TECHNOLOGY REVIEW (MINI-HTA)

ETHOS THERAPY FOR CANCER PATIENT

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
012/2024

IPT Mark
Mini-HTA
INAHTA

DISCLAIMER

This technology review (mini-HTA) is prepared to assist health care decision-makers and health care professionals in making well-informed decisions related to the use of health technology in health care system, which draws on restricted review from analysis of best pertinent literature available at the time of development. This technology review has been subjected to an external review process. While effort has been made to do so, this document may not fully reflect all scientific research available. Other relevant scientific findings may have been reported since the completion of this technology review. MaHTAS is not responsible for any errors, injury, loss or damage arising or relating to the use (or misuse) of any information, statement or content of this document or any of the source materials.

Please contact htamalaysia@moh.gov.my if further information is required.

EVIDENCE INFORMED DELIBERATIVE PROCESS

This Technology Review underwent evidence informed deliberative process during the Health Technology Assessment (HTA) Technical Advisory Committee meeting, chaired by the Director, Medical Development Division, MOH. Then it was endorsed in the HTA-CPG Council meeting chaired by the Director General of Health.

Published by

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Government Office Complex
62590, Putrajaya
Tel: 603 8883 1229
Available online via the official Ministry of Health Malaysia website: http://www.moh.gov.my


Cataloguing-in-Publication Data
Perpustakaan Negara Malaysia
A catalogue record for this book is available from the National Library of Malaysia
eISBN 978-967-2887-94-2

e-ISBN: 978-967-2887-94-2

SUGGESTED CITATION: Muhammad AA, Roza S and Izzuna MMG. Ethos Therapy for Cancer. Technology Review. Ministry of Health Malaysia: Malaysian Health Technology Assessment Section (MaHTAS); 2024. 51p. Report No.: 012/2024.

DISCLOSURE: The author of this report has no competing interest in this subject and the preparation of this report is entirely funded by the Ministry of Health Malaysia.

AUTHORS

Dr. Muhammad Ainuddin bin Alias
Assistant Director
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

REVIEWERS

Dr. Roza Sarimin
Public Health Physician
Senior Principal Assistant Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Dr. Izzuna Mudla Mohamed Ghazali
Public Health Physician
Deputy Director
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

EXTERNAL REVIEWERS (alphabetical order)

YBrs. Dr. Ros Suzanna binti Ahmad Bustamam
Ketua Kepakaran Onkologi Klinikal
Pakar Perubatan Perunding Kanan Onkologi Klinikal
Hospital Kuala Lumpur

YBrs. Encik Zainudin bin Yasak @ Yusof
Ketua Penolong Pengarah
Cawangan Kawalselia Radiasi Perubatan
Jabatan Kesihatan Negeri Pulau Pinang

EXECUTIVE SUMMARY

Background

Cancer is a leading health concern in Malaysia, with its incidence rising steadily each year, placing a growing burden on the healthcare system. Radiotherapy remains a critical treatment modality for approximately 50% of cancer patients, playing essential roles in curative, palliative, and adjuvant settings. However, its effectiveness is often hindered by challenges in delivering accurate doses to tumours while sparing surrounding healthy tissues. Anatomical changes during treatment, such as tumour shrinkage, organ motion, or variations in patient positioning, can result in deviations from planned doses, potentially leading to suboptimal tumour control or increased toxicity to healthy tissues.

Adaptive radiotherapy (ART) addresses these challenges by enabling treatment plan modifications based on changes in patient anatomy. Unlike conventional radiotherapy, which relies on a static treatment plan, ART evolves throughout the treatment course. Early forms of ART were applied offline, making adjustments based on cumulative data from previous sessions, but they lacked real-time adaptability. Online ART (oART), enabled by advancements in artificial intelligence (AI), deformable image registration, and imaging technologies like cone-beam CT, allows clinicians to make real-time adjustments during each session. Emerging evidence suggests that oART enhances treatment precision, improving tumour targeting, reducing planning margins, and minimizing exposure to surrounding healthy tissues, offering a more personalized approach to cancer care.

Objective/ aim

The objective of this review is to assess the effectiveness, safety, cost-effectiveness, and organisational impact of online adaptive radiotherapy (oART) using the Varian Ethos system for the treatment of cancer patients.

Methods

A systematic search was conducted on the following databases with restriction on English and Human. The Ovid interface: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to July 2024. Searches were also run in PubMed databases. Google was used to search for additional web-based materials and information. The last search was conducted on 15th July 2024.

Results and conclusion

A total of 77 titles were retrieved from the scientific databases such as Medline via OVID, and PubMed, using the search term; *radiotherapy*, *radiotherapy planning*, *image guided radiotherapy*, *computer assisted*, *artificial intelligence*, *deep learning*, *Ethos TPS*, *Varian Ethos*, and *Ethos Therapy*. Search were limited to *English*, and *Human*. After reading, appraising and applying the inclusion and exclusion criteria, 10 observational studies were included in this review

Effectiveness
There was moderate quality evidence showing that online adaptive radiotherapy (oART) may improve target coverage while reducing normal tissue exposure, palpable by superior dosimetric benefits in many observational studies. However, additional clinical data is needed to fully evaluate its clinical impact especially in term of clinical goal such as tumour control and organ toxicity. Across the evidence retrieved, oART is feasible to be done in clinical setting with treatment time reported ranging 13.9 – 34.5 minutes.

Safety
There was limited evidence reporting on safety aspect of online adaptive radiotherapy.

Cost/Cost-effectiveness
There was no retrievable evidence on the cost or cost-effectiveness of online adaptive radiotherapy using Ethos therapy in cancer population. However, there was one study in United States concluded that incremental cost per additional adaptive fraction is $103.58.

Organisational
Organisational issue highlighted in implementing online adaptive radiotherapy (oART) includes; 1) increased time required per treatment session, 2) requires a highly skilled multidisciplinary team with additional staff training, 3) careful patient selection, 4) compatibility issue with existing infrastructure or system, 5) additional infrastructure needed and 6) risk of algorithm bias in Artificial Intelligence (AI)-driven plan generation.

[redacted]

TABLE OF CONTENTS

ABBREVIATION

OAR	Organ-at-risk
CT	Computed Tomography
ART	Adaptive Radiotherapy
oART	Online Adaptive Radiotherapy
AI	Artificial Intelligence
CBCT	Cone Beam Computed Tomography
CNN	Convolutional Neural Networks
IOE	Intelligent Optimization Engine
IMRT	Intensity-Modulated Radiotherapy
VMAT	Volumetric-Modulated Arc Therapy
DVH	Dose-volume Histogram
MOH	Ministry of Health
CASP	Critical Appraisal Skill Programme
PTV	Planning Target Volume
EUD	Equivalent Uniform Dose
CTV	Clinical Target Volume
AOD	Adaptive-on-demand
ITV	Internal Tumour Volume
ASD	Average Surface Distance
DSC	Dice Similarity Coefficient
CI	Conformity Index
HI	Homogeneity Index
IQR	Interquartile Range
PS	Plan Selection
SCRT	Short Course Radiotherapy
LCRT	Long Course Radiotherapy
FDA	Food and Drug Administration
CE	Conformité Européenne
TDABC	Time-Driven Activity Based Costing
SBRT	Stereotactic Body Radiation Therapy

1.0 BACKGROUND

Cancer is among leading health issue in Malaysia with an increasing incidence trend year by year.[1] It placed a significant burden on healthcare services with expected increasing in number of patients in future. It is estimated that approximately 50% of cancer patients will require some form of radiotherapy as a modality in their treatment journey. These demands cause substantial pressure on radiotherapy resources and personnel, necessitating the exploration of more efficient and effective treatment modalities.[2]

Radiotherapy has been a cornerstone in the management of various cancers, playing a critical role in curative, palliative, and adjuvant treatment settings. However, the effectiveness of radiotherapy is often hampered by challenges in delivering precise doses to tumours while minimising exposure to surrounding healthy tissues.[3] Achieving this precision is particularly difficult in anatomically complex regions or where there are significant inter- and intra-fractional variations, such as in the pelvic area and head and neck region.[4]

One of the most pressing challenges in radiotherapy is the variability in patient anatomy during treatment sessions, which can occur due to tumour shrinkage, organ motion, or changes in patient positioning.[4] These anatomical changes, both inter- and intra-fractional, can lead to deviations between the planned and actual dose delivered to the target tissues and organs at risk (OARs).[5] In conventional radiotherapy, treatment planning is based on a single computed tomography (CT) scan taken prior to the first treatment session. As a result, treatment plans cannot account for daily anatomical changes, potentially leading to over- or under-dosing of the tumour and increased toxicity to nearby healthy tissues.[6]

To address these limitations, adaptive radiotherapy (ART) was developed. ART allows for modifications to the treatment plan during the course of treatment, based on changes in patient anatomy.[7] In its earlier form, ART was typically applied in an offline manner, where adjustments were made based on cumulative data from previous treatment sessions. While offline ART offers improvements over conventional radiotherapy, it is still limited by its inability to account for real-time anatomical variations.[8]

Online adaptive radiotherapy (oART) represents the next evolution of ART. Unlike offline ART, oART incorporates real-time data during each treatment session, allowing clinicians to adjust the treatment plan on the spot to reflect the patient's current anatomy.[9] This innovation is made possible by advancements in artificial intelligence (AI), deformable image registration, and improvements in imaging techniques, such as cone-beam CT (CBCT), which provide up-to-date visualisations of the tumour and surrounding tissues immediately before each fraction.[10]

There is emerging evidence that this transition from offline to online ART enables clinician to potentially reduce planning margins, improve target coverage, and better spare OARs, aiming for a more personalised and precise treatment.[6, 11-21] Hence, this technology review was requested to assess the effectiveness, safety and cost on the use of online adaptive radiotherapy by Ethos™ in cancer population.

2.0 OBJECTIVE / AIM

The objective of this technology review is to assess the effectiveness, safety and cost-effectiveness of online adaptive radiotherapy (oART) by Ethos™ in cancer population.

3.0 TECHNICAL FEATURES

Ethos™ therapy, developed by Varian Medical Systems, is a radiotherapy platform that incorporates artificial intelligence (AI) and machine learning to enable real-time adaptive radiation therapy. This system is designed to address the challenges of traditional radiotherapy by allowing on-the-spot adjustments based on daily anatomical changes in patients. The key feature of Ethos is its ability to perform on-couch adaptive therapy, where the treatment plan is recalculated and optimised while the patient remains on the treatment couch. This real-time adaptation is powered by AI-driven algorithms that automatically contour and adjust target volumes and organs at risk (OARs) based on daily cone-beam CT (CBCT) imaging.[22]

