UiT The Arctic University of Norway

Faculty of Health Sciences

Volumetric Arc Therapy v*ersus* Conventional Image Guided Radiotherapy in Head and Neck Cancer Patients

A retrospective quality study of patients receiving radiotherapy at the Department of Oncology, UNN Tromso between 2005-2015

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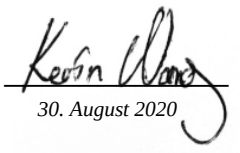
Forewords

When confronted with finding a topic for my fifth-year thesis, I knew it had to involve physics in some way. I initially decided to contact a radiologist I knew from our lectures, to see if maybe he had some available projects for a thesis. This first attempt failed and made me postpone thesis-finding for a while.

I eventually realized that radiotherapy is also high-tech and physicist-like. I contacted the head of the oncology department who sent me to Dr Kilvær, a specialist in radiotherapy. He suggested the topic and offered to be the supervisor for my thesis. This was almost two years ago. Now, the thesis is complete.

I want to thank my supervisor Thomas Kilvær for spending his time helping me with statistics, the writing process, and for teaching me about the fascinating field of radiotherapy. I also want to thank my fiancé Synne and my family for always supporting me.



30. August 2020

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1 Abstract

Research goal

To compare the survival outcomes, and patterns of loco-regional and metastatic recurrence of patients treated with primary radiotherapy for H&N cancer in different time periods where either conventional IGRT, IMRT or VMAT were available.

Introduction

Conformal techniques are attractive for treating H&N cancer as fields may be shaped to spare critical organs. As a result, H&N cancer emerged as one of the first standard indications of IMRT/VMAT when these techniques became available. However, there exists few studies which evaluates patterns of recurrences.

Methods

292 patients receiving definitive radiotherapy for H&N cancer at the Department of Oncology at UNN Tromso between 2005-2015 were included. Patients were grouped according to available treatment technique (IGRT, IMRT and VMAT). Overall, disease-specific, loco-regional failure free and metastasis free survival were compared.

Results

Our study suggests a slightly longer loco-regional recurrence free survival (p=0,066) in the period IMRT/VMAT were available, compared to when only 3D-IGRT was available. However, increased understanding of the tumor biology and the introduction of advanced diagnostic tools during the study period, precludes a definitive conclusion. Overall survival, disease specific survival, and metastasis free survival were similar between the groups.

Keywords: Radiotherapy, head and neck cancer, 3D-IGRT, image guided radiotherapy, IMRT, Intensity modulated radiotherapy, VMAT, Volumetric arc therapy, advancements, survival.

2 Introduction

2.1 Research goal

The goal of this study is to compare the survival outcomes, and patterns of loco-regional and metastatic recurrence of patients treated with primary radiotherapy for head and neck (H&N) cancer. Patients were grouped by different time-periods according to the single most advanced treatment technique available (IGRT<IMRT<VMAT,) at the Department of Oncology, UNN Tromso, in the period from 2005-2015.

2.2 Background

2.2.1 Head and neck tumors

2.2.1.1 Epidemiology

Head and neck cancers include malignant tumors arising from the lips, mouth, oral cavity, nasal cavity, nasal sinuses, larynx, pharynx and collum lymph nodes. In Norway there were 644 new cases of H&N cancer in 2008, which contributed to 2.4% of total domestic cancer cases (1). Worldwide, 640k people are diagnosed with H&N cancer each year, making it the sixth most common cancer. The majority of H&N cancers are squamous cell carcinomas in the oral cavity, larynx and oropharynx, accounting for over 90% of cases (2). As seen in figure 1, the incidence increases with age and has a higher incidence in males than females.

