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Positron Emission Tomography and Computed Tomographic Imaging Prior to Radiotherapy for Anal Cancer

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VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Positron Emission Tomography and Computed Tomographic Imaging Prior to Radiotherapy for Anal Cancer [PET/CT inför strålbehandling av analcancer]

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1. Abstract

Background
Anal cancer is a rare malignant disease that in many cases can be treated with organ-conserving treatment. Chemoradiation therapy is the cornerstone in such therapy. A combination of positron emission tomography (PET) and computed tomographic (CT) imaging (PET/CT) may provide the radiation therapist with more accurate data on primary tumour extension within nearby tissues, as well as data on involvement of lymph nodes. It is plausible that this technology would better select suitable patients for curative radiation therapy, as well as to increase the likelihood to correctly delineate tumour tissue. Hereby, the probability to achieve an improved tumour control, and in the long run an improved survival, may be increased. Furthermore, the radiation to normal tissue will decrease and, thereby, reduce radiation-induced side effects.

Objective
To evaluate whether the combination of PET and CT is superior to CT alone for target delineation and radiotherapy planning in patients with anal cancer suitable for curative radiotherapy treatment.

Search methods
In March 2015 a systematic literature search was conducted in PubMed, Embase, the Cochrane Library, Medline, Embase, the Cochrane Library, Centre for Reviews and Dissemination, and in the lists of HTA reports at the websites of the Swedish Agency for Health Technology Assessment and Assessment of Social Service, the Norwegian Knowledge Centre for the Health Services and the Danish Health Authority. Two authors independently screened titles, abstracts and full-text articles for inclusion.

Selection criteria
Only articles published later than 1999 and written in the English or in any of the Scandinavian language were included.

Data collection and analysis
Two authors independently extracted data. The certainty of evidence was appraised according to the GRADE system. The grading of the cross-sectional studies started at the ⊕⊕⊕⊕ level, similarly to cross-sectional studies of diagnostic accuracy with effect measures that may be indirectly important to patients.

Main results
Ten cross-sectional studies articles were included in the report. None of them reported any data on survival, tumour free or progression free survival, or health related quality of life. The proportion of patients in whom a change in target definition was made varied between 12.5% to 43% with a summary estimate of 23% (95 % confidence interval: 18 % to 33 %). Change in treatment intent from curative to palliative treatment varied between 0 % to and 5 % with a summary estimate of 3 % (95 % confidence interval: 2 % to 6 %).

Conclusion
The use of PET/CT (dose planning) probably results in an important change in target definition (GRADE ⊕⊕⊕◯), and may result in an important change of treatment intent from curative to palliative (GRADE ⊕⊕◯◯). The prognostic impact on survival and quality of life still remains to be clarified.

2. Svensk sammanfattning – Swedish summary

Bakgrund
Analcancer är en relativt ovanlig malign sjukdom. En central del av behandlingen är cytostatika samtidigt med strålning. Genom att kombinera resultaten från undersökning med "positron emission tomography" (PET) med de från datortomografi (CT), kan en detaljerad bild av primärtumörens utbredning och förekomst av lymfkörtelengagemang erhållas. Detta kan öka möjligheterna att mer exakt bestämma vilka vävnadsområden som ska ges strålning och vilka delar som inte ska utsättas för strålning. Som konsekvens av detta följer att risken för strålningsorsakade biverkningar med stor sannolikhet minskar, och möjligen kan även överlevnaden förbättras. Tekniken kan sannolikt även förbättra möjligheterna att välja ut de patienter som ska ges strålningsterapi i botande syfte från de som endast bör ges palliativ terapi.

Syfte
Att utvärdera om kombinationen av PET och CT är bättre än enbart CT avseende bestämning av strålningsfält och mål för strålningsbehandlingen hos patienter med analcancer som primärt bedöms vara kandidater för strålningsbehandling i kurativt syfte.

Metoder
En systematisk litteratursökning gjordes under mars månad 2015 i Medline, Embase, Cochrane Library, Centre for Reviews and Dissemination, och av publicerade HTA rapporter från SBU, det norska Kunnskapssenteret, och den danska Sundhedsstyrelsen. Två av författarna granskade oberoende av varandra artiklarnas titlar, abstrakts och slutligen artiklar som uppfyllde kriterierna för inklusion i fulltext. Endast studier som publicerats efter 1999 på engelska eller något av de skandinaviska språken inkluderades.

Datasammanställning och analys
Två av författarna sammanställde oberoende av varandra resultaten från studierna. Graden av evidens bedömdes därefter enligt GRADE systemet. På samma sätt som vid bedömning av tvärsnittsstudier avseende diagnostiska test startades evidensgraderingen på ⊕⊕⊕⊕ nivån.

Resultat
Tio tvärsnittsstudier identifierades och inkluderades. Ingen av dem redovisade resultat avseende total överlevnad, tumörfri eller pogressionsfri överlevnad eller hälsorelaterad livskvalitet. Andelen patienter där förändring i "target definition" (vävnadsområdet aktuellt för bestrålning) skedde varierade mellan 12.5% till 43 % i de olika studierna med ett sammanvägt estimat på 23 % (95 % konfidensintervall: 18 % till 33 %). Variationen avseende hur ofta man ändrade beslutat från kurativ till palliativ behandling var 0 % to till 5 % med ett sammanvägt estimat på 3 % (95 % konfidensintervall: 2 % to 6 %).

Sammanfattande slutsatser
Användningen av PET/CT för dosplanering av strålningsterapi till patienter med analcancer"(dose planning") förbättrar troligen definitionen av vävnadsområdet aktuellt för bestrålning ("target definition"), GRADE ⊕⊕⊕◯, och kan resultera i liten eller ingen skillnad i beslut om patienten ska erhålla kurativ eller palliativ behandling, GRADE ⊕⊕◯◯. Effekterna på överlevnad och hälsorelaterad livskvalitet kvarstår att utvärdera.

The above summaries were written by representatives from the HTA-centrum. The HTA-report was approved by the Regional board for quality assurance of activity-based HTA. The abstract is a concise summary of the results of the systematic review. The Swedish summary is a brief summary of the systematic review intended for decision makers, and is ended with a concluding summary.

Christina Bergh, Professor, MD
Head of HTA-centrum of Region Västra Götaland, Sweden, 2016-02-23

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3. Summary of Findings SoF-table)

Outcomes	Study design No. of studies (No. of patients)	Relative effect	Absolute effect	Certainty of evidence GRADE*
Change in target definition	9 cross-sectional studies (275)	Not applicable	23 % 95% CI 16-33 %	⊕⊕⊕◯ Moderate[1]
Change in treatment intent (from curative to palliative treatment)	10 cross-sectional studies (312)	Not applicable	3 % 95% CI 2-6 %	⊕⊕◯◯ Low[2]

*The grading of the cross-sectional studies started at the ⊕⊕⊕⊕ level, similarly to cross-sectional studies of diagnostic accuracy with effect measures that may be indirectly important to patients.