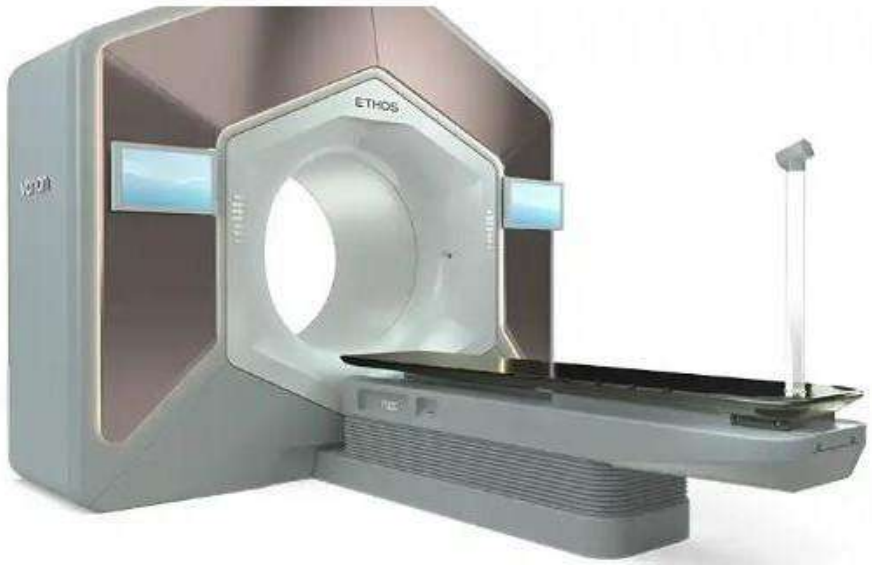


Figure 1: Ethos™ Therapy

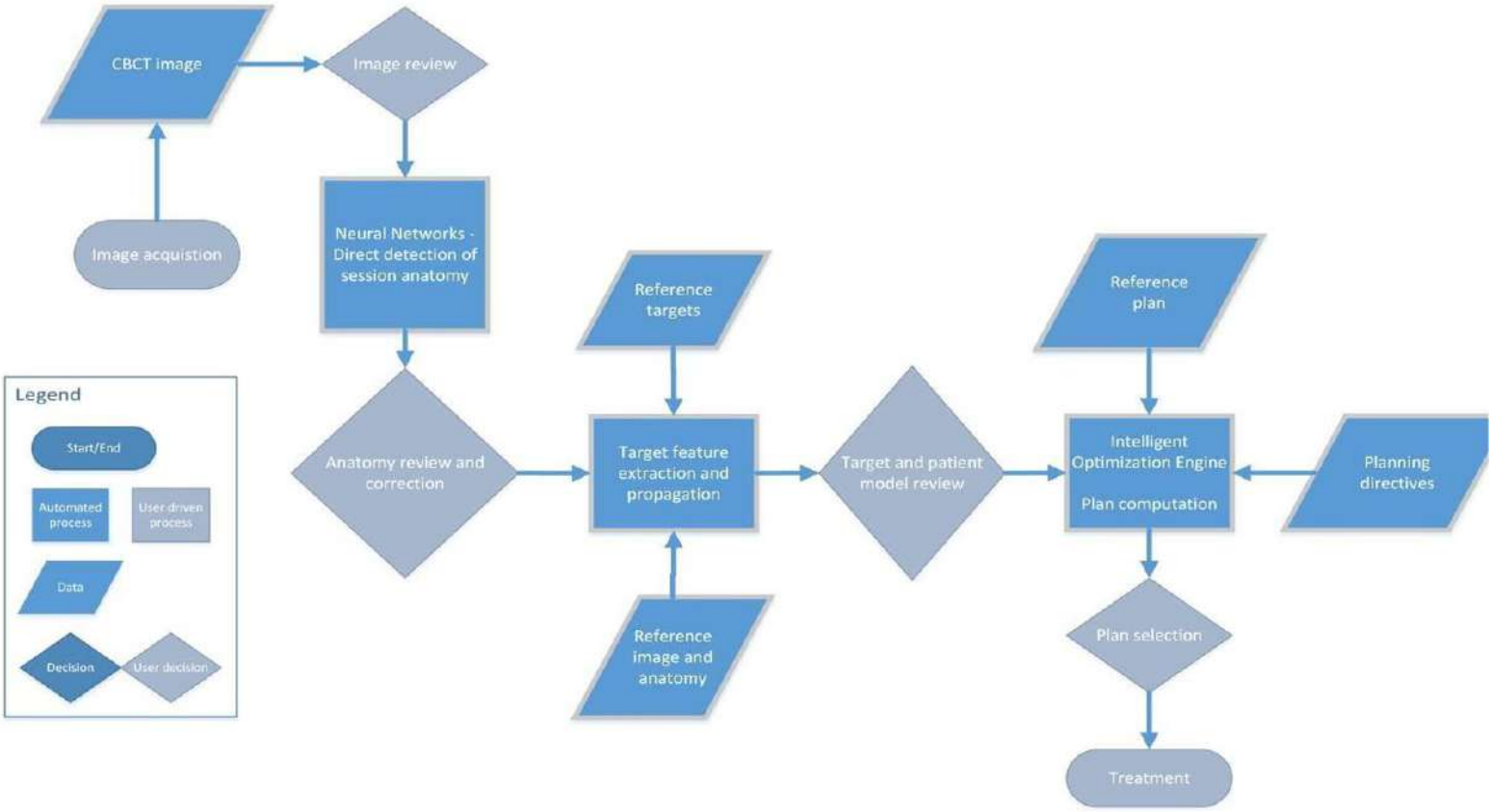
The platform's is based on convolutional neural networks (CNNs) where it detects and segment key anatomical structures, referred to as "influencers," which have the most significant impact on tumour and OAR positioning. Once the daily anatomy is captured, the system generates both the original and an adapted treatment plan, giving clinicians the flexibility to choose the optimal plan for that day's session.[22]

Ethos utilised an Intelligent Optimization Engine (IOE) to automate the treatment planning process. This engine translates clinical goals into objective functions, optimising the plan based on real-time patient anatomy. The system can produce both intensity-modulated

radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) plans, optimising beam configurations and dose delivery.[22]

Ethos also integrated with RapidPlan® knowledge-based planning, which uses historical treatment data to predict dose-volume histograms (DVH) for modelled structures. The system also includes features like automated dose accumulation, which reconstructs and tracks the dose delivered to the patient each day, monitor treatment progress as initially intended.[22]

Figure 2: Ethos Therapy on-couch adaptive workflow adapted from Archambault et al. (2020). [23]



4.0 METHODS

4.1 SEARCHING

Electronic databases searched through the Ovid interface:

- MEDLINE(R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE (R) 1946 to July 12, 2024
- EBM Reviews – Cochrane Central Registered of Controlled Trials – June 2024
- EBM Reviews – Cochrane Database of Systematic Reviews – 2005 to July 10, 2024
- EBM Reviews – Health Technology Assessment – 4th Quarter 2016
- EBM Reviews - NHS Economic Evaluation Database - 1st Quarter 2016

Other databases:

- PubMed
- Other websites: US FDA, INAHTA, MOH

General databases such as Google Scholar was used to search for additional web-based materials and information. Additional articles retrieved from reviewing the bibliographies of retrieved articles. The search was limited to articles on humans. There was no language limitation in the search. **Appendix 1** showed the detailed search strategies. The last search was conducted on the 15th July 2024

4.2 SELECTION

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria. Relevant articles were then critically appraised depending on the type of the study design. Studies were graded according to *US/ Canadian Preventive Services Task Force* (**Appendix 2**). All data were extracted and summarized in the evidence table as in **Appendix 3.**

The inclusion and exclusion criteria were:

Inclusion criteria:

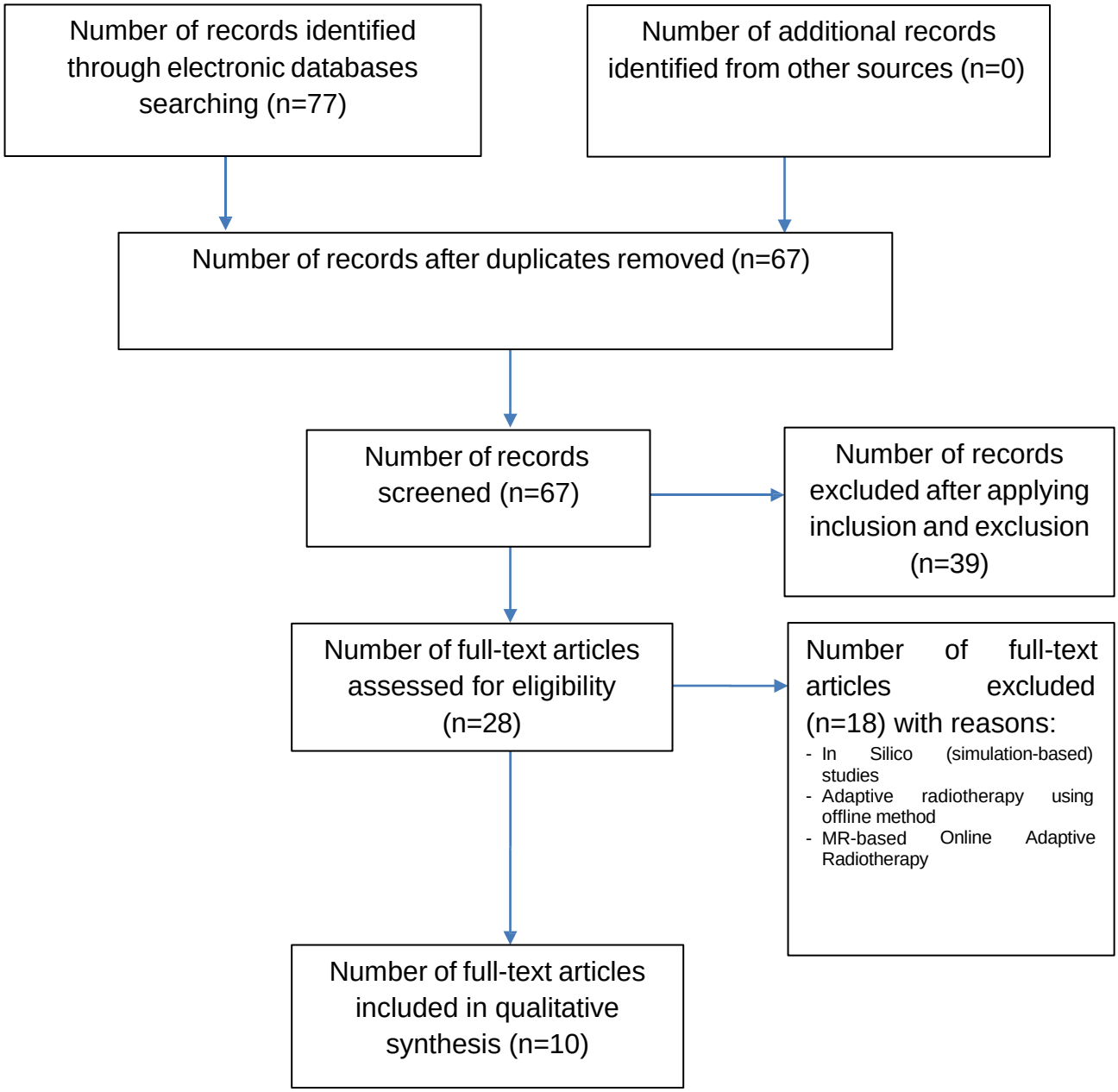
Population	Cancer patient
Interventions	Online adaptive radiotherapy using Ethos
Comparators	Conventional radiotherapy, Other type of radiotherapy
Outcomes	<u>Effectiveness:</u> Dosimetry Benefit Time Efficiency Accuracy of contouring Plan Quality Patient / User Satisfaction <u>Safety:</u> Adverse event, complications Acute organ toxicities <u>Organizational:</u> Training, resource/infrastructure implication <u>Economic Implications:</u> Cost, cost-analysis, cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis, cost-minimization, budget impact analysis
Study design	Health Technology Assessment (HTA), Systematic reviews (SR), Randomised control trials (RCTs), Observational studies
Type of publication	English, full text articles

Exclusion criteria:

Study design	Case report, case series survey, anecdotal, animal studies, simulation studies.
Type of publication	Non-English

5.0 RESULTS

A total of 77 titles were retrieved from the scientific databases such as Medline via OVID, and PubMed, using the search term; *radiotherapy*, *radiotherapy planning*, *image guided radiotherapy*, *computer assisted*, *artificial intelligence*, *deep learning*, *Ethos TPS*, *Varian Ethos*, and *Ethos Therapy*. Search were limited to *English*, and *Human*. After reading, appraising and applying the inclusion and exclusion criteria, 10 observational studies were included in this review. An overview of the search and study selection is depicted in **Figure 3.**



5.1 RISK OF BIAS / QUALITY ASSESSMENT OF INCLUDED STUDIES

All of the observational cohort studies included in this review were appraised using Critical Appraisal Skill Programme (CASP) checklist to assess for risk of bias. These assessments involved answering a pre-specified question of those criteria assessed and assigning a judgment relating to the risk of bias.

+	Indicates low risk of bias
?	indicates unclear risk of bias / some concerns
-	Indicates high risk of bias

Assessment of Cohort Study using Critical Appraisal Skills Programme (CASP) Checklist

Criteria assessed	Selection of cohort	Exposure accurately measured	Outcome accurately measured	Confounding factors	Follow-up of subjects
Li R et al. (2024)[5]	+	+	+	+	?
Zhang Y et al. (2024)[24]	+	+	+	+	?
Guberina M et al. (2024)[9]	+	+	+	+	?
Bak ME et al. (2023)[25]	+	+	+	+	?
Nellisen KJ et al. (2023)[26]	+	+	+	+	?
Zwart LG et al. (2022)[3]	+	+	+	+	?
Astrom LM et al. (2022)[27]	+	+	+	+	?
Byrne M et al. (2022)[28]	+	+	+	+	?
Sibolt P et al. (2021)[8]	+	+	+	+	?
De Jong R et al. (2020)[29]	+	+	+	+	?