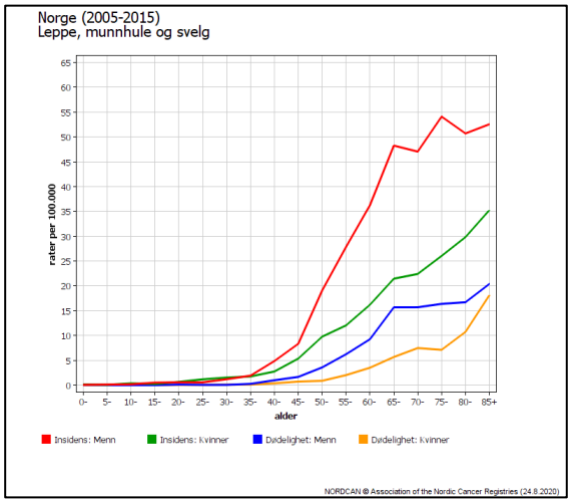


Figure 1: *Graph showing the average incidence by age of lip, mouth and pharynx cancer in Norway during 2005-2015. X: age Y: Incidence/100k. Data retrieved from Nordic cancer registries.*

2.2.1.2 Prognostication

The most established associations with H&N cancer are tobacco, alcohol and human papillomavirus. Use of tobacco and alcohol indicates a worse prognosis (3), while HPV

positive tumors tend to have a better prognosis (4-6). HPV associated tumors are becoming increasingly more common and is approaching alcohol and tobacco as the leading cause in developed countries. The increase in HPV associated tumors with, along with a decrease in smoking, is believed to partly explain the increased survival for H&N cancer patients in recent years (2). Old age and advanced tumor stage are both associated with worse outcomes (7).

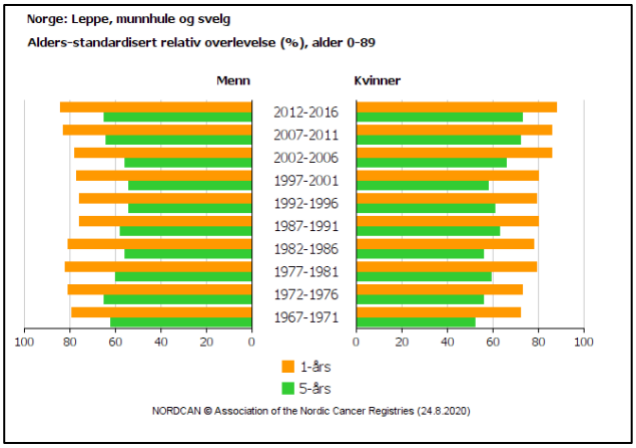


Figure 2: *X: Age-adjusted survival percentage Y: Year. Right: women. Left: Men. Data retrieved from Nordic cancer registries.*

2.2.1.3 Classification

Precise classification of cancer plays a crucial role in clinical decision-making, research and prognostication of malignant conditions. H&N cancers are classified using the TNM grading system. It classifies cancer as either I, II, III or IV, using tumor size, involvement of surrounding structures and growth pattern (T), lymph node involvement (N), metastases (M), cancer cell type and HPV status.

The most recent version is TNM-8, which was introduced in 2017. It replaced TNM-7 which was used from 2009-2017 (8). Some changes in TNM-8 compared to TNM-7, are that lymph nodes are graded both clinically (cN), pathologically (pN) and that different staging for HPV associated tumors are used (9).

2.2.1.4 Treatment

Surgery alone can sometimes be sufficient in early stages of H&N cancer when the tumor is small and can be resected with wide surgical margins. However, additional treatment with radiotherapy is indicated when the tumor is incompletely resected or in cases with metastasis. Advanced stages of H&N cancer is often treated with a multimodal approach using both surgery, radiotherapy and chemotherapy. Sometimes, due to either invasive growth or proximity to critical organs, the tumor can not be resected surgically and is treated with radiotherapy alone. The head and neck serve important functions such as vision, smell, taste, ingestion of food, speech and social interaction, and the risks of potential side effects must be carefully considered when selecting treatment (10). Often, treatment planning is done in

multidisciplinary meetings by a team consisting of relevant specialists such as oncologists, surgeons, pathologists and radiologists (11).

2.2.2 Radiotherapy

The goal of radiotherapy, regardless of technology, is to deliver high enough doses to kill malignant cells, while sparing the surrounding tissue as much as possible to minimize side effects.