[1] Serious study limitations. Cut-off level for change in radiation fields was not defined in many studies.
[2] Serious study limitations; unclear decisions on change of treatment. Imprecision due to few events.

Certainty of evidence	
High certainty ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty ⊕⊕⊕◯	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty ⊕⊕◯◯	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty ⊕◯◯◯	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

4. Abbreviations/Acronyms

ARR	Absolute risk reduction
AP-PA	Anterior-posterior - Posterior-anterior
CT	Computed tomography
CTV	Clinical target volume
CRT	Chemoradiation therapy
EORTC	European organisation for research and treatment of cancer
FDG	^{18}Fluoro-deoxy-glucose
GTV	Gross tumour volume
HRQL	Health Related Quality of Life
IAEA	International atomic energy agency
IMRT	Intensity modulated radiation therapy
NCCN	National comprehensive cancer network
PET	Positron emission tomography
PTV	Planning target volume
RCT	Randomized controlled trial
SCCAC	Squamous Cell Carcinoma of the Anal Canal
VGR	Region of Västra Götaland
VMAT	Volumetric arc therapy

5. Background

Anal cancer is a rare malignant disease that in many cases can be treated with organ-conserving treatment. Chemoradiation therapy is the cornerstone in such therapy. Modern radiotherapy can provide steeper gradients of radiation doses while at the same time have high degree of conformality, resulting in the need of a well-defined clinical target volume to prevent irradiation of healthy tissue. The use of positron emission tomography (PET) and computed tomographic imaging (CT) to guide target delineation has been in use for intended curative chemoradiation therapy in anal cancer since 2011. A combination of PET and CT (PET/CT) may provide the radiation therapist with more accurate data on primary tumour extension within nearby tissues, as well as data on involvement of lymph nodes.

It is plausible that PET/CT would better select suitable patients for curative radiation therapy, as well as to increase the likelihood to correctly delineate tumour tissue. Hereby, the probability to achieve an improved tumour control, and in the long run an improved survival, will be increased. Furthermore, the radiation to normal tissue will decrease and thereby reduce radiation-induced side effects.

The purpose of this HTA is to evaluate whether the combination of PET and CT (i.e. PET/CT) is superior to CT alone for target delineation and radiotherapy planning in patients with anal cancer suitable for curative radiotherapy treatment.

Incidence of anal cancer

Anal cancer (in the international literature often specified as Squamous Cell Carcinoma of the Anal Canal, SCCAC) is a rare disease. Though there has been an increasing number of cases in Western countries during the early 21st century the prevalence and incidence of SCCAC are relatively low compared to other cancer forms. The annual age-standardised incidence rate is 1 per 100,000 for males and 2.7 per 100,000 for females. In 2014 there were 154 cases new cases diagnosed in Sweden, with about 20 % of them in Västra Götaland (VGR) (www.socialstyrelsen.se Cancer incidens i Sverige 2014: December 2015; ISSN 1400-3511, ISBN 978-91-7555-354-2).

Present treatment of anal cancer

Up until the mid-1980s surgery was the treatment of choice in patients with SCCAC, while later studies have shown equal or superior results with chemoradiation therapy (CRT), resulting in increased organ preservation, i.e. the anal sphincter (Ryan DP, 2000). Chemotherapy is given together with radiation to the primary tumour in the anal canal, and to the mesorectal, obturator, presacral, iliacal and inguinal lymph nodes to reduce the risk of loco-regional failure (Wright JL, 2010).

With increasingly advanced methods used in radiation therapy, such as intensity-modulated radiation therapy (IMRT) and volumetric arc therapy (VMAT), it is possible to provide a very steep gradient of irradiation to reach the edges of the tumour tissue you want to treat, i.e. the clinical target volume (CTV). This leads to less radiation to the surrounding healthy tissues, and a decrease in both the short-term and the long-term side effects of radiation such as gastrointestinal symptoms, and the risk of secondary malignancies (Wright JL, 2010). However, this also considerably increases the demand on the definition of the CTV so that micro-metastases will not be excluded from the radiation field, with the consequence of an increased the risk of recurrence. Guidelines for the adjuvant radiotherapy treatment volumes to irradiate for SCCAC has been published (Myerson RJ, 2009) and (Ng, 2012).

With PET/CT the possibility to better define the metastatic lymph node localization opens an opportunity for treatment optimization by selectively irradiate with a higher dose only those grossly affected lymph nodes. This will potentially increase cure and/or decrease morbidity in SCCAC-patients.

After a complete clinical work-up, i.e. a full medical history, complete physical examination and histopathology assessment and a MRI, the patient is referred to the department of Oncology at Sahlgrenska University Hospital. The patient will there be further examined by local palpation in sedation. This tumour staging is performed by both a qualified surgeon and an oncologist specialised in gastroenterological oncology. Only very small T1 marginal cancers may be selected for primary surgery. The vast majority of patients with tumour stage T1N+ to stage T4 are recommended an organ-conserving treatment option of CRT, i.e. to save the sphincter and its function. Prior to 2011 metastatic screening needed to be performed by a CT thorax and CT abdomen. With the current use of PET/CT based target definition, both these radiological examinations can be omitted since the staging accuracy is higher with PET/CT compared to contrast-enhanced CT (Jones M, 2015). Finally, following a discussion between the surgeons and the oncologists a treatment recommendation is made for the patient.

Treatment planning

Nearly all patients with anal cancer will require CRT. They are referred to the radiation therapy department for PET/CT based radiotherapy. Prior to the start of treatment an individual fixation device is made for each patient so that an identical position of the patient is used at each of the treatment sessions. This device is usually a vacuum pillow. The treatment typically consists of 30 sessions (i.e. 30 fractions of the total radiation dose) throughout a period of six weeks.

The PET/CT is adjusted to the radiotherapy accelerator with a fix zero-point in the X-, Y- and Z-planes, as well as controlled and calibrated in the recorded HU (Hounsfield units) to the dose planning software (Eclipse). A specialist in nuclear medicine delineates all tumour positive areas of the PET on each CT slice. Thereafter, the images are transferred to radiation therapy department, where a trained oncologist delineates a gross tumour volume (GTV) that takes into account the nuclear medicine delineation from the PET/CT, the MRI findings, as well as the clinical findings from the palpation.