Figure 4: Quality assessment of cohort studies (CASP)

All studies had a clearly focused research question related to the feasibility, efficacy, and dosimetric benefits of online adaptive radiotherapy (oART) in many cancers' population, such as prostate, bladder, rectal, and head and neck cancer. Most studies recruited their cohorts from consecutive clinical populations, particularly those treated with oART. This approach generally minimises selection bias. However, a few studies, especially those involving smaller sample sizes might exposed to selection bias due to limited generalisability and could potentially overestimate the effects due to smaller patient pools. The exposure, which was online adaptive radiotherapy using technologies like Varian Ethos, CBCT, and image-guided planning, was clearly defined and consistently measured across the studies. The adaptive workflow was rigorously documented in all studies. The outcomes measured in all of the studies were mostly comprises of objective dosimetric measurement (target coverage, dose to organs at risk [OARs], and plan quality). This dosimetric measurement were measured accurately using standardised and established metrics such V95%, V45Gy, and Dmean, which are clinically accepted measures in radiotherapy. However, although short-term dosimetric outcomes were robustly measured throughout the studies, the lack of long-term follow-up in all studies introduces a potential bias in understanding the full clinical impact. None of the studies included survival, tumour control, or long-term toxicity data, which are critical for assessing the real-world effectiveness of oART.

5.2 OVERVIEW OF INCLUDED STUDIES

This review includes 10 studies published between 2020 and 2024, conducted in various countries such as the United States, Denmark, the Netherlands, Germany, China and Australia, primarily in advanced radiotherapy centres. The studies involved a total of 244 patients with cancer who received over 2,000 fractions of radiotherapy. Multiple different research designs are being used, including prospective cohort studies, retrospective cohort studies, and mixed-method studies combining in silico modelling with clinical observations. These designs aimed to evaluate the efficacy and feasibility of online adaptive radiotherapy (oART), mainly delivered through the Varian Ethos system, which integrates artificial intelligence (AI)-assisted contouring and real-time plan adjustments.

The primary intervention was oART, and the comparator in most studies was traditional image-guided radiotherapy (IGRT) or non-adaptive scheduled treatment plans. The key outcomes measured across the studies included target volume coverage, dose to organs-at-risk (OARs), and treatment efficiency. Dosimetric parameters such as planning target volume (PTV) coverage (V95% or V100%) and OAR doses (e.g., bladder, rectum, lung, heart) were consistently reported. Several studies also examined secondary outcomes like treatment time, workflow efficiency, and patient satisfaction.

Study	Study Design	Number of patients	Intervention	Comparison	Key Outcomes
Guberina et al. (2024) Germany	Prospective Cohort	59 head and neck cancer patients, applied to 46 treatment fractions.	Adaptive Plan	Scheduled Plan	**1. <u>Target Coverage:</u>** EUDCTV values by the adaptive plans 97.1% (95% CI 96.6–99.5%) vs scheduled plans 78.1% (95% CI 61.8–88.7%) EUDCTV stayed above 95% at PTV margins of = 3 mm in adapted plan vs for all the scheduled plans did for margins = 5 mm **2. <u>Organ Sparing:</u>** The EUDOAR- values for the larynx and the parotid gland were **significantly lower** for the adaptive compared with the scheduled plans. (p<0.001) **3. <u>Time efficiency:</u>** The adaptive treatment lasted in median **34.5min** (range: 12.0 – 49.0 min)
Zwart et al. (2022) Netherlands	Prospective Cohort	11 prostate cancers patients with a total of 220 fractions.	Adaptive Plan	Scheduled Plan	**1. <u>Target Coverage:</u>** Adaptive plans **improved PTV coverage** in all fractions. PTV60Gy and CTV60Gy coverage for scheduled plan vs adapted plan were (**86.7%** ± 6.2%. vs **99.4%** ± 0.5%.) and (**99.5%** ± 1.0%. vs **99.9%** ± 0.4%.), respectively. **2. <u>Organ Sparing:</u>** In **14% of fractions (30/220)**, the V60Gy of bladder and rectum were below the constraints only in the adapted plan. Mean Decrease in V60Gy for bladder and rectum in the adapted plan was **3.9%** ± 1.8% (range: 0.6–9.5%) **3. <u>Plan Quality:</u>** The adapted plan was **chosen in all 220 fractions** due to better PTV60Gy coverage compared to the scheduled plan **4. <u>Time Efficiency:</u>** Mean total treatment time were **17.5 ± 3.2** (range: 10.8 – 28.8) minutes
Byrne et al. (2022) Australia	Mixed retrospective simulation and clinical study	12 prostate cancers patients with 182 simulated fractions with additional 6 prostate cancer patient with 184 clinical fractions.	Adaptive Plan	Scheduled Plan	**1. <u>Plan Quality:</u>** Adaptive plan was selected in **95%** of fractions. In **78%** of fractions, the adaptive plan met more clinical goals than the scheduled plan. Only **7%** of fractions, the scheduled plan met more clinical goals than the adaptive plan. **2. <u>Time Efficiency:</u>** The online adaptive recontouring and replanning process was carried out in **19 min** on average.
Li et al. (2024) United States	Retrospective Cohort	26 locally advanced lung cancers with total 126 oART fractions.	Adaptive Plan	Schedule Plan	**1. <u>Target Coverage:</u>** For oART, the ITV and planning target volume (PTV) coverage (V100%) remained high at **99.2%** and **93.9%** respectively. Adapted plan marked an **improvement of 2.9%** for ITV and **6.8%** for PTV (P< 0.05) vs non- adapted plan. In cases where tumours grew by more than 10%, oART achieved 93.1% V100% coverage compared to 76.4% with non-adaptive plans, representing a **17.2% improvement** in PTV coverage (P < .05) **2. <u>Organ Sparing:</u>**

15**94.1%** of adapted plan met critical organ-at-risk (OAR) contraint compared to **81.9%** in non-adaptive

					Gy). **3. Plan Quality:** Of the oART fractions, 4 (4.8%) used scheduled plans, and **122 (95.2%)** used adaptive plans. **4. Time Efficiency:** The mean total time for the online ART session, was **17.14** ± 6.30 minutes
Bak et al. (2023) Denmark	Retrospective Cohort	20 vulvar carcinoma patients with 527 fractions.	Adaptive Plan	Schedule Plan	**1. Target Coverage:** Adaptive plans provided a mean CTV D95% coverage of **100.0%** ± 0.8%, compared to 98% ± 5% in scheduled plans. (p<0.0001). **2. Organ Sparing:** Dose reductions for normal tissues were not significant in all cases, but the implementation of **margin reduction** is feasible in adaptive plans. **3. Plan Quality:** Out of 527 fractions**, 335 (63.5%)** used the adapted plan. **4. Time Efficiency:** Average adaptation time of **15** (range: 12-17) minutes
Zhang et al. (2024) China	Prospective Cohort	10 cervical cancer patients with 265 fractions	Adaptive Plan	Schedule Plan	**1. Target Coverage:** Adaptive plans resulted in **superior target volume coverage** (V100% for CTV-N was 99.94% ± 0.08%, and CTV-V 99.8% ± 0.04%) compared to scheduled plans. **2. Organ Sparing:** The oART also provided **better sparing of organs-at-risk** (OARs), significantly reducing high-dose exposure to the bladder, rectum, and bowel. **3. Plan Quality:** **92%** of the automatically generated contours required no or only minor edits. The paired CTV had high overlap rates, with DSC values **greater than 0.75**. **4. Time Efficiency:** Average total adaptive time is **7 min 46 s (range 6 min 47 s to 9 min 22 s)** for postoperative cervical cancer and **8 min 29 s (range 7 min 11 s to 10 min 03 s)** for oART uterine cervical cancer.
Nellisen et al. (2023) Netherlands	Prospective Cohort	43 bone metastases patients with 47 treatment fractions	Adaptive Plan	Schedule Plan	**1. Target Coverage:** Adaptive plans were preferred in 100% of cases due to **significant improvements in target coverage** (PTV/CTV V95%, p-value <0.005) compared to the original treatment plan. **2. Time Efficiency:** The average total treatment time using oART took a median of **85 minutes**, including **30 minutes for on-couch adaptation**
Åström et al. (2022) Denmark	Prospective Cohort	16 patients with muscle invasive bladder carcinoma with 297 oART fractions.	Adaptive Plan	Schedule Plan	**1. Target Coverage:** 292 out of 297 oART fractions were delivered using adapted plans due to **improved PTV60Gy coverage** compared to scheduled plans. PTV-T coverage was inadequate (V95% < 99%), in 89.5% of the scheduled plan, and with re-optimization, PTV-T coverage was increased to 99.7% of the adapted plans. In addition, CTV-T Coverage was insufficient in 19.6% of scheduled plans, but all adapted plans regained full coverage (p

					< 0.001). **2. <u>Organ Sparing:</u>** Adapted plan cause a **70.7%** (IQR: 35.9-94.8%). relative reduction in rectal V50Gy and an **18.8%** (IQR: 12.7-27.9%) relative reduction in bowel bag V45Gy. **3. <u>Plan Quality:</u>** CI and HI (Conformity Index and Homogeneity Index) are significantly better in adapted plans **(p < 0.001).** 4. **<u>Time Efficiency:</u>** The median adaptation time was **13.9** (IQR: 11.9–16.6) minutes.
Sibolt et al. (2021) Denmark	Mixed retrospective simulation and clinical study	26 pelvic cancer patients with 100 simulated fractions and additional 5 pelvic cancer patients with 20 clinical oART fractions.	Adaptive Plan	Schedule Plan	**1. <u>Target Coverage:</u>** In regards to CTV V95% Coverage**, all adapted plans achieved 100% coverage**, while 4 of 15 scheduled bladder treatments had CTV V95% < 98%. **2. <u>Organ Sparing:</u>** Adapted plan cause a **24–30% reduction** in V45Gy to the bowel cavity, compared to non-adapted plan. **3. <u>Plan Quality:</u>** The automated TPS were **comparable** to clinical plans (>95% VMAT) (p < 0.001). Over **75% of AI-generated** segmentations during simulated online adaptive radiotherapy (oART) required either **no edits or only minor** adjustments **4. <u>Time Efficiency:</u>** Mean adaptation time were **17.6** (IQR: 4.0)
De Jong et al. (2020) Netherlands	Prospective Cohort	20 rectal cancer patients with 300 fractions.	Adaptive Plan	Schedule Plan	**1. <u>Target Coverage:</u>** Improved CTV D99% from 98.5% (plan selection) to 98.7% (oART) **2. <u>Organ Sparing:</u>** Median normal tissue irradiated with 95% of the prescribed dose **reduced** from 642 cm^3 (plan selection) to 237 cm^3 (ART) **(p < 0.001).** Median reduction of V15Gy bowel bag by **126 cm^3** (range: -206 to -40 cm^3) in LCRT **and 62 cm^3** (range: -105 to -51 cm^3) in SCRT. V15Gy bladder similarly reduced with median reduction by **24%** in LCRT and **11%** in SCRT.