The first attempts at treating cancer with radiation occurred over 100 years ago, shortly after the discovery of X-rays (12). Today, radiation is one of the most important modalities in the treatment of cancer together with surgery, chemotherapy and hormonal therapy (13). The precision of radiotherapy has previously been limited. However, during the past decades, advances in imaging, radiotherapy techniques and computer processing power have enabled more sophisticated target acquisition and precise dose calculations. Image guided radiotherapy (IGRT) can now utilize CT imaging to precisely determine distinct volumes for subsequent radiation before a tailored dose of ionizing radiation, consisting of photons or electrons typically in the megavoltage spectrum are delivered to the target (14).

2.2.2.1 Conventional radiotherapy

Classically, external beam radiotherapy (EBRT) used anatomical landmarks and conventional two-dimensional X-rays. The radiographs were taken orthogonal to each other, one in the frontal view and one in the lateral view. When these radiographs were used to navigate, the following radiotherapy fields had to align with the viewing angle of the images. The fields of conventional radiotherapy are therefore cross-shaped, with a central cube receiving curative doses. The weakness of such a field is that it isn't well conformed around the tumor. This leads to a significant amount of healthy tissue being treated and more side effects which limits the treatment. The crudeness of conventional radiotherapy may however reduce the potential for a miss due to errors in delivery (15, 16).

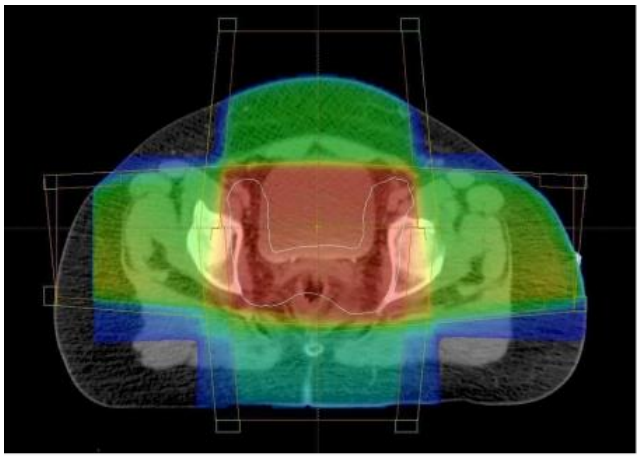


Figure 3: *A typical conventional field. The therapautic radiation is delivered from only two separate angles, with a central cube receiving doses lethal to tumor cells. (Reproduced with permission from Cancer imaging).*

2.2.2.2 Intensity modulated radiotherapy (IMRT)

In modern radiotherapy, the dose is delivered from many different angles, with the goal of tumor control, while sparing the surrounding tissue (17). This could be achieved by a conventional set-up with multiple static fields, but in the last 10-15 years intensity-modulated radiotherapy (IMRT) and volumetric arch therapy (VMAT) have emerged as the methods of choice.

In contrast to conventional radiotherapy, IMRT uses a beam consisting of multiple beamlets. Each beamlet has their respective predetermined intensity and creates a heterogenous beam. Most modern accelerators use multiple leaflets made of tungsten to limit the borders of outgoing radiation. These leaflets change their position depending on the shape of the tumor and the angle radiation is sent from, so that most of the surrounding tissues are spared. A potential disadvantage of IMRT is that the multiangular approach leads to a higher total dose of radiation, even if the organs at risk individually receives lower doses (18).