Beside the tumour areas, the organs at risk are also delineated on each CT slice. Following delineation, a calculation of the planned dose is made by specially trained radiation nurses together with radiation therapy physicists. A specialised software (Eclipse) is used to optimize the radiation dose to the tumour area while minimizing the dose to organs at risk.
Chemotherapy is given for five days and is administered during the first and 4th week of irradiation therapy.
After completed therapy the patients are followed at the department of Oncology for 5 years.

Number of patients per year who undergo chemoradiation therapy for anal cancer

It is estimated that each year about 30 - 35 patients in Region Västra Götaland will need chemoradiation therapy for anal cancer.

Present recommendations from medical societies or health authorities

In the National comprehensive cancer network (NCCN) Version 2.2015 it is concluded that for anal carcinoma “PET/CT should be considered for treatment planning”. This statement was first added in v2.2012. *(https://www.tri-kobe.org/nccn/guideline/colorectal/english/anal.pdf).*
The Swedish “Nationella vårdprogrammet” is currently being finalised. According to personal communication (M Perman, January 20, 2016) it will refer to the recommendations made by NCCN.

6. Health Technology at issue:

Positron emission tomography and computed tomography for dose planning

Positron emission tomography (PET) is a technique that utilizes the uptake of sugar in human cells. The glucose molecules are marked with radioactive ^{18}F (2-deoxy-2-[fluorine-18]fluoro- D-glucose; FDG). When the molecules decay they emit positrons, which in turn annihilates into gamma rays that can be detected by a PET-scanner. Cancer cells are highly metabolic active and therefore incorporate also radioactive sugar whereby malignant tissue can be visualized by PET.

Today the PET technique is used together with computed tomography (”PET/CT”), i.e. co-registered, that enhance the diagnostic imaging over the separate interpretation of PET alone or CT alone (Bar-Shalom R, 2003). The combined technique enables the physician to anatomically correlate the pathologic uptake to a radiographic structure. The gold standard for correctly identify lymph node metastasis is histological analysis, no such data are available today for SCCAC, and will not likely be reported on, as treatment recommendation is chemoradiation therapy. A histology confirmed series from operated lymph node ectomies in endometrial cancer report sensitivity, specificity, accuracy, positive predictive value and negative predictive value of PET/CT for pelvic lymph node metastasis of 73.7%, 98.7%, 93.6%, 93.3%, 93.6% respectively (Signorelli M, 2015).

7. Objective

Does dose planning based on ^{18}FDG-PET/CT compared to CT alone, in adult patients with anal cancer, lead to improved survival, increased quality of life, changes in target definition and changes in treatment intention?

PICO - P= Patients, I= Intervention, C= Comparison, O=Outcome

P	Newly diagnosed patients with anal carcinoma intended for curative treatment including radiation therapy
I	Target definition followed by external beam radiation therapy based on dose-planning PET/CT
C	Target definition followed by external beam radiation therapy based on dose-planning CT
O	<u>Critical for decision making</u> Overall survival Tumour free or progression free survival Health related quality of life (HRQL) <u>Important but not critical for decision making</u> Symptom score CTC, RTOG Change in target definition Change in treatment intent Change in interobserver variability <u>Not important for decision making</u> - <u>Complications</u>

8. Methods

Systematic literature search (Appendix 1)

During March 2015, with an update in September 2015, two librarians (EB, AL) performed systematic searches in Medline, Embase, the Cochrane Library, Centre for Reviews and Dissemination, and in the lists of HTA reports at the websites of the Swedish Agency for Health Technology Assessment and Assessment of Social Service, the Norwegian Knowledge Centre for the Health Services and the Danish Health Authority. Reference lists of relevant articles were also scrutinized for additional references. The search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. The librarians conducted the literature searches. Thereafter two participants in the project group (PA, AH), independently of one another, assessed the obtained abstracts and made a first selection of full-text articles for possible inclusion in the final assessment. Any disagreements were resolved in consensus. These articles were sent to all the participants of the project group, who all read the articles, and then finally decided in a consensus meeting which articles to be included.

Critical appraisal and certainty of evidence

The included studies and their design and patient characteristics are presented in Appendix 2. The excluded studies and the reasons for exclusion are presented in Appendix 3. The articles were critically appraised using a slightly modified, previously published checklist for case series (Guo et al., 2013), and SBU's checklist regarding cohort studies (SBU 2015). A summary result for the outcome variables and the associated certainty of evidence are presented in a Summary of Findings table (page 8). The certainty of evidence was graded according to the GRADE system (Atkins et al, 2004; GRADE Working group). The grading of the cross-sectional studies started at the ⊕⊕⊕⊕ level, similarly to cross-sectional studies of diagnostic accuracy with effect measures that may be indirectly important to patients.

9. Results

Systematic literature search (Appendix 1)

The literature search identified a total of 54 articles (after removal of duplicates). Twenty articles were then excluded after reading their abstracts. Another 24 articles were excluded after reading the articles in full text. Ten articles were finally included in the report. All of them were cross-sectional studies, two of which with a prospective design.
The included articles with patient characteristics are presented in Appendix 2. The excluded articles, with reasons for exclusion, are listed in Appendix 3. Extracted data for each outcome variable and the quality assessment of the individual articles are summarised in Appendix 4.1 and Appendix 4.2
An overview of the results and the certainties of evidence per outcome are presented in the Summary-of-findings table (see Section 3).

General comments regarding the included articles

There was no uncertainty in the directness in any of the studies with regard to the type of patients. However, there were some uncertainties as to when curative treatment was changed from curative to palliative treatment. There were some study limitations with about half of the studies having an unblinded evaluation of PET/CT. Furthermore, the cut-off levels for a significant change of the target definition were not always reported in the different studies. All studies were rather small with an individual low precision.

PICO

Target definition followed by external beam radiation therapy based on dose-planning PET/CT compared to target definition followed by external beam radiation therapy based on dose-planning CT

Outcomes critical for decision-making

Survival, tumour free or progression free survival, and health related quality of life
These outcome variables were not reported in any of the studies.

Outcomes important for decision-making

Change in target definition (Appendix 4:1)
Change in target definition was reported in nine studies with a total of 275 patients. The proportion of patients in whom a change in target definition was made varied between 12.5% to 43% with a summary estimate of 23% (with a 95 % confidence interval of 18 to 33 in a random effects model).
Conclusion: The use of PET/CT (dose planning) probably improves target definition (⊕⊕⊕◯).

Change in treatment intent (Appendix 4:2)
Change in treatment intent from curative to palliative treatment was reported in all 10 cross-sectional trials with a total of 312 patients. The change in treatment intent varied between 0 % to 5 % with a summary estimate of 3 % (with a 95 % confidence interval of 2 to 6 in a random effects model).
Conclusion: The use of additional PET/CT (dose planning) may add information leading to a change in the treatment intent from curative to palliative (⊕⊕OO).