5.3 EFFECTIVENESS

5.3.1 Online adaptive radiotherapy in head and neck cancer

Guberina et al. (2024) conducted a prospective cohort study in Germany to investigate the use of kV-CBCT-based online adaptive radiotherapy (oART) for head and neck cancer. Fifty-nine patients from the period of 1.12.2021 to 31.01.2023 were treated with oART, applied to 46 treatment fractions. The adaptive plans generated during oART were compared with initial schedule plans. The adaptive plans provided better dosimetric outcomes, with the equivalent uniform dose (EUD) for the clinical target volume (CTV) achieving 97.1% (95% CI 96.6 to 99.5%) in adaptive plans compared to 78.1% (95% CI 61.8 to 88.7%) in scheduled plans. EUD_{CTV} for the accumulated dose distributions stayed above 95% at PTV margins of = 3 mm for all 8 analysed treatment phases. In comparison, the scheduled (non-adaptive) treatment plans required PTV margins of 5mm to achieve similar target coverage. Doses to organs at risk (OARs) (EUD_{OAR-} for larynx and parotid glands), were significantly reduced ($p < 0.001$) in the adaptive plans, showing benefit for using oART in sparing critical structures in the head and neck region. The median adaptive treatment time were reported 34.5min (range: 12.0 to 49.0 min) from opening patient file online to treatment delivery.[9]

5.3.2 Online adaptive radiotherapy in prostate cancer

Zwart et al. (2022) conducted a study in Netherlands to evaluate the feasibility of the clinical implementation of cone-beam computed tomography (CBCT)-guided online adaptive radiotherapy (oART) for prostate cancer patients. This prospective cohort study involved 11 prostate cancer patients recruited between February and July 2020, treated with CBCT-guided oART. A total of 220 fractions were delivered, with adaptive planning compared to scheduled treatment. The main findings showed that adaptive plans improved PTV coverage in all fractions. The adapted plan was chosen in all 220 fractions. The PTV60Gy and CTV60Gy coverage for scheduled plan vs adapted plan were (86.7% ± 6.2%. vs 99.4% ± 0.5%.) and (99.5% ± 1.0%. vs 99.9% ± 0.4%.), respectively. The V60Gy dose to the bladder and rectum was reduced in 30 out of 220 fractions with the adaptive plan, leading to a significant reduction in toxicity risks. Mean Decrease in V60Gy for bladder and rectum in the adapted plan was 3.9% ± 1.8% (range: 0.6 to 9.5%). In this study, 2 out of 11 patients were identified to be having treatment-related acute toxicities. One patient experienced grade 1 proctitis and one patient grade 2 urinary urgency after treatment. The mean total treatment time from CBCT acquisition to delivery was 17.5 ± 3.2 (range: 10.8 to 28.8) minutes.[3]

Byrne et al. (2022) conducted a mixed-method study in Australia to evaluate the accuracy of artificial intelligence (AI)-generated contours and treatment quality in prostate cancer using the Ethos system. This mixed retrospective simulated and clinical study analyzed 182 simulated fractions and 184 clinical fractions. A total of 182 simulated fractions were taken from retrospective dataset of 12 prostate cancer patients of intact prostate and prostate bed, with and without nodes. A further 184 clinical fractions were added from six clinical patients that underwent Ethos adaptive treatment. The adaptive plan was compared to scheduled plan. From the fractions analysed, 11% of the AI-generated contours, referred to as influencer contours, did not require any changes, while 81% required only minor adjustments in any given fraction. The frequency of edits for both target volumes and non-influencer organs at risk (OARs) varied considerably between different targets and OARs. Overall, 72% of all target contours did not require any editing. The adaptive plan was selected as the preferred option in 95% of the treatment fractions, as it met more treatment goals than the scheduled plan in 78% of cases. In 15% of the cases, both the adaptive and scheduled plans achieved an equal number of goals. The process of recontouring and replanning with the online adaptive system took an average of 19 minutes per session[28]

5.3.3 Online adaptive radiotherapy in locally advanced lung cancer

Li et al. (2024) conducted a retrospective cohort study in United States to evaluate the efficacy and workflow of the adaptive-on-demand (AOD) radiation therapy using the Ethos system for locally advanced lung cancer. Twenty-six patients with locally advanced lung cancer were included, and the study compared adapted plan to non-adaptive scheduled plans. From total 792 fractions evaluated in this study, 666 (84.1%) were IGRT, and 126, (15.9%) with oART. Of the oART fractions, 4 (4.8%) used scheduled plans, and 122 (95.2%) used adaptive plans. This study reported that average internal tumour volumes (ITV) reduced by 26.6% ± 23.3% from the initial by the final treatment week. Despite these changes, with oART, the ITV and planning target volume (PTV) coverage (V100%) remained high at 99.2% and 93.9% respectively. When in compared to non-adaptive plan, this marked an improvement of 2.9% for ITV and 6.8% for PTV ($P < 0.05$). In cases where tumours grew by more than 10%, oART achieved 93.1% V100% coverage compared to 76.4% with non-adaptive plans, representing a 17.2% improvement in PTV coverage ($P < .05$). Critical organs-at-risk (OAR) constraints were met 94.1% of the time with oART, compared to 81.9% with non-adaptive plans. There were reductions in dose to the heart (1.32 Gy), oesophagus (1.34 Gy), and lung (1.75 Gy). The mean time for the online ART session, from the end of CBCT acquisition to final plan approval, was 17.14 ± 6.30 minutes.[5]

5.3.4 Online adaptive radiotherapy in cervical and vulvar cancer

Bak et al. (2023) conducted a retrospective cohort study in Denmark where 20 patients with vulvar carcinoma underwent online adaptive radiotherapy (oART) with the Varian Ethos system. The study is aimed to explore whether oART is relevant for these patients and if it improves CTV coverage and/or reduces dose to organs at risk (OARs). The study compared scheduled and adaptive treatment plans over 527 fractions. Out of 527 fractions, 335 (63.5%) used the adapted plan; 293 of these were verified, while 42 fractions had issues with data import, especially with one patient due to incompatible CBCT scans. The study findings indicated that adaptive plans provided a mean CTV D95% coverage of 100.0% ± 0.8%, compared to 98% ± 5% in scheduled plans, ($p<0.0001$). Dose reductions for normal tissues were not significant in all cases, but the implementation of margin reduction is feasible in adaptive plans. Additionally, 63.5% of the fractions used the adaptive plan due to superior dosimetric outcomes, with an average adaptation time of 15 (range: 12 to 17) minutes.[25]

Zhang et al. (2024), conducted a prospective cohort study in China evaluating the feasibility and accuracy of daily online adaptive radiotherapy (oART) for cervical cancer patients using automatic contouring. A total of 10 patients were enrolled between December 2022 and June 2023, receiving a combined 265 treatment fractions (125 for postoperative and 140 for uterine cervical cancer). The intervention was daily oART guided by iterative cone-beam computed tomography (iCBCT), with the comparator being non-adaptive scheduled plans. The study assessed the accuracy of automatic contouring using metrics such as average surface distance (ASD), centroid deviation, and dice similarity coefficient (DSC). Main findings showed that 92% of the automatically generated contours required no or only minor edits. The paired CTV had high overlap rates, with DSC values greater than 0.75. In dosimetric terms, the oART plans resulted in superior target volume coverage (V100% for CTV-N was 99.94% ± 0.08%, and CTV-V 99.8% ± 0.04%) compared to scheduled plans. The oART also provided better sparing of organs-at-risk (OARs), significantly reducing high-dose exposure to the bladder, rectum, and bowel. The average total adaptive time for oART postoperative cervical cancer and oART uterine cervical cancer from first iCBCT acquisition to plan selection were 7 min 46 s (range 6 min 47 s to 9 min 22 s) and 8 min 29 s (range 7 min 11 s to 10 min 03 s).[24]

5.3.5 Online adaptive radiotherapy in bone metastases.

Nellisen et al. (2023) conducted a prospective cohort study in Netherland focusing on a same-day adaptive radiotherapy workflow for bone metastases. The aim of this study was to describe the implementation of CT-free adaptive workflow using Ethos for patients referred for palliative radiotherapy. Forty-three unique patients were selected from December 2021 till October 2022. Forty-seven treatments were performed, with 4 patients treated twice due to different metastatic locations. Adaptive plan was compared with the scheduled plan. Adaptive plans were preferred in 100% of cases due to significant improvements in target coverage (PTV/CTV V95%, $p <0.005$) compared to the original treatment plan calculated on daily anatomy. All treatment

plans had a high gamma pass rate, with an average of 99.7% and none below clinical acceptance criteria (>95%). In terms of patient satisfaction, 60% of patients found the time spent on the treatment couch acceptable, and 80% indicated they would choose the same treatment pathway for future procedures. The average total treatment time using oART took a median of 85 minutes, including 30 minutes for on-couch adaptation.[26]

5.3.6 Online adaptive radiotherapy in bladder cancer

Åström et al. (2022) conducted a prospective cohort study in Denmark to investigate the feasibility and dosimetric impact of online adaptive radiotherapy (oART) and compare it to the standard cone-beam computed tomography (CBCT) guided (non-adaptive) approach, for patients with urinary bladder cancer. In this clinical study, he included 16 patients with muscle-invasive bladder cancer who received a total of 512 treatment fractions. Out of 512 fractions, 297 of them being delivered using oART. About 292 of the adapted plans were chosen due to improved PTV60Gy coverage compared to scheduled plans. The CI and HI (Conformity Index and Homogeneity Index) were significantly better in adapted plans ($p < 0.001$). In terms of dosimetric outcomes, PTV-T coverage was inadequate (V95% < 99%), in 89.5% of the scheduled plan, and with re-optimization, PTV-T coverage was increased to 99.7% of the adapted plans. In addition, CTV-T Coverage was insufficient in 19.6% of scheduled plans, but all adapted plans regained full coverage ($p < 0.001$). Compared to non-adaptive plans, oART reduced the PTV by a median of 33.9% (IQR: 24.2 to 45.0%), which translated to a 70.7% (IQR: 35.9 to 94.8%). relative reduction in rectal V50Gy and an 18.8% (IQR: 12.7 to 27.9%) relative reduction in bowel bag V45Gy. The adaptive plans consistently provided full target coverage while reducing dose exposure to the gastrointestinal tract. The median adaptation time was 13.9 (IQR: 11.9 to 16.6) minutes from CBCT completion to plan review and quality assurance (QA).[27]

Sibolt et al. (2021) conducted a mixed method study in Denmark to evaluate the feasibility, time-efficiency, and potential clinical impact of cone-beam computed tomography (CBCT)-guided and artificial intelligence (AI)-driven online adaptive radiotherapy (oART) using Ethos for pelvic cancer This study involved pre-treatment planning simulations using retrospective clinical data of 26 pelvic cancer patient with additional 5 patient that were actually treated with Ethos systems. The automated TPS achieved PTV coverage and OAR doses comparable to clinical plans (>95% VMAT) ($p < 0.001$). Over 75% of AI-generated segmentations during simulated online adaptive radiotherapy (oART) required either no edits or only minor adjustments, and in 88% of cases, the adapted plan outperformed the standard approach. Bladder cancer patients saw a 42% (IQR: 19%) ($p<0.001$) median reduction in primary PTV when using oART approach. In regards to CTV V95% coverage, all adapted plans achieved 100% coverage, while 4 of 15 scheduled bladder treatments had CTV V95% < 98%. High-dose PTV volume reduction in bladder cases led to a 24–30% reduction in V45Gy to the bowel cavity, compared to non-ART. For the clinical adaptive treatment session using Ethos, a median procedure time of 17.6 (IQR: 4.0) minutes from CBCT acceptance to the start of treatment.[8]

5.3.7 Online adaptive radiotherapy in rectal cancer.

De Jong et al. (2020) conducted a prospective cohort study in Netherlands, to compare online adaptive radiotherapy (oART) with a plan selection strategy (PS) for rectal cancer. The first 20 patients treated with PS between May–September 2016 were included. The study used 300 CBCT scans for 20 patients (10 short-course radiotherapy [SCRT] and 10 long-course radiotherapy [LCRT]). Online adaptive radiotherapy (oART) treatment plan was compared with pre-treatment plan selection strategy. Result showed that oART improved CTV D99% from 98.5% (plan selection) to 98.7% (oART). Median normal tissue irradiated with 95% of the prescribed dose reduced from 642 cm^3 (plan selection) to 237 cm^3 (ART) ($p < 0.001$). In addition, oART resulted in lower doses to OARs, with V15Gy bowel bag reduced by a median of 126 cm^3 (range: -206 to -40 cm^3) in LCRT and 62 cm^3 (range: -105 to -51 cm^3) in SCRT. V15Gy bladder similarly reduced with median reduction by 24% in LCRT and 11% in SCRT.[29]

5.3 SAFETY

There was limited evidence on the safety of online adaptive radiotherapy by Ethos. In all of the studies that were reviewed, only one study mentioned regarding acute toxicities after the treatment. Zwart et al (2022) reported two out of 11 patients were identified to be having treatment-related acute toxicities. One patient experienced grade 1 proctitis and one patient had grade two urinary urgency after treatment.[3]

Ethos therapy by Varian has received 510(k) clearance from U.S Food and Drug Administration (FDA) and CE mark in February 2023.[30]

5.4 COST / COST-EFFECTIVENESS ANALYSIS

There was no retrievable evidence on the cost or cost-effectiveness of online adaptive radiotherapy (oART).

