existing datasets.

Conclusion

PET-CT antibody imaging is a promising route for detecting pancreatic cancer or even its precursor lesions. The development of this technology should be investigated with speed, haste and increased resources allotted to hasten them into clinical trials in the wake of their success in prostate cancer detection. This is essential due to the growing number of people subjected to environmental risk factors for PDAC, which will see an uptick in the rate of PDAC globally in the coming years. Thus it is essential to improve and develop PDAC screening modalities in order to allow for effective, early detection of PDAC. Even today pancreatic cancer is responsible for 6% of all cancer deaths despite only accounting for 3% of all British cancer cases1. It is likely that in order to address the heterogeneity of tumours, these antibodies will have to target multiple antigens. This paper predicts the most promising targets for detection will be Mesothelin, MUC-1, and MUC-4. This is due to how their unique combination gives rise to a high specificity, sensitivity and accuracy in screening for PDAC. This method may, however, be limited by the potential for antibodies to bind to antigens present in the blood and antigens regularly expressed by other cells in the body may lead to difficulties in accurately detecting the presence of PDAC. Particular attention should be paid to how to combine this modality with the results of other existing pancreatic cancer screening modalities with a focus on its potential to detect small malignancies and precursor lesions. For example, this modality could allow for a preliminary screening prior to EUS-FNA and biopsy of the lesion which may give rise to higher accuracy in screening for smaller PDAC lesions. These advancements may serve as an improved indicator for pancreatic cancer and pancreatic cancer development allowing for a radical decline in the high mortality of PDAC in the coming years. In the coming years, it may be possible to improve the accuracy of this method further by improving the sensitivity and specificity of complementary antibodies.

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