Outcomes important for decision-making

Change in interobserver variability
Change in interobserver variability was not evaluated in any of the studies.

10. Ethical consequences

There are no obvious ethical concerns for the individual patient if a dose planning CT is replaced by a dose planning PET/CT. A false positive lesion could possibly lead to a treatment decision that are unfavourably for the patient. The PET/CT capacity is currently approximately 2,000 per year. A second PET/CT camera is scheduled for May 2016. This means that the capacity of PET/CT then will be doubled. There is no risk that other patients in need of a PET/CT will not have their examinations done because of the patients with anal cancer in need of a PET/CT. The PET/CT has been used in anal cancer patients since 2011, and there are only about 30 new patients with anal cancer each year.

11. Organisational aspects

Time frame for the putative introduction of positron emission tomography and computed tomography for dose planning

The technology of PET/CT is already in use for therapy planning at Sahlgrenska University Hospital/Sahlgrenska.

Present use of positron emission tomography and computed tomography for dose planning in other hospitals in Region Västra Götaland

The technology of PET/CT is only available at Sahlgrenska University Hospital/Sahlgrenska in VGR. Radiation therapy is provided at Sahlgrenska University hospital and at Södra Älvsborgs sjukhus (SÄS). In the latter hospital there is one CT-scanner for dose planning, but they do not have the technology with PET/CT.

Consequences of positron emission tomography and computed tomography for dose planning for personnel

None at Sahlgrenska University Hospital/Sahlgrenska. The technology has already been successfully implemented.

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland

None.

12. Economic aspects

Present cost of chemoradiation therapy

Radiotherapy is only performed at Sahlgrenska University Hospital, Göteborg, and Södra Älvsborgs Hospital, Borås, in VGR. The number of anal cancer patients accepted for treatment with chemoradiation therapy with curative intent is approximately 30 patients per year. The calculated cost for a standard treatment course for one patient, including patient visits, chemotherapy, radiotherapy planning and treatment, body scans, hospitalization time, and follow up for 3 months is around 313,700 SEK. With 30 patients treated annually in VGR the present total cost is 9,411,000 SEK per year.

Expected costs of positron emission tomography and computed tomography for dose planning

Today there is only one PET/CT scanner in VGR, located at Sahlgrenska University Hospital. The current cost in 2015 for a treatment planning-PET/CT is 22,604 SEK. For 2016, an expected increase by 2 % would result in a cost of 23,056 SEK. With 30 patients treated per year the total cost of PET/CT for dose planning would be an additional 691,700 SEK annually.

Total change of cost

The cost for the use of PET/CT for dose planning is an addition of 23,056 SEK to the standard treatment course of 313,700 SEK per patient. This is a relative increase of 7 % and adds up to a total cost of 336,800 SEK per patient. Savings of the cost for the CT scan performed today prior to dose planning at the radiation therapy department can be estimated to 3,500 SEK per patient. The new total cost per year for the patients with anal cancer accepted for treatment with curative intent chemoradiation therapy in VGR can subsequently be estimated to 10,000,000 SEK, in comparison to the prior cost of 9,411,000 SEK.

Available analyses of health economy or cost advantages or disadvantages

No published health economy analysis has been identified in the literature search.

13. Discussion

Summary of main results
To our knowledge this is the first health technology assessment of the use of PET/CT for dose planning purposes prior to irradiation of anal tumours. We did not find any data in the literature of its effects on overall survival, tumour free and progression free survival and quality of life. However, the use of PET/CT probably results in an important change in the target definition with about one in five patients in whom the target definition will be significantly changed. Whether PET/CT will change the intention to offer the patient palliative instead of curative treatment is less clear as this has been reported to occur in less than one in every 20 patients.

Overall completeness and applicability of evidence
We choose to limit the literature search from the year 2000 and onwards. The reason for this was that the radiation techniques with introduction of the more conformal techniques of intensity modulated radiation therapy started in the early 2000 and the co-registered PET/CT technique in the mid 2000. Both these advances in technology are integral for the possibility to maximally use the PET information in radiation therapy planning. Thus, the results of these studies are valid for what is currently being used in the clinical routine.

It may be argued that the use of different cut off levels for “change in target definition” in the different included studies is a weakness in the analysis. Many of the studies have used older radiation therapy with simpler box-like beam arrangements where the detailed PET/CT-based information of tumour versus normal tissue was less important than with modern techniques. Since the treatment planning used today aims at giving high dose to tumour tissue while having a step gradient to all normal healthy tissue almost all findings on a PET/CT scanning will likely impact the target definition. Hence, the impact of PET/CT is probably underestimated in the early studies.

Agreements and disagreements with other studies and reviews
The conclusions of this HTA are in line with the statement of NCCN from 2012 that radiation therapy planning should be considered to be based on PET/CT.

Implications for research
To what extent the changes in delineation of target structures influence the clinical- and patient reported outcome (i.e. survival, side effects, HRQL) are, so far, not studied at all in anal carcinoma. The ongoing study at Duke University in North Carolina, USA, (see below) might shed light on this, but exactly how many patients with anal carcinoma they will be able to evaluate is unknown. There are no phase III trials, ongoing or planned, and it is not likely that such will be performed. The technology of PET/CT is being widely more accessible and radiation therapy research is ongoing where PET/CT information using also other tracers than FDG may be used to select different therapy doses for different regions of the tumor, e.g. with more dose to regions of hypoxia using hypoxia markers.

14. Future perspective

Scientific knowledge gaps

There is a lack of data on the effects of PET/CT for dose planning purposes on tumour control, survival and side effects from normal tissues.

Ongoing research

A search in clinicaltrials.gov (July 2015) using the search string *(anal OR anus) AND (PET OR PETCT OR PET/CT OR Positron-Emission Tomography OR petscan)* identified 10 studies. Six of them were not relevant to our question at issue or used another PET tracer, and one study does not address anal cancer. Three relevant studies are ongoing:

1. The Adaptive PET study, NCT01908504, is a study performed at Duke University, NC, USA. The study plan is to enrol 320 patients with several different malignancies, including also anal cancer, in single group study to determine the benefit of using PET in addition to the standard CT to plan radiation therapy for cancer treatment. Locoregional control, freedom from distant metastases, overall survival, and acute and late toxicities are predefined secondary outcome variables. It is estimated to be completed in 2018.

2. The Anal Cancer Radiotherapy Study (ANCARAD), NCT01937780, is a Norwegian study (Oslo) in which they plan to recruit 75 patients in a prospective observational study of treatment outcome. The utility of PET-CT and MRI for radiotherapy and for prediction of treatment effect will be investigated**.** The primary outcome variable is diseases free survival, and one secondary outcome variable is local recurrence. It is estimated to be completed in 2021.