McComas et al. (2023) has conducted a study to evaluate the opportunity cost associated with cone-beam computed tomography (CBCT) guided online adaptive radiotherapy (oART) focusing on time and human resource requirement in comparison to conventional image-guided radiation therapy (IGRT). The goal was to determine if the dosimetric benefits of oART justify the additional time and cost. This study involved 21 patients who received adaptive radiation therapy across various genitourinary disease sites including prostate, prostate bed, bladder and rectum. Collectively, these patients underwent 417 treatment fractions, with 415 being adapted plans. The study used a time-driven activity-based costing TDABC) model to quantify the time and resources requirement of oART. Time between two CBCT in each adaptive fractions in oART workflow was taken as a metric for the added workload. In result, the study found that median time for each adaptive fraction was 15.97 (IQR: 13.23 to 18.83) minutes, with more complex treatments, such as those involving pelvic nodal coverage or stereotactic body radiation therapy (SBRT), required more time. The per fraction cost of online ART was estimated at $103.58, accounting for the time and involvement of a radiation oncologist, physicist, dosimetrist, and two therapists. This represents the

additional cost on top of standard IGRT treatments. Dosimetric benefits were notable, with the adapted plans improving planning target volume (PTV) coverage by an average of 15.8% compared to scheduled (non-adaptive) plans.[31]

5.5 ORGANISATIONAL

Few organisational issues have been identified throughout the studies included. A major limitation in implementing online adaptive radiotherapy (oART) is the increased time required per treatment session due to added task such real-time imaging, contouring, and replanning processes inherent to oART.[9] This increased duration can put a strain on clinical schedules and available resources, especially in high-volume treatment centres. Apart from that, implementing oART requires a highly skilled multidisciplinary team including radiation oncologist, physicist, dosimetrist and therapist who must be available during each session to perform real-time adjustment. There also the need for additional staff training, particularly in editing and validating AI automated contouring system.[8,28] Online adaptive radiotherapy potential clinical benefits may vary depending on the anatomical site being treated. The benefit of oART may be enhanced in more anatomically complex areas such as pelvic and bladder region and its advantages might be less pronounced in regions with more stable anatomy and tumour progression.[25,27] Thus, careful patient selection may be needed when considering oART. System such oART might needed extra infrastructure added to existing system for example to process and store real-time data. There is also a question of whether it can be integrated to already existing system in the local hospital.[32] Incorporated AI-generated contouring system may be exposed to the risk of bias depending on its training set data, which may not be representative of the local population. In any case, AI models should ideally be trained on a representative national population.[32]

5.6 LIMITATION

One of the limitations of this review is the language restriction applied during the systematic search, which may have led to the exclusion of relevant studies published in languages other than English, thereby narrowing the scope of the review. Additionally, the lack of higher-quality evidence, such as randomised controlled trials or systematic reviews, makes it challenging to establish causality. The relatively small number of patients included in the studies may potentially overestimated the outcome measures. Furthermore, the varying approaches to online adaptive workflows used across different centres may affect the generalizability of the results in local contexts. Many of the studies also had relatively short follow-up periods, limiting the availability of long-term data. While several studies reported short-term dosimetric improvements, there is still insufficient comprehensive data on the long-term clinical outcomes of oART, such as survival rates, tumour control, and quality of life. Finally, the lack of evidence regarding the cost-effectiveness of oART complicates efforts to assess its financial impact on healthcare systems.

6.0 CONCLUSION

There is moderate quality of evidence from observational studies showing that online adaptive radiotherapy (oART) improves short-term dosimetric outcomes, such as target coverage and organ sparing, in patients with head and neck, lung, bone metastases, and pelvic cancer. However, adaptive treatment time requires an additional 13 to 34 minutes for plan re-optimization based on the patient's anatomy of the day. In terms of safety, there is limited evidence available on the safety aspects of oART. Regarding cost and cost-effectiveness, no retrievable evidence exists on the economic impact of using Ethos therapy for cancer treatment. From an organizational perspective, implementing oART necessitates a multidisciplinary team with additional training in editing and validating AI-driven contouring. Considerations must also be given to ensuring interoperability for seamless integration into the existing healthcare ecosystem.

[redacted]

[redacted]

7.0 REFERENCE

1. Ministry of Health Malaysia. Summary of Malaysia National Cancer Registry Report 2017-2021 [Internet]. Available from: https://nci.moh.gov.my/images/pdf_folder/SUMMARY-OF-MALAYSIA-NATIONAL CANCER-REGISTRY-REPORT-2017-2021.pdf
2. Yahya N, Roslan N. Estimating radiotherapy demands in South East Asia countries in 2025 and 2035 using evidence-based optimal radiotherapy fractions. Asia-Pacific Journal of Clinical Oncology. 2018;14(5):e543-7.
3. Zwart LG, Ong F, Ten Asbroek LA, et al. Cone-beam computed tomography-guided online adaptive radiotherapy is feasible for prostate cancer patients. Phys Imaging Radiat Oncol 2022; 22: 98–103.
4. Thörnqvist S, Hysing LB, Tuomikoski L, et al. Adaptive radiotherapy strategies for pelvic tumors–a systematic review of clinical implementations. Acta Oncologica. 2016;55(8):943-58.
5. Li R, Zhuang T, Montalvo S, et al. Adapt-On-Demand: A Novel Strategy for Personalized Adaptive Radiation Therapy for Locally Advanced Lung Cancer. Practical Radiation Oncology. 2024.
6. Yoon SW, Lin H, Alonso-Basanta M, et al. Initial evaluation of a novel cone-beam CT-based semi-automated online adaptive radiotherapy system for head and neck cancer treatment–a timing and automation quality study. Cureus. 2020;12(8).
7. Lim-Reinders S, Keller BM, Al-Ward S, et al. Online adaptive radiation therapy. International Journal of Radiation Oncology* Biology* Physics. 2017;99(4):994-1003.
8. Sibolt P, Andersson LM, Calmels L, et al. Clinical implementation of artificial intelligence-driven cone-beam computed tomography-guided online adaptive radiotherapy in the pelvic region. Physics and imaging in radiation oncology. 2021; 17:1-7.
9. Guberina M, Guberina N, Hoffmann C, et al. Prospects for online adaptive radiation therapy (ART) for head and neck cancer. Radiation Oncology. 2024;19(1):4.
10. Stanley DN, Harms J, Pogue JA, et al. A roadmap for implementation of kV-CBCT online adaptive radiation therapy and initial first year experiences. Journal of Applied Clinical Medical Physics. 2023;24(7):e13961.
11. Uehara T, Nishimura Y, Ishikawa K, et al. Cone-beam computed tomography-guided online adaptive radiotherapy for pharyngeal cancer with whole neck irradiation: dose-volume histogram analysis between adapted and scheduled plans. Journal of Radiation Research. 2024;65(2):223-30.
12. Dohopolski M, Visak J, Choi B, et al. In silico evaluation and feasibility of near margin-less head and neck daily adaptive radiotherapy. Radiotherapy and Oncology. 2024; 197:110178.
13. Morgan HE, Wang K, Yan Y, et al. Preliminary evaluation of PTV margins for online adaptive radiation therapy of the prostatic fossa. Practical Radiation Oncology. 2023;13(4):e345-53.

14. Visak J, Inam E, Meng B, et al. Evaluating machine learning enhanced intelligent-optimization-engine (IOE) performance for ethos head-and-neck (HN) plan generation. Journal of applied clinical medical physics. 2023;24(7):e13950.
15. Nelissen KJ, Versteijne E, Senan S, et al. Evaluation of a workflow for cone-beam CT-guided online adaptive palliative radiotherapy planned using diagnostic CT scans. Journal of applied clinical medical physics. 2023;24(3):e13841.
16. Branco D, Mayadev J, Moore K, et al. Dosimetric and feasibility evaluation of a CBCT-based daily adaptive radiotherapy protocol for locally advanced cervical cancer. Journal of Applied Clinical Medical Physics. 2023;24(1):e13783.
17. Nasser N, Yang GQ, Koo J, et al. A head and neck treatment planning strategy for a CBCT-guided ring-gantry online adaptive radiotherapy system. Journal of Applied Clinical Medical Physics. 2023;24(12):e14134.
18. Mao W, Riess J, Kim J, et al. Evaluation of auto-contouring and dose distributions for online adaptive radiation therapy of patients with locally advanced lung cancers. Practical Radiation Oncology. 2022;12(4):e329-38.
19. Schiff JP, Price AT, Stowe HB, et al. Simulated computed tomography-guided stereotactic adaptive radiotherapy (CT-STAR) for the treatment of locally advanced pancreatic cancer. Radiotherapy and Oncology. 2022;175:144-51.
20. Schiff JP, Stowe HB, Price A, et al. In silico trial of computed tomography-guided stereotactic adaptive radiation therapy (CT-STAR) for the treatment of abdominal oligometastases. International Journal of Radiation Oncology* Biology* Physics. 2022;114(5):1022-31.
21. Moazzezi M, Rose B, Kisling K, et al. Prospects for daily online adaptive radiotherapy via ethos for prostate cancer patients without nodal involvement using unedited CBCT auto-segmentation. Journal of applied clinical medical physics. 2021;22(10):82-93.
22. Varian Medical Systems. Ethos adaptive therapy [Internet]. Available from: https://www.varian.com/products/adaptive-therapy/ethos
23. Archambault Y, Boylan C, Bullock D, et al. Making on-line adaptive radiotherapy possible using artificial intelligence and machine learning for efficient daily re-planning. Med Phys Int J. 2020;8(2).
24. Zhang Y, Wang G, Chang Y, et al. Prospects for daily online adaptive radiotherapy for cervical cancer: Auto-contouring evaluation and dosimetric outcomes. Radiation Oncology. 2024;19(1):6.
25. Bak ME, Jensen NK, Nøttrup TJ, et al. Clinical experiences with online adaptive radiotherapy of vulvar carcinoma. Acta Oncologica. 2023 Oct 3;62(10):1230-8.
26. Nelissen KJ, Versteijne E, Senan S, et al. Same-day adaptive palliative radiotherapy without prior CT simulation: Early outcomes in the FAST-METS study. Radiotherapy and Oncology. 2023;182:109538.
27. Åström LM, Behrens CP, Calmels L, et al. Online adaptive radiotherapy of urinary bladder cancer with full re-optimization to the anatomy of the day: Initial experience and dosimetric benefits. Radiotherapy and Oncology. 2022;171:37-42.
28. Byrne M, Archibald-Heeren B, Hu Y, et al. Varian ethos online adaptive radiotherapy for prostate cancer: Early results of contouring accuracy, treatment plan quality, and treatment time. Journal of applied clinical medical physics. 2022;23(1):e13479.
29. De Jong R, Crama KF, Visser J, et al. Online adaptive radiotherapy compared to plan selection for rectal cancer: quantifying the benefit. Radiation Oncology. 2020;15:1-9.
30. Varian Medical Systems. Varian receives FDA 510(k) clearance for Halcyon and Ethos [Internet]. 2020. Available from: https://www.varian.com/about-varian/newsroom/press-releases/varian-receives-fda-510k-clearance-halcyon-and-ethos

31. McComas KN, Yock A, Darrow K, et al. Online adaptive radiation therapy and opportunity cost. Advances in Radiation Oncology. 2023;8(3):101034.
32. National Institute for Health and Care Excellence. Artificial intelligence technologies to aid contouring for radiotherapy treatment planning: early value assessment: Health technology evaluation. Available from: www.nice.org .uk/guidance/hte11

APPENDIX 1: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

APPENDIX 2: SEARCH STRATEGY

Ovid MEDLINE® In-Process & Other Non-indexed Citations and Ovid MEDLINE® 1946 to present

Database: Ovid MEDLINE(R) ALL <1946 to February 20, 2024>
Search Strategy:
1 NEOPLASMS/
2 (benign adj1 neoplasm*).tw.
3 cancer*.tw.
4 malignanc*.tw.
5 (malignant adj1 neoplasm*).tw.
6 neoplasia*.tw.
7 neoplasm*.tw.
8 tumor*.tw.
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10 Ethos Therapy.tw.
11 Varian Medical System*.tw.
12 10 or 11
13 RADIOTHERAPY PLANNING, COMPUTER-ASSISTED/
14 (computer assisted adj1 (radiotherap* planning or dosimetry calculation)).tw.
15 RADIOTHERAPY, INTENSITY-MODULATED/
16 ((intensity modulated or volumetric modulated) adj1 arc therap*).tw.
17 (intensity-modulated adj1 radiotherap*).tw.
18 RADIOTHERAPY, IMAGE-GUIDED/
19 (Image-guided adj2 radiation therap*).tw.
20 image-guided radiotherapy*.tw.
21 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22 ARTIFICIAL INTELLIGENCES/
23 (ai adj1 "artificial intelligence").tw.
24 (acquisition adj2 knowledge computer).tw.
25 (artificial adj1 intelligence).tw.
26 (computational adj1 intelligence).tw.
27 (computer adj1 reasoning).tw.
28 (computer adj2 vision system*).tw.
29 (intelligence adj1 machine).tw.
30 (knowledge adj2 representation* computer).tw.
31 MACHINE LEARNING/
32 (learning adj1 machine).tw.
33 (learning adj1 transfer).tw.
34 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35 21 or 34
36 12 and 35
37 9 and 36
38 limit 37 to (english language and humans)