3. Phase II Study of Concomitant Intensity-modulated Radiotherapy Combined to Capecitabine, Mitomycin and Panitumumab in Patients with Stage II-IIIB Squamous-cell Carcinoma of the Anal Canal, NCT01843452, is a single group study from Universitaire Vaudois in Switzerland. It will enrol 65 patients with anal cancer. The primary outcome variable is 2-year locoregional control. Predefined secondary outcome variables are complete 5-year response rate, coloctomy-free survival, overall survival, progression-free survival, tolerability and safety, and the role of PET for staging and outcome prediction. It is estimated to be completed in 2020.

Interest at the clinic to start studies within the research field at issue

Since 2011 this technology has been used in the clinical routine. A research project in which all recurrent patients in the period 2011 - 2014 are compared to the recurrences found in the same time period *prior* to the implementation of the technology could be performed (approved by the ethical committee).Additional treatment planning post hoc could be performed using only the CT images on randomly chosen ten patients prior to and after the implementation. A detailed protocol should be written for this.

15. Participants in the project

The question was nominated by

Marie Lindh, Head of the Department of Oncology, Sahlgrenska University Hospital, Göteborg, Sweden.

Participaiting health care professionals

Per Albertsson, MD, Associate professor, Consultant,
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Declaration of interest

None

Project time

The HTA was accomplished during the period of 2015-02-19 – 2016-02-23
Literature searches were made in March 2015, and updated in September 2015.

Appendix 1, Search strategy, study selection and references

Question(s) at issue:
Does dose planning based on ^{18}FDG-PET/CT compared to CT alone, in adult patients with anal cancer, lead to improved survival, increased quality of life, changes in target definition and changes in treatment intent?

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

P	Newly diagnosed patients with anal carcinoma intended for curative treatment including radiation therapy
I	Target definition followed by external beam radiation therapy based on dose-planning PET/CT
C	Target definition followed by external beam radiation therapy based on dose-planning CT
O	Critical for decision making Overall survival Tumour free or progression free survival Health related quality of life (HRQL) Important but not critical for decision making Symptom score CTC, RTOG Change in target definition Change in treatment intent Change in interobserver variability Not important for decision making - Complications

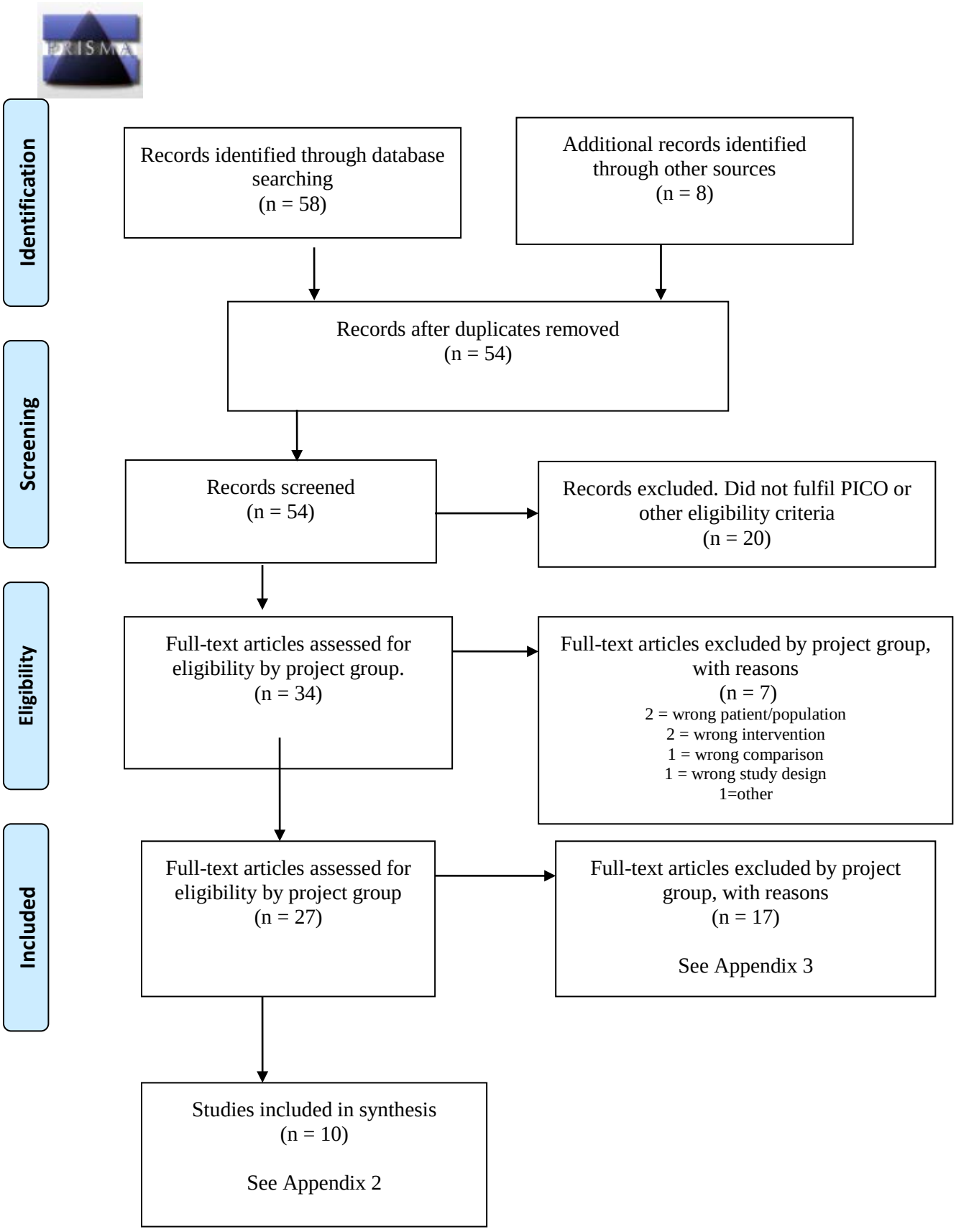
Eligibility criteria

Study design:
Systematic reviews
Randomized controlled trials
Non-randomized controlled studies
Case series

Language:
English, Swedish, Norwegian, Danish

Publication date: 2000-

Selection process – flow diagram



Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
Date: 2015-03-25
No of results: 15
Search updated: 2015-09-22, 1 results