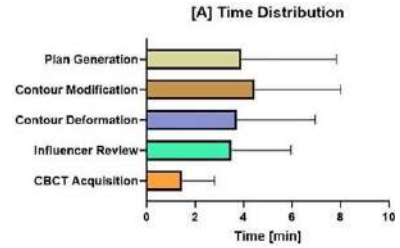
OTHER DATABASES	
EBM Reviews – Cochrane Central Registered of Controlled Trials	Similar MeSH, keywords, limits used as per MEDLINE search
EBM Reviews – Database of Abstracts of Review of Effects	
EBM Reviews – Cochrane database of systematic reviews	
EBM Reviews – Health Technology Assessment	
NHS economic evaluation database	
PubMed	Similar MeSH, keywords, limits used as per MEDLINE search
INAHTA	
US FDA	

APPENDIX **3: EVIDENCE TABLE**

Evidence Table : Efficacy/ safety/ organisational (ETHOS THERAPY IN HEAD AND NECK CANCER)
Question : What is the efficacy, safety, and organisational issue related to the use of Ethos Therapy (online ART with AI) to cancer patient?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow up (if applicable)	Outcome Measures/ Effect Size	General Comments
Guberina M, Guberina N, Hoffmann C, et al. Prospects for online adaptive radiation therapy (ART) for head and neck cancer. Radiation Oncology. 2024 Jan;19(1):4. Germany	Prospective cohort study Aim: to examine the value of CBCT online ART in clinical setting of patients with tumours in the head and neck. Study Design: Cohort of patient included are patients with tumours in the head and neck area who were treated at the linear accelerator ETHOS (Varian, Palo Alto, US) at the University Hospital Essen from the period 1.12.2021 to 31.01.2023. All fractions of patients who received radiation therapy in adaptive mode were assessed. Main exclusion criteria were tumour infiltration of the skin or the necessity of using bolus material. Treatment was delivered in plain free breathing once daily with a homogenous fractionation dose of 5*2 Gy/w (q.e.d) to a total prescription dose of 64-66Gy for postoperative and of 70 Gy to the macroscopic tumor for definitive treatments with 32-35 fractions as a continuous course using two or three sequential treatment phase. In the adaptive mode, the system displays an adaptive	III	59 patients with tumours in the head and neck area were treated at the ETHOS system. 10 of all 59 patients (10/59; 16.9%) received at least one phase within a course with the adaptive mode. Altogether 30/46 fractions in the adaptive mode were delivered with the adaptive plan (65.2% applied adaptive fractions).	Adaptive plan from ETHOS platform	Initial Scheduled plan		1. <u>Timing of workflow</u> The adaptive treatment lasted in median 34.5min (range: 12.0 – 49.0 min) from opening patient file online to treatment delivery. 2. <u>EUD of CTV and OAR:</u> The dispersion of the distributions of EUD_{CTV} values from the 46 dose fractions differed significantly between the scheduled and adaptive plans (p=0.0158) the 2.5^{th} percentile of the EUD_{CTV} values by the adaptive plans amounted 97.1% (95% CI 96.6–99.5%) and by the scheduled plans 78.1% (95% CI 61.8–88.7%). EUD_{CTV} for the accumulated dose distributions stayed above 95% at PTV margins of = 3 mm for all 8 analyzed treatment phases the scheduled plans did for margins = 5 mm. The EUD_{OAR}- values for the larynx and the parotid gland were significantly lower for the adaptive compared with the scheduled plans	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow up (if applicable)	Outcome Measures/ Effect Size	General Comments
	dose distribution and a planned dose distribution for each fraction between which the more appropriate plan for the treatment must be selected. StudySite: University Hospital of Essen. Outcome measures: 1. Equivalent uniform dose (EUD) of CTV and OAR 2. Dosimetric outcome (V100, Dmax, D99. D95, D90 and D_{min} 3. Acute toxicity							

Evidence Table : Question : What is the efficacy, safety, and organisational issue related to the use of Ethos Therapy (online ART with AI) to cancer patient?								
Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow up (if applicable)	Outcome Measures/ Effect Size	General Comments
Li R, Zhuang T, Montalvo S, et al. Adapt-On-Demand: A Novel Strategy for Personalized Adaptive Radiation Therapy for Locally Advanced Lung Cancer. Practical Radiation Oncology. 2024 Apr United State	Retrospective cohort study Aim: to analyse a novel adaptive-on-demand (AOD) workflow combining online ART and IGRT for locally advanced lung cancer (LALC) Study Design: 26 patients with LALC treated with curative intent using novel AOD workflow, adapting weekly, between June 2021 and December 2022. Patient had a diagnosis of either small cell or non-small cell lung cancer and received conventional dose regimens of 66Gy or 60Gy, administered at 2Gy per fraction, respectively. <u>AOD workflow:</u>  StudySite: UT Southwestern Medical Center, Dallas, Texas. Outcome measures: Tumour regression statistics Dosimetry outcomes Workflow timing and efficiency	III	26 patients (16 male patients,10 female patients; age range,36- 91 years)	AOD	Scheduled plan		1. <u>Tumor regression statistics:</u> Initial ITV volumes ranged from 15.3 to 999.6 cm^3 (median,179.8 cm^3). The average ITV volume decreased by 26.6% ± 23.3% from the initial by the final treatment week. Average weekly ITV shrinkage rate was 5.3% during treatment. Among patients, 69% had a >10% ITV reduction, while 19.6% showed <10% regression. 3 patients exhibited a >10% ITV volume increase, indicating progression. 2. <u>Workflow timing and efficiency:</u> of total 792 fractions evaluated, 666 (84.1%) were IGRT, and 126, (15.9%) with online ART. Of the online ART fractions, 4 (4.8%) used SCH plans, and 122 (95.2%) used ADP plans. The mean time for the online ART session, from the end of CBCT acquisition to final plan approval, was 17.14 ± 6.30 minutes.  3. <u>Dosimetry outcomes:</u> Overall, online ART improved target coverage and OAR sparing. When comparing adapted plan with non-adapted (scheduled) plan, PTV V100% and D99% were reduced by 6.3% and 12.4%, respectively. The PTV coverages were restored in the adapted plans, and the aforementioned V100% and D99% for ITV/PTV were not violated in any patients.	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow up (if applicable)	Outcome Measures/ Effect Size	General Comments
							ITV and (PTV) coverage (V100%) were 99.2% in adapted and 93.9% non-adapted plan. This represented a 2.9% and 6.8% improvement over nonadaptive plans (P<0.05) The Wilcoxon signed rank test revealed significant improvement of PTV V100% (P=.029), D99% (P=.006), and ITV D99% (P=.033) in adapted plans compared with non-adapted plans. Similarly, the dose to OARs were significantly reduced in the ADP plans compared with that in the SCH plans. With online ART, mean doses to the heart, esophagus, and lung were numerically reduced on average by 1.32Gy (P=.002), 1.34Gy (P=.001), and 1.75Gy (P=.001), respectively. The effect was larger when tumours had shrunk more than 10%. These reductions appear to be driven by continuous shrinkage of the ITV and re-optimization that took advantage of more favorable geometry because of increased separation between OARs and PTVs. 4. <u>Planning robustness analysis:</u> All plans achieved PTV/ITC coverage (V100%). Critical OAR constraints were met for 94.1% of the adapted plans, compared with 81.9% of the non-adapted plans. While OAR doses reduced in adapted plans. Violation of institutional guidelines were observed in 3 patients.	

Evidence Table : Efficacy/ safety/ organisational (ETHOS THERAPY IN CERVICAL CANCER)
Question : What is the efficacy, safety, and organisational issue related to the use of Ethos Therapy (online ART with AI) to cancer patient?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow up (if applicable)	Outcome Measures/ Effect Size	General Comments
Zhang Y, Wang G, Chang Y, et al. Prospects for daily online adaptive radiotherapy for cervical cancer: Auto-contouring evaluation and dosimetric outcomes. Radiation Oncology. 2024 Jan 12;19(1):6. China	Prospective Cohort Study Aim: to assess the accuracy of daily automatic contouring and dosimetric outcomes for cervical cancer with or without uterus. Study Design: Between December 2022 and June 2023, 125 online ART fractions from five postoperative cervical cancer patients and 140 online ART fractions from five uterine cervical cancer patients treated with daily iCBCT-guided online ART (Ethos Linac) were enrolled. Postoperative patients had indications for adjuvant pelvic radiotherapy and received 45 Gy in 1.8 Gy daily fraction to PTV, while patients with radical radiotherapy received 50.4 Gy in 28 fractions. StudySite: Outcome measures: Timing data Contouring accuracy Dosimetric outcomes	III	125 online ART fractions from five postoperative cervical cancer patients and 140 online ART fractions from five uterine cervical cancer patients treated with daily iCBCT-guided online ART (Ethos Linac)	Auto contouring using Ethos	Supervised Reference Plan by Physicians		1. <u>Timing data and contouring accuracy:</u> The average total adaptive time for A-ART postoperative cervical cancer and A-ART uterine cervical cancer from first iCBCT acquisition to plan selection were 7 min 46 s (range 6 min 47 s to 9 min 22 s) and 8 min 29 s (range 7 min 11 s to 10 min 03 s). While the average time for S-ART postoperative cervical cancer and S-ART uterine cervical cancer were 14 min 32 s (range 10 min 35 s to 20 min 35 s) and 17 min 55 s (range 11 min 37 s to 28 min 33 s). Overall, for postoperative cervical cancer, 92.3% (346/375 times) of the influencers and 92% (230/250 times) of CTV needed no or minor edits. In addition, 92.1% (387/420 times) of the influencers and 91.4% (384/420 times) of CTV needed no or minor edits for cervical cancer treated by radical online ART. The paired CTV had high overlap rates, with DSC values greater than 0.75. The uterus had the largest consistency differences, with ASD, centroid deviation, and 95% HD being 2.67 ± 1.79 mm, 17.17 ± 12 mm, and 10.45 ± 5.68 mm, respectively. The consistency differences of the lower nodal CTV left and nodal CTV right were relatively large, with ASD, centroid deviation, and 95% HD being 0.59 ± 0.53 mm, 3.6 ± 2.67 mm, and 5.41 ± 4.08 mm, and 0.59 ± 0.51 mm, 3.6 ± 2.54 mm, and 4.7 ± 1.57 mm, respectively. 2. <u>Dosimetric outcome:</u> For postoperative cervical cancer, the adapted plan achieved superior dosimetry coverage for the target volume compared to the scheduled plan, with V100% of CTV-N (99.94% ± 0.08%) and CTV-V (99.98% ± 0.04%). Compared with the S- Scheduled plan over all sessions, the S- Adapted plan	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow up (if applicable)	Outcome Measures/ Effect Size	General Comments
							could significantly improve the OAR dosimetry from high dose coverage to low dose coverage, including in the bladder, rectum and bowel. Although the A-Adapted plan met the clinical requirements; it was inferior to the S-Adapted plan.	