#	Searches	Results
1	exp Anus Neoplasms/	4987
2	((anus or anal) adj5 (cancer$ or carcinoma$ or tumor or tumors or tumour or tumours or neoplas$ or malignan$ or metasta$ or sarcoma$ or adenocarcinoma$ or adeno?carcinoma$ or adenoma$)).ab,ti.	4638
3	1 or 2	6874
4	exp Positron-Emission Tomography/	34370
5	exp Tomography, Emission-Computed/	80818
6	(pet or petscan$).ab,ti.	59488
7	(emission$ adj10 (tomograph or tomographs or tomographic$ or tomography or tomographies)).ab,ti.	51773
8	4 or 5 or 6 or 7	111269
9	exp Tomography, X-Ray Computed/	313378
10	(comput$ adj8 (tomograph or tomographs or tomographic$ or tomography or tomographies)).ab,ti.	200960
11	(ct or cat).ab,ti.	307252
12	9 or 10 or 11	560781
13	8 and 12	43451
14	" pet/ct ".ab,ti.	12371
15	PETCT.ab,ti.	20
16	14 or 15	12378
17	13 or 16	43452
18	exp Radiation/	336352
19	exp Radiotherapy/	142477
20	(radiation$ or radiotherap$ or x-ray$ or x ray$).ab,ti.	573081
21	18 or 19 or 20	869941
22	(defining or define$ or delineat$ or target$ or planning$ or target definition$ or paint$ or contour$).ab,ti.	1744259
23	3 and 17 and 21 and 22	16
24	(animals not (animals and humans)).sh.	3909043
25	23 not 24	16
26	(comment or editorial or letter).pt.	1388932
27	25 not 26	16
28	**limit 27 to (danish or english or norwegian or swedish)**	**15**

Database: EMBASE (OVID) 1980 to Present
Date: 2015-03-25
No of results: 30
Search updated: 2015-09-22, 4 results

#	Searches	Results
1	exp positron emission tomography/	88838
2	exp computer assisted emission tomography/	18020
3	(Pet or petscan$).ti,ab.	92534
4	(emission$ adj10 (Tomograph or Tomographs or tomographic$ or tomography or tomographies)).ti,ab.	63397
5	1 or 2 or 3 or 4	156932
6	exp Tomography, X-Ray Computed/	638365
7	(comput$ adj8 (Tomograph or Tomographs or tomographic$ or tomography or tomographies)).ti,ab.	235650
8	(CT or CAT).ti,ab.	418014
9	6 or 7 or 8	859671
10	5 and 9	83387
11	'"pet/ct"'.ti,ab.	23523
12	petct.ti,ab.	293
13	11 or 12	23634
14	10 or 13	83459
15	(Defining or Define$ or delineat$ or Target$ or planning$ or target definition$ or paint$ or contour$).ti,ab.	2191691
16	exp radiation/	424368
17	exp radiotherapy/	392794
18	(Radiation$ or Radiotherap$ or x-ray$ or x ray$).ti,ab.	669811
19	16 or 17 or 18	1106228
20	exp anus tumor/	6639
21	((anus or anal) adj5 (cancer$ or carcinoma$ or tumor or tumors or tumour or tumours or neoplas$ or malignan$ or metasta$ or sarcoma$ or adenocarcinoma$ or adeno?carcinoma$ or adenoma$)).ti,ab.	6502
22	20 or 21	9114
23	20 or 21	9114
24	14 and 15 and 19 and 22	61
25	(animal not (animal and human)).sh.	1215410
26	24 not 25	61
27	limit 26 to (danish or english or norwegian or swedish)	57
28	**limit 27 to (article or conference paper or note or "review")**	**30**

Database: The Cochrane Library
Date: 2015-03-25
No of results: 1
Search updated: 2015-09-22,1 results

#	Searches	Results
#2	MeSH descriptor: [Positron-Emission Tomography] explode all trees	1035
#3	MeSH descriptor: [Tomography, Emission-Computed] explode all trees	2631
#4	Pet or petscan*:ti,ab,kw (Word variations have been searched)	2220
#5	(emission* near/10 (Tomograph or Tomographs or tomographic* or tomography or tomographies)):ti,ab,kw (Word variations have been searched)	3794
#6	#2 or #3 or #4 or #5	4400
#7	MeSH descriptor: [Tomography, X-Ray Computed] explode all trees	4107
#8	(comput* near/8 (Tomograph or Tomographs or tomographic* or tomography or tomographies)):ti,ab,kw (Word variations have been searched)	9816
#9	CT or CAT:ti,ab,kw (Word variations have been searched)	40981
#10	#7 or #8 or #9	46670
#11	#6 and #10	2869
#12	"pet/ct":ti,ab,kw (Word variations have been searched)	392
#13	PETCT:ti,ab,kw (Word variations have been searched)	4
#14	#12 or #13	394
#15	#11 or #14	2870
#16	MeSH descriptor: [Radiation] explode all trees	3422
#17	MeSH descriptor: [Radiotherapy] explode all trees	5314
#18	Radiation* or Radiotherap* or x-ray* or x ray*:ti,ab,kw (Word variations have been searched)	26694
#19	#16 or #17 or #18	29162
#20	MeSH descriptor: [Anus Neoplasms] explode all trees	82
#21	((anus or anal) near/5 (cancer* or carcinoma* or tumor or tumors or tumour or tumours or neoplas* or malignan* or metasta* or sarcoma* or adenocarcinoma* or adeno?carcinoma* or adenoma*)) (Word variations have been searched)	299
#22	#20 or #21	299
#23	**#15 and #19 and #22**	**1**

Database: CRD
Date: 2015-03-25
No of results: 1
Search updated: 2015-09-22, 0 results

Line	Search	Hits
2	MeSH DESCRIPTOR Positron-Emission Tomography EXPLODE ALL TREES	416
3	MeSH DESCRIPTOR Tomography, Emission-Computed EXPLODE ALL TREES	653
4	((Pet OR petscan*))	515
5	((emission* near10 (Tomograph or Tomographs or tomographic* or tomography or tomographies)))	684

6	#2 OR #3 OR #4 OR #5	787
7	MeSH DESCRIPTOR Tomography, X-Ray Computed EXPLODE ALL TREES	996
8	((comput* near8 (Tomograph or Tomographs or tomographic* or tomography or tomographies)))	1394
9	((CT or CAT))	1498
10	#7 OR #8 OR #9	2364
11	#6 AND #10	477
12	(pet-ct)	202
13	(petct)	1
14	#12 OR #13	202
15	#11 OR #14	477
16	MeSH DESCRIPTOR Anus Neoplasms EXPLODE ALL TREES	25
17	(((anus or anal) NEAR5 (cancer$ or carcinoma$ or tumor or tumors or tumour or tumours or neoplas$ or malignan$ or metasta$ or sarcoma$ or adenocarcinoma$ or adeno?carcinoma$ or adenoma$)))	3
18	#16 OR #17	28
19	**#15 AND #18**	**1**

The web-sites of **SBU, Kunnskapssenteret** and **Sundhedsstyrelsen** were visited
2015-03-25
5 relevant to the question at issue was found

Reference lists
A comprehensive review of reference lists brought 8 new records

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Project: PET/CT prior to radiotherapy for anal cancer
Appendix 2. Characteristics of included studies

*Blinding
1. No blinding/ blinding not reported.
2. Evaluator first has access to CT only and makes delineation/judgment, thereafter access to PET/CT and remakes delineation/judgment.
3. Different evaluators make CT and PET(CT) delineation followed by joint discussion.
4. Different evaluator make CT based delineation and PET/CT delineation independent of each other.

Author Year Country	Study Design	Blinding *	Study period (years)	Number of patients with anal cancer	Radiation technique	Mean Age (years)	Men (%)	Outcome variables
Andersson 2007 USA	Cross-sectional retrospective design	2	March 2003– Nov 2003	3 (part of larger cohort tot. n=23)	AP-PA Shrinking field	NR.	NR	Change in target definition Change in treatment intent
Bannas 2011 Germany	Cross-sectional retrospective design	3	2008-2009	22	NR (3D conformal planning)	61 (median) 39-70 (range)	59	Change in target definition Change in treatment intent
Ciernik 2003 Switzerland	Cross-sectional retrospective design	2	NR	7 (part of larger cohort tot. n=38)	NR (assumed AP-PA)	64.9 38–82 (range)	71	Change in target definition Change in treatment intent
de Winton 2009 Australia	Cross-sectional prospective design	4	Aug 1997– Nov 2005	61	AP-PA + 3 Field box for shrinking field	57 27–88 (range)	44	Change in target definition Change in treatment intent
Krengli 2010 Italy	Cross-sectional retrospective design	2	Jan 2005 – May 2008	27	NR (3D conformal planning)	66 36-90 (range)	33	Change in target definition Change in treatment intent
Mai 2009 Germany	Cross-sectional Retrospective design	4	2003 - 2006	39	4 Field box, shrinking field technique (Addressed only lymph node status)	56 37-86 (range)	44	Change in target definition Change in treatment intent
Mistrangelo 2012 Italy	Cross-sectional prospective design	0/2	Oct 2004 – Dec 2009	53 (40 both PET/CT and CT pre-treatment	30 pts 3D conformal RT 3 pts IMRT	56.6 (median) 32-75 (range)	36	Change in target definition Change in treatment intent
Nguyen 2008 Australia	Cross-sectional retrospective design	4	March 1996- Sept 2006	50 (48 with pre-treatment PET or PET/CT)	NR (assumed AP-PA or possibly box technique)	58 (median) 36-85 (range)	38	Change in target definition Change in treatment intent
Wells 2012 United Kingdom	Cross-sectional retrospective design	4	June 2008 – May 2011	44 (30 with pretreatment PET/ CT)	NR	NR	NR	Change in target definition Change in treatment intent
Vercellino 2011 France	Cross-sectional Prospective design	4	Oct 2004 – July 2008	44 (22 with pretreatment PET/CT)	NR	62 38-85 (range)	30	Change in treatment intent

NR= Not reported. AP-PA= anterior-posterior and posterior-anterior. PET/CT= positron emission tomography/computed tomography, 3D= three dimensional, IMRT= Intensity-Modulated Radiation Therapy

Project: PET/CT prior to radiotherapy for anal cancer
Appendix 3. Excluded articles

Study (author, publication year)	Reason for exclusion
Agarwal, 2014	Non-systematic review. No original data.
Benson, 2012	NCCN Guidelines. No original data.
Bhuva, 2012	PET/CT compared to MRI
Cotter, 2006	Staging study
Czito, 2013	No original study
Gauthe, 2015	Non-systematic review. No original data.
Grigsby, 2009	Non-systematic review, opinion
Iagaru, 2009	No relevant radiation therapy data
Lambrecht, 2010	Non-systematic review. No original data.
Pepek, 2010	Non-systematic review. No original data.
Saboo, 2013	Non-systematic review.
Scher, 2014	Non-systematic review. No original data.
Schwarz, 2008	No pre-radiation therapy data
Spiers, 2015	Non-systematic review. No original data.
Trautman, 2005	Staging study.
Tsai, 2011	Non-systematic review. No original data.
Wang, 2013	Wrong P (rectal cancer), non-systematic review

NCCN= National Comprehensive Cancer Network (USA). MRI= magnetic resonance imaging.
PET/CT= positron emission tomography /computed tomography

Project: PET/CT prior to radiotherapy for anal cancer
Appendix 4.1
Outcome variable: Change in target definition

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	No. of pats. n=	With drawals - dropouts	Results		* Directness	* Study limitations	* Precision
				Change in target definition	Specific details			
Anderson, 2007 USA	Cross-sectional	3		1/3 (33 %)	Subgroup of anorectal tumors	?/+	+	-
Bannas, 2011 Germany	Cross-sectional	22		5/22 (23 %)		+	?	?
Ciernik, 2003 Switzerland	Cross-sectional	7		4/7 (43 %)	PTV increase in 3 patients and decreased in one.	+	?	-
de Winton, 2009 Australia	Cross-sectional	61	2	8/59 (14 %)	PET/CT results in additional 5 cases that indicated change were ignored as specified by authors.	+	?	?
Krengli, 2010 Italy	Cross-sectional	27		10/27 (37 %)	GTV changed 15/27 (56 %), (in T3-4 12/15 (80 %) T1-2 3/12 (25 %)) CTV changed in 10/27 (38 %).	+	+/?	?
Mai, 2009 Germany	Cross-sectional	39		6/39 (15 %)	3/39 N2 → N0 and 3/39 N3 → N0	+	+	?
Mistrangelo, 2012 Italy	Cross-sectional	53	13	5/40 (12.5 %)	5/40 radiation field change due to PET/CT findings relative CT. While 15/40 upstaged and 10/40 downstaged. With IMRT and VMAT techniques the impact on radiation therapy may significantly higher than 12.5 % reported.	+	?	?
Nguyen, 2008 Australia	Cross-sectional	48		9/48 (19 %)	Only node status change is reported. Pet vs clinical examination or CT (38 underwent pre therapy CT).	+	?	?
Wells, 2012 United Kingdom	Cross-sectional	44	14	11/30 (37 %)		+/?	?	?
Summary ratio:				59/275				
Summary estimate of ratios from individual articles:				23 % 95% CI 16-33 %	Meta-analysis conducted in the software R, applying a random effects model.			