Evidence Table : Efficacy/ safety/ organisational (ETHOS THERAPY IN VULVA CANCER)
Question : What is the efficacy, safety, and organisational issue related to the use of Ethos Therapy (online ART with AI) to cancer patient?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow up (if applicable)	Outcome Measures/ Effect Size	General Comments
Bak ME, Jensen NK, Nøttrup TJ, et al. Clinical experiences with online adaptive radiotherapy of vulvar carcinoma. Acta Oncologica. 2023 Oct 3;62(10):1230-8. Copenhagen, Denmark	Retrospective cohort study Aim: to explore whether online ART is relevant for these patients and if it improves CTV coverage and/or reduces dose to organs at risk (OARs). Study Design: A retrospective analysis on first 20 vulvar carcinoma patient treated with online ART at the centre. Patient include among postoperative radiotherapy at the primary tumour site in vulva if the surgical margins were <3mm, with a dose of 1.85Gy x 27 fractions (total 49.95Gy). If surgery was not possible on the primary site or if residual macroscopic tumour persisted after surgery the dose was 2Gy x 32 fractions (total 64Gy). In case of one or more groin lymph nodes with metastases patients received 1.85Gy x 27 fractions (total 49.95Gy). In the cases where the metastatic lymph nodes were not surgically removed the dose was 2Gy x 32 fractions (total 64Gy). Plans were created with 7, 9, and 12 equidistant IMRT fields plans for adaption. The best IMRT plan, based on 12 preset dose constraints and CTV and PTV coverage for planning, was chosen as the reference plan Setup CBCTs were acquired daily for adaptive planning. Verification CBCTs were	III	20 patients treated between January 2021 and September 2023. All patients were female with a median age of 70. 527 fractions were taken from these patients and were analysed.	Adaptive Plan	Scheduled Plan		Out of 527 fractions, 335 (63.5%) used the adapted plan; 293 of these were verified, while 42 fractions had issues with data import, especially with one patient due to incompatible CBCT scans. 1. <u>Dosimetry Outcome:</u> For CTV coverage, mean D95% for scheduled plans was 98±5%, improved to 100.0±0.3% and 100.0±0.8% for the adapted and verified plans, respectively. ($p<0.0001$) For PTC coverage, mean D95% for scheduled plans was 97% ± 7%, increased to 100.0±0.3% and 99.0±2.0% for adapted and verified plans, respectively. ($p<0.0001$) 2. <u>OARs:</u> Bladder dose was increased from scheduled to adapted plans by 106% ± 22% to 107% ± 24% ($p=0.043$), and further to 112% ± 36% at verification ($p=0.007$). Meanwhile for rectum dose, scheduled plans had higher rectum doses (102% ± 27%) compared to adaptive (99% ± 24%, $p=0.0007$). 3. <u>Plan Edits and Recontouring:</u> 63% of fractions for the bladder required major edits meanwhile lesser number of major edits required in rectum which are 40%. For CTV, 43% of fractions required major edits. 4. <u>Adaptation time:</u> Median adaptation time is 15 minutes (range: 12-17 minutes).	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow up (if applicable)	Outcome Measures/ Effect Size	General Comments
	acquired immediately prior to dose delivery. CTV dose coverage and dose to bladder and rectum were extracted from the scheduled and adapted plans as well as from adapted plans recalculated based on verification CBCTs. StudySite: Department of Oncology, Rigshospitalet, Copenhagen, Denmark Outcome measures: Dosimetric outcome Organ sparing Plan quality Adaptation time							

Evidence Table : Efficacy/ safety/ organisational (ETHOS THERAPY IN PALLIATIVE BONE METASTASIS CANCER)
Question : What is the efficacy, safety, and organisational issue related to the use of Ethos Therapy (online ART with AI) to cancer patient?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow up (if applicable)	Outcome Measures/ Effect Size	General Comments
Nelissen KJ, Versteijne E, Senan S, et al. Same-day adaptive palliative radiotherapy without prior CT simulation: Early outcomes in the FAST-METS study. Radiotherapy and Oncology. 2023 May 1; 182:109538. Amsterdam.	Prospective cohort study Aim: To describes the implementation of CT-free adaptive workflow using Ethos for patients referred for palliative RT. To report on the experience of the first 43 patients (47 fractions) treated using workflow. Study Design: Prospective cohort study between December 2021 and October 2022 involving 43 patients. Eligible patients were identified by two radiation oncologists if they had been referred for palliative RT to metastases including complex palliation, which was defined as cases requiring re-irradiation, receiving concurrent systemic treatment, or bedbound patients. Patients had to have preferably a dCT that was less than four weeks old. Excluded were patients with solitary metastasis with good expected survival, tumors that were likely to be mobile, and targets that exceeded field size of 24cm. Volumetric-arc therapy (VMAT) and IMRT techniques were used for treatment planning, with a prescribed dose of 8 Gy in a single fraction. The clinical goals included planning target volume (PTV):	III	47 treatments were performed involving 43 unique patients. Four patients were treated twice for different metastatic locations. Median age was 67 years, ranging from 37 to 92. 22 patients required complex palliation due to factors like being bed-bound, undergoing re-irradiation, concurrent systemic treatment, or poor health condition. PTV Margins varied across treatments with margins of 5 mm (N=33), 8 mm (N=10), and 10 mm (N=4).	Online ART workflow			1. <u>Adaptation and Treatment Planning.</u> In, all treatments, adapted treatment plans were chosen due to significant improvements in target coverage (PTV/CTV V95%, p-value <0.005) compared to the original treatment plan calculated on daily anatomy. In term of monitor units, the median difference between the treatment plans (TPA and TPR) was 0.4%, with variations ranging from -24% to +37%. Some patients required significant adaptations due to issues like diaphragm position, changes in arm positioning, or tumor progression. Specific cases like scapular and cervical spine metastases required extensive manual contour adaptations. All treatment plans had a high gamma pass rate, with an average of 99.7% and none below clinical acceptance criteria (>95%). 2. <u>Workflow and Time Metrics:</u> The total online ART workflow took a median of 85 minutes, including 30 minutes time spent for adaptation in the RT room. 3. <u>Patient Satisfaction:</u> 60% of patients found the time spent on the treatment couch acceptable, and 80% indicated they would choose the same treatment pathway for future procedures.	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow up (if applicable)	Outcome Measures/ Effect Size	General Comments
	V95%_95 % and D0.1 cm3 < 114 %, clinical target volume (CTV): V98% _ 95 %, and spinal canal + 3 mm: Dmax < 8 Gy. OARs goals were site-specific and optimized per patient <u>Ethos treatment workflow:</u> 1. Entering the treatment room, explanation of the procedure, patient setup, CBCT1; 2. synthetic CT (sCT) and influencer structures are generated using a deformable image registration (DIR) between CBCT1 and the dCT and, if necessary, adapted 3. Target structures and OARs are propagated to CBCT1 using influencer-guided DIR, followed by adaption and/or approval by the RO; 4. Optimization of the TPA, and doses calculated for TPA and scheduled treatment plan (TPS) which is the TPR calculated on the sCT; 5. Choice between TPA and TPS and approval, CBCT2; 6. Treatment, CBCT3 if necessary and leaving the treatment room StudySite: Amsterdam University Medical Centre.							

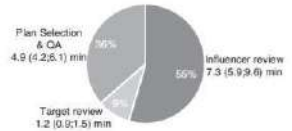
Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow up (if applicable)	Outcome Measures/ Effect Size	General Comments
	Outcome measures: Adaptation and Treatment Planning Timing and efficiency Patient satisfaction							

Evidence Table : Efficacy/ safety/ organisational (ETHOS THERAPY IN PROSTATE CANCER)
Question : What is the efficacy, safety, and organisational issue related to the use of Ethos Therapy (online ART with AI) to cancer patient?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow up (if applicable)	Outcome Measures/ Effect Size	General Comments
Zwart LG, Ong F, Ten Asbroek LA, et al. Cone-beam computed tomography-guided online adaptive radiotherapy is feasible for prostate cancer patients. Phys Imaging Radiat Oncol 2022; 22: 98–103. Netherlands.	Prospective cohort study Aim: to evaluate the feasibility of the clinical implementation of CBCT-guided online adaptive radiotherapy (oART) for prostate cancer patients. Study Design: Between February and July 2020, eleven consecutive biopsy-proven intact prostate cancer patients underwent CBCT-guided oART with Ethos therapy. Patients with nodal involvement were excluded. All patients were treated using a fractionation scheme of 20 times 3 Gy to the prostate. For patients with more advanced stages, an additional total dose of 54 Gy (four patients) or 60 Gy (three patients) was given to the (base of the) seminal vesicles using a simultaneous integrated boost technique The CTV was expanded to a planning target volume (PTV) using a margin of 7 mm in the lateral and anterior posterior direction and 8 mm in the cranial-caudal direction For each patient, a nine field intensity-modulated radiotherapy pre-treatment reference plan was created on the planning CT. The adaptive workflow can be divided into three main components: 1. Influencer contouring	III	11 prostate cancer patients underwent CBCT-guided oART with Ethos therapy.	Online ART workflow	Scheduled Plan		1. <u>Treatment time:</u> Mean total treatment time were 17.5 ± 3.2 (range: 10.8 – 28.8) minutes from CBCT acquisition to the end of treatment delivery. 2. <u>Contour Quality:</u> Clinically acceptable edits were required for all fractions. No need for manual target adjustments or couch shifts based on the second CBCT prior to treatment. 3. <u>Plan selection:</u> The adapted plan was chosen in all 220 fractions due to better PTV60Gy coverage compared to the scheduled plan. PTV60Gy and CTV60Gy Coverage for scheduled plan vs adapted plan were (86.7% ± 6.2%. vs 99.4% ± 0.5%.) and (99.5% ± 1.0%. vs 99.9% ± 0.4%.), respectively. For bladder and rectum doses: 78% of the fractions (171/220) were below the V60Gy constraints for both bladder and rectum in both scheduled and adapted plans. In 14% of fractions (30/220), the V60Gy of bladder and rectum were below the constraints only in the adapted plan. Mean Decrease in V60Gy for bladder and rectum in the adapted plan: 3.9% ± 1.8% (range: 0.6–9.5%). 9% of fractions (19/220) exceeded V60Gy constraints for the bladder, rectum, or both, even in the adapted plan. Mean V60Gy of bladder or rectum in the adapted plan: 4.7% ± 1.2% (range: 3.1–6.9%). 4. <u>Treatment acute toxicities:</u> Treatment-related acute toxicities were identified for 2 out of 11 patients. One patient	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow up (if applicable)	Outcome Measures/ Effect Size	General Comments
	and review. 2. Target propagation and review and treatment plan adaptation 3. Plan QA and review StudySite: Department of Radiotherapy, Medisch Spectrum Twente, Koningsplein Outcome measures: Treatment duration Treatment-related acute toxicities (within 3 months) Influencer and target contour edits Proportion of adapted fractions						experienced grade 1 proctitis and one patient grade 2 urinary urgency after treatment. For the other 9 patients, no treatment-related acute toxicities were reported	

Evidence Table : Efficacy/ safety/ organisational (ETHOS THERAPY IN URINARY BLADDER CANCER)
Question : What is the efficacy, safety, and organisational issue related to the use of Ethos Therapy (online ART with AI) to cancer patient?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow up (if applicable)	Outcome Measures/ Effect Size	General Comments
Åström LM, Behrens CP, Calmels L, et al. Online adaptive radiotherapy of urinary bladder cancer with full re-optimization to the anatomy of the day: Initial experience and dosimetric benefits. Radiotherapy and Oncology. 2022 Jun 1;171:37-42. Copenhagen, Denmark	Prospective cohort study Aim: to investigate the feasibility and dosimetric impact of online ART and compare it to the standard non-adaptive CBCT guided (non-adaptive ART) approach, for patients with urinary bladder cancer. Study Design: Prospective cohort study that included 6 consecutive patients with muscle invasive urinary bladder cancer treated with curative-intended radiotherapy in 32 fractions between September 2019 and February 2021. All patients received online ART for two or more (median = 23) fractions, with remaining fractions delivered as non- ART A total dose of 64 Gy was delivered to the primary CTV (CTV-T). If indicated according to Danish national guidelines, 50 Gy and 64 Gy were simultaneously delivered to pelvic lymph nodes (CTV-E) and positive lymph nodes (CTV-N), respectively. Online ART treatments were carried out on the Ethos system v2.0 (VMS), with bladder and rectum as so-called influencers, and targets and OARs re-generated at each fraction StudySite: Department of	III	6 patient with muscle invasive bladder cancer	Online ART workflow	Non adapted ART		1. <u>Treatment Delivery:</u> Out of 512 fractions, 297 were delivered using oART (online Adaptive Radiotherapy), with the remaining using non-ART plans. The variations were due to staff availability, COVID-19 impacts, and system downtime. 2. <u>Treatment Time:</u> Median oART Procedure Duration: 13.9 minutes (IQR: 11.9–16.6 minutes) from CBCT completion to plan review and QA.  Fig. 1. Median (IQR) duration of the different steps in the oART procedure and the distribution between them. 3. Plan Selection: In 292 out of 296 fractions due to improved PTV60Gy coverage compared to scheduled plans. CI and HI (Conformity Index and Homogeneity Index) is significantly better in adapted plans ($p < 0.001$). 4. <u>Dosimetric Outcomes:</u> In 89.5% of scheduled plans, PTV-T coverage was inadequate (V95% < 99%), whereas re-optimization regained coverage in 99.7% of adapted plans. CTV-T Coverage was insufficient in 19.6% of scheduled plans, but all adapted plans regained full coverage ($p < 0.001$). PTV-T Volume Reduction has median reduction of 33.9% (IQR: 24.2–45.0%) in online ART plans compared to non-ART.	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow up (if applicable)	Outcome Measures/ Effect Size	General Comments
	Oncology, Copenhagen University Hospital						Meanwhile PTV-E Volume Reduction has median reduction of 7.1% (IQR: 4.5–10.3%) in online ART plans. 5. <u>Organ at risk sparing:</u> Online ART resulted in median (IQR) reductions of rectum V50Gy and V40Gy of 6.6 (1.5;11.6) percentage points and 12.4 (4.0;21.4) percentage points, respectively, compared to non-ART. In terms of relative reductions of 70.7 (35.9;94.8) % and 38.8 (14.9;57.2) %. The reductions in bowel bag V45Gy and V30Gy were 78.8 (48.1;103.5) cm3 and 67.4 (30;103.5) cm3, respectively, corresponding to 18.8 (12.7;27.9) % and 12.6 (6.0;18.8) %. The maximum dose to the femoral heads was below 52Gy for all plans.	