PET/CT= positron emission tomography /computed tomography, PTV= planning target volume, CTV= Clinical target volume, GTV= gross tumor volume,
IMRT= Intensity-Modulated radiation Therapy, VMAT= VoluMetric Arc Therapy

Project: PET/CT prior to radiotherapy for anal cancer
Appendix 4.2
Outcome variable: Change in treatment intent (change from curative to palliative treatment)

* + No or minor problems
? Some problems
- Major problems

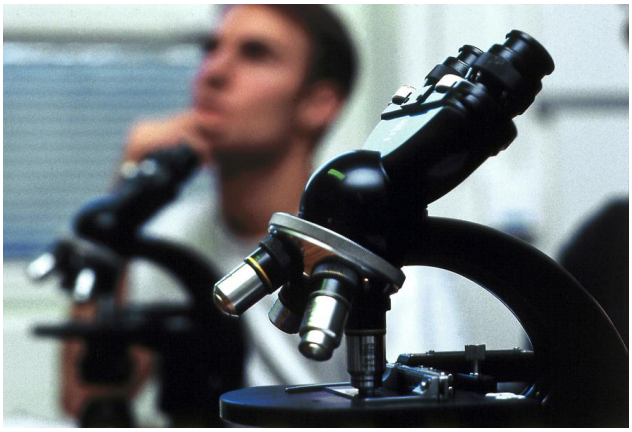
Author, year, country	Study design	Number of patients	With drawals dropouts	Results Change in treatment intent	Comments	Directness *	Study limitation *	Precision *
Andersson, 2007 USA	Cross-sectional	3		0/3		?/+	+	-
Bannas, 2011 Germany	Cross-sectional	22		0/22		+	?	-
Ciernik, 2003 Switzerland	Cross-sectional	7		0/7		+	?	-
de Winton, 2009 Australia	Cross-sectional	61		2/61		+	?	-
Krengli, 2010 Italy	Cross-sectional	27		1/27		+	+/?	-
Mai, 2009 Germany	Cross-sectional	39		2/39		+	+	-
Mistrangelo, 2012 Italy	Cross-sectional	53		1/53	1/53 stage IV. 3/40 with RT were stage IV i.e. downstaged by PET/CT	+	?	-
Nguyen, 2008 Australia	Cross-sectional	48		0/48	Outcome not specifically stated	+	?	-
Wells, 2012 United Kingdom	Cross-sectional	44	14	1/30	4/48 PET/CT scans could free suspicious distant metastases	+/?	?	-
Vercellino, 2011 France	Cross-sectional	44	22	0/22	No radiation therapy data.			
			Summary ratio:	7/312				
			Summary estimate of ratios from individual articles:	3 % 95% CI 2-6 %	Meta-analysis conducted in the software R, applying a random effects model.			

PET/CT= positron emission tomography /computed tomography

2016-02-18

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

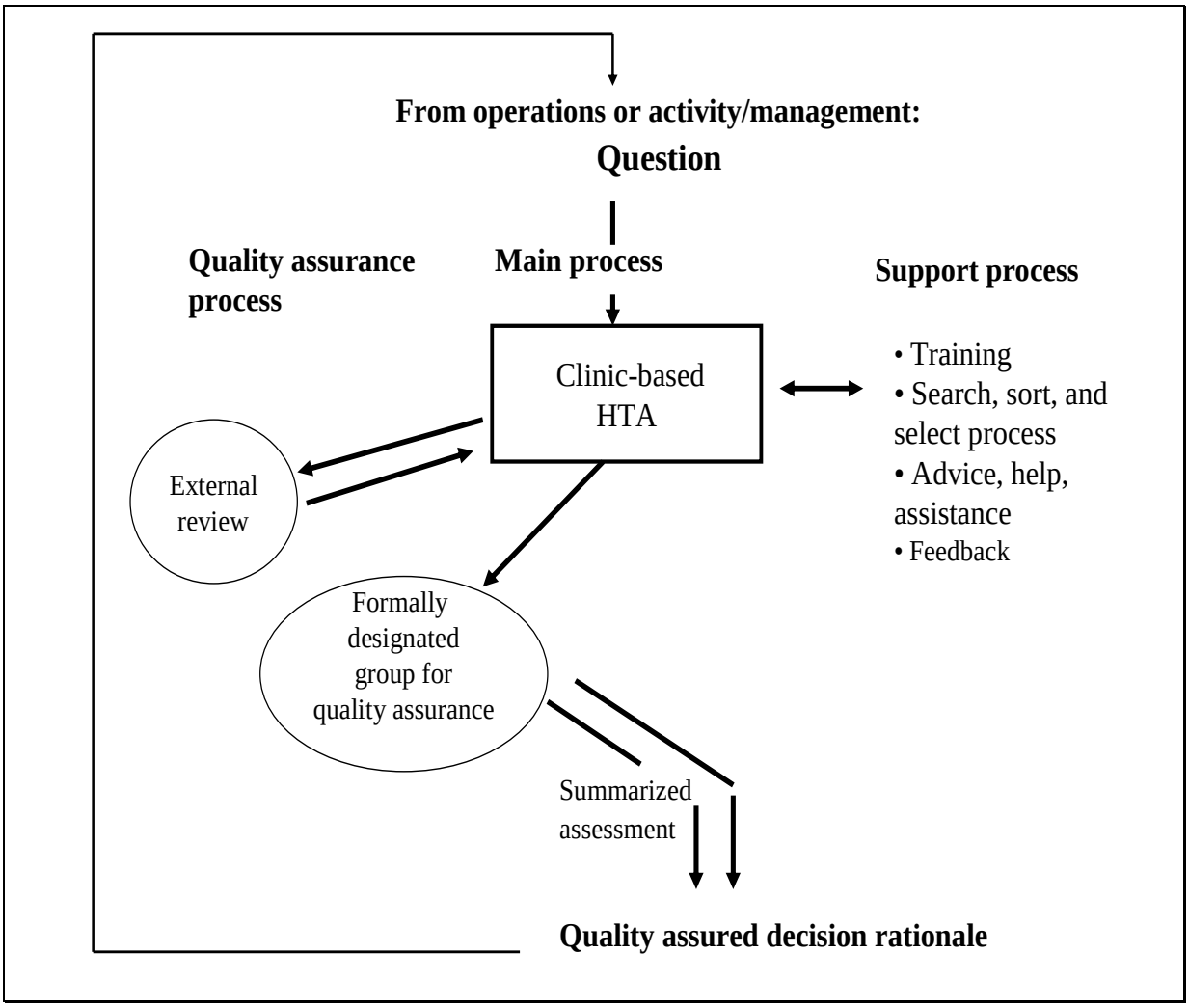
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= (GRADE⊕⊕⊕⊕)
Moderate quality of evidence	= (GRADE ⊕⊕⊕O)
Low quality of evidence	= (GRADE ⊕⊕OO)
Very low quality of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh, Professor, MD.
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

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