Evidence Table : Efficacy/ safety/ organisational (ETHOS THERAPY IN PROSTATE CANCER)
Question : What is the efficacy, safety, and organisational issue related to the use of Ethos Therapy (online ART with AI) to cancer patient?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow up (if applicable)	Outcome Measures/ Effect Size	General Comments
Byrne M, Archibald-Heeren B, et al. Varian ethos online adaptive radiotherapy for prostate cancer: Early results of contouring accuracy, treatment plan quality, and treatment time. Journal of applied clinical medical physics. 2022 Jan;23(1):e13479. Australia	Mixed retrospective simulated and clinical study. Aim: To report early results on the accuracy of automated contouring, plan quality, and treatment fraction timing for Ethos Online ART to the prostate. Study Design: 18 patients were selected for the study dataset. This was made up of 12 patients previously treated on a Halcyon that had a simulated treatment performed on the Ethos treatment emulator. This retrospective dataset was supplemented with six clinical adaptive cases treated on the Ethos system. At our institution, prescribed doses and organ at risk (OAR) limits are primarily based on the eviQ guidelines (an Australian evidence-based and peer-reviewed guideline). StudySite: Amsterdam University Medical Centre. Outcome measures: frequency and magnitude of contour edits, changes in plan quality, and time required for Online ART to the prostate.	III	The 12 retrospective patients consisted of four intact prostate cases (prescribed 60 Gy/20 Fx), four prostate bed and node cases (prescribed 66 Gy/33 Fx), and four prostate and node cases (prescribed 78 Gy/39 Fx). 12 retrospective datasets consisted of 182 simulated fractions. The six clinical adaptive cases included two intact prostate cases, two prostate and node cases, and two prostate bed and node cases. These patients were treated using the same online adaptive workflow tested on the retrospective patients. This dataset included every fraction, 184 in total.	Online ART workflow	Schedule Plan		1. <u>Influencer Contouring Accuracy:</u> In 11% of the fractions, no edits were needed. In 81% of fractions, only minor edits were necessary. The patient with a hip prosthesis required major edits in the bladder contour for several fractions. However, bowel influencer was excluded from this study due to inconsistent results. 2. <u>Target Contouring Accuracy:</u> More than 80% of the time, no changes were needed for the prostate CTV. Overall, 72% of CTVs required no changes, and 91% required either no or only minor changes. Cases involving nodes and prostate bed saw a significant increase in the frequency of CTV edits. 3. <u>OAR Contouring Accuracy (Excluding Influencers):</u> Sigmoid Colon required the most frequent changes among non-influencer OARs, especially in prostate bed cases. 4. <u>Clinical Goals Met:</u> In 78% of fractions, the adaptive plan met more clinical goals than the scheduled plan. In 15% of fractions, both the adaptive and scheduled plans met the same number of clinical goals. Only 7% of fractions, the scheduled plan met more clinical goals than the adaptive plan. Adaptive plan was selected in 95% of fractions. Adaptive plans were selected less frequently for cases of prostate bed and node treatments. 5. <u>Timing Data:</u> The online adaptive recontouring and replanning process was carried out in 19 min on average.	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow up (if applicable)	Outcome Measures/ Effect Size	General Comments
							TABLE 4 Timing data for retrospective and clinical patient fractions **Treatment site** / **Retrospective data Adaptive time (average ± SD) (mm:ss)** / **Clinical data Adaptive time (average ± SD) (mm:ss)** Intact prostate / 15:21 ± 03:18 / 33:57 ± 05:13 Intact prostate and nodes / 19:30 ± 04:06 / 34:12 ± 06:23 Prostate bed and nodes / 21:20 ± 03:55 / 34:17 ± 07:23 All sites / 19:11 ± 04:29 / 34:11 ± 06:34	

Evidence Table : Efficacy/ safety/ organisational (ETHOS THERAPY IN BLADDER, PROSTATE AND RECTUM CANCER)
Question : What is the efficacy, safety, and organisational issue related to the use of Ethos Therapy (online ART with AI) to cancer patient?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow up (if applicable)	Outcome Measures/ Effect Size	General Comments
Sibolt P, Andersson LM, Calmels L, et al. Clinical implementation of artificial intelligence-driven cone-beam computed tomography-guided online adaptive radiotherapy in the pelvic region. Physics and imaging in radiation oncology. 2021 Jan 1;17:1-7. Denmark	Mixed simulated study using retrospective clinical data and case report of 5 patient Aim: to describe the clinical implementation of a commercial solution for CBCT-guided and AI-driven oART. To evaluate the feasibility, time-efficiency, and potential clinical impact of the Ethos for pelvic cancer. Study Design: Twenty-six patients (eight bladder, eight prostate, six rectum, four anus) were selected for simulated oART. A total of one hundred (forty-seven bladder, thirty-six prostate, thirteen rectum, four anus) adaptive sessions were simulated, using an emulator of the oART module. The simulated oART sessions were based on retrospectively collected CBCT images. Plan comparisons were carried out by a single medical physicist (LMA) and was based on the fulfillment of clinical goals (CTV/PTV coverage and dose to OAR) and plan complexity (MU/Gy). In addition, the first five patients treated on the AI-driven and CBCT-based oART system at the centre were reported. Twenty oART sessions conducted for these patients were evaluated in terms of treatment duration, structure editing, primary PTV volume	III	<u>Simulated oART:</u> Twenty-six patients (eight bladder, eight prostate, six rectum, four anus) were selected for simulated oART. A total of one hundred (forty-seven bladder, thirty-six prostate, thirteen rectum, four anus) adaptive sessions <u>Clinical oART:</u> Five patients consisted of three patients with bladder cancer, one with rectum cancer, and one with a gastro-intestinal stromal tumor (GIST) located between rectum and vagina.	Online ART			1. <u>Pre-treatment Plan Generation:</u> The automated TPS achieved PTV coverage and OAR doses comparable to clinical plans (>95% VMAT). The median doses to 95% of the high-dose PTV (D95%) achieved with the automated TPS (all IMRT and VMAT plans) and the previous clinical standard TPS were 96.5% and 97.5%, respectively ($p < 0.001$). The plan quality indices were comparable between the two TPS, with the exceptions of an inferior HI for auto-generated VMAT plans, a superior CI for manually generated VMAT plans and higher MU/Gy for auto-generated VMAT plans. the auto-generated IMRT plans fulfilled more clinical goals than corresponding auto-generated VMAT plans and were therefore preferred as adaptive reference plans. 2. <u>Simulated Online ART (oART):</u> The AI-segmented influencers required none or minor editing in 76% out of the 259 influencers, while the corresponding value for the 100 propagated CTVs (primary and elective combined) was 90%. Re-optimizing the treatment plan to the anatomy of the day resulted in the adapted plan being selected in 88% of the simulated treatment sessions (98%, 83%, 67% and 100% for bladder, prostate, rectum and anal cases, respectively). Reasons for selection includes CTV and PTV coverage (60%), combination of target coverage and OAR sparing (30%), or OAR sparing alone (3%). 3. <u>Patient Specific QA:</u>	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow up (if applicable)	Outcome Measures/ Effect Size	General Comments
	changes, and fulfilment of dose constraints. StudySite: Department of Oncology, Herlev & Gentofte Hospital, Herlev, Denmark						Overall, both calculation- and measurement-based QA demonstrated good agreements with dose calculations by the automated TPS, with all plans acceptable for treatment delivery independent of QA method. Local gamma passing rate: Median of 99.2% (IQR: 1.2%). 4. <u>First clinical adaptive treatment:</u> Median procedure time was 17.6 minutes (IQR: 4.0 minutes) from CBCT acceptance to treatment start. AI-driven influencer segmentation took 3–6 minutes. CTV review took an additional 1–3 minutes. For the bladder cases, margin reductions resulted in a statistically significant median reduction of the high-dose PTV by 42% (IQR 19%) when moving from a non-ART to the studied oART = approach ($p < 0.001$). The high-dose PTV V95% dose coverage was reduced to a median of 88.2% (IQR = 9.7%) for the scheduled plans, while regained at a median of 99.6% (IQR = 0.1) for the adapted plans. CTV V95% Coverage: All adapted plans achieved 100% coverage, while 4 of 15 scheduled bladder treatments had CTV V95% < 98%. High-dose PTV volume reduction in bladder cases led to a 24–30% reduction in V45Gy to the bowel cavity, compared to non-ART. The adapted plans were selected in favor of the scheduled for 15 out of 15, 1 out of 2, and 0 out of 3 oART sessions for the bladder, rectum, and GIST patients, respectively.	

Evidence Table : Efficacy/ safety/ organisational (ETHOS THERAPY IN RECTAL CANCER)
Question : What is the efficacy, safety, and organisational issue related to the use of Ethos Therapy (online ART with AI) to cancer patient?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow up (if applicable)	Outcome Measures/ Effect Size	General Comments
De Jong R, Crama KF, Visser J, et al. Online adaptive radiotherapy compared to plan selection for rectal cancer: quantifying the benefit. Radiation Oncology. 2020 Dec;15:1-9. Netherlands.	Prospective cohort study comparing online ART to plan selection strategy for rectal cancer. Aim: To describes the implementation of CT-free adaptive workflow using Ethos for patients referred for palliative RT. To report on the experience of the first 43 patients (47 fractions) treated using workflow. Study Design: The first 20 patients treated with PS between May–September 2016 were included. The study used 300 CBCT scans for 20 patients (10 short-course radiotherapy [SCRT] and 10 long-course radiotherapy [LCRT]). New dual arc VMAT plans were generated using auto-planning for both the online ART and PS strategy. For each fraction bowel bag, bladder and mesorectum were delineated on daily CBCTs. The dose distribution planned was used to calculate daily DVHs. Coverage of the CTV was calculated. For each fraction the difference between the plan selection and online adaptive strategy of each DVH parameter was calculated. Study Site: University of Amsterdam, Meibergdreef	III	20 patients: 10 SCRT (5x5 Gy) and 10 LCRT (25x2 Gy). Patient characteristics were based on resectability of the primary tumor.	Online adaptive radiotherapy (ART).	Pre-treatment plan selection strategy	N/A (single treatment course of short or long-course radiotherapy).	1. <u>Target Coverage:</u> Online ART improved CTV D99% from 98.5% (plan selection) to 98.7% (ART). 2. <u>Normal Tissue Sparing:</u> Median normal tissue irradiated with 95% of the prescribed dose reduced from 642 cm^3 (plan selection) to 237 cm^3 (ART) ($p < 0.001$). 3. <u>OAR Dose Reduction:</u> Bowel Bag (V15Gy): LCRT reduced by a median of 126 cm^3 (range: -206 to -40 cm^3). SCRT reduced by 62 cm^3 (range: -105 to -51 cm^3). Bladder V15Gy: Median reduction by 24% in LCRT and 11% in SCRT.	

TECHNOLOGY REVIEW (MINI HTA) ETHOS THERAPY FOR CANCER

e ISBN 978-967-2887-94-2

MAHTAS
(online)