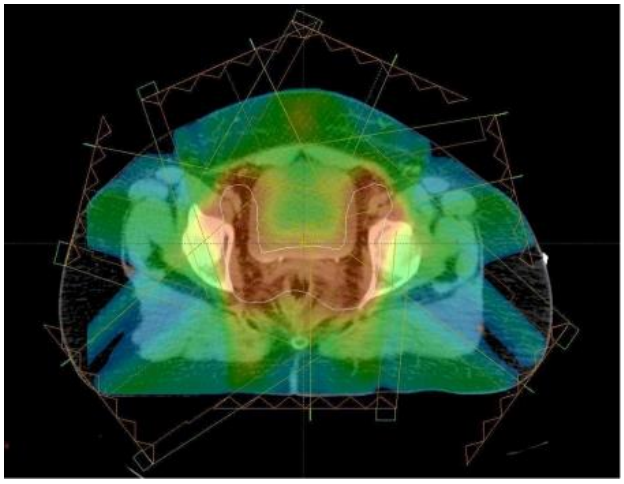


Figure 4: *An IMRT field. The dose is delivered to the target from several angles to achieve a higher conformity. Reproduced with permission from Cancer imaging.*

When planning a treatment with IMRT the use of modern computers allows for simulations. During these it is possible to add parameters such as maximum acceptable dose to organs at risk and target dosage for the malignant tumor. The computer can then generate a field which can be adjusted and simulated multiple times until a satisfying treatment plan is made (18).

However, as precision increases, the robustness of the treatment may suffer. The high conformity comes with a higher risk of missing tumor cells due to errors in delivery, if for example the patient moves, or the tumor location changes throughout the course of the treatment. Compared to conventional techniques, IMRT and VMAT are therefore more prone to target under-coverage. A potential miss may lead to malignant cells receiving an inadequate radiation dose or deliver excessive dose to normal cells (18).

The benefits of IMRT are particularly useful in the treatment of cancer which lies in areas with radiosensitive surrounding structures such as the head and neck area, where the target volume can be very complex and critical structures such as the brainstem must be carefully avoided (18).

2.2.2.3 Volumetric arch therapy (VMAT)

VMAT is a further development of IMRT. Before the introduction of VMAT, the accelerator had to stand still while delivering the dose. VMAT improves on IMRT by adding the ability to send conformal radiation while simultaneously moving around the patient. The intensity of the different beamlets varies and the leaflets continually change along with the angle of the accelerator without stopping. The benefits of VMAT are even better conformity and a more even distribution of radiation to the surrounding tissues. It is however uncertain if a small dose to many cells is less carcinogenic than a higher dose to few cells. The use of VMAT also reduces the time needed for delivery, thereby reducing the chance of patient movement. The shorter delivery time is also more manageable for patients (19).

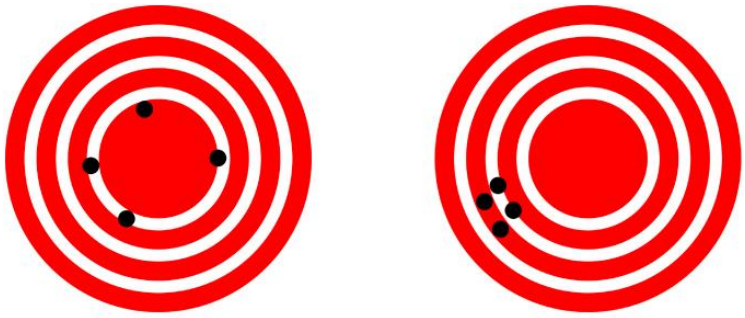


Figure 5: *Illustration showing how accuracy and precision affects the target being hit. IMRT and VMAT have high precision and, theoretically, higher risk of missing due factors that lower accuracy. One such factor could be a patient moving during treatment delivery. Image from openstax.org.*

2.2.3 Radiotherapy for H&N cancer

Tumors in the head and neck (H&N) region are particularly challenging to treat, because of the proximity to many critical parallel (salivary glands, lacrimal glands, swallowing muscles etc.) as well as serial (spinal cord, brainstem, optic chiasm, plexus brachialis etc.) organs. As an example, excessive radiation dose to the spinal cord can have severe consequences such as demyelination, fibrosis and loss of nerve function, ultimately leading to paralysis caudal to the damage (20-22). Beam angles that provide high doses to the spinal cord are therefore avoided, thereby limiting potential delivery of radiation to tumor. These challenges make conformal techniques attractive for treating H&N tumors as fields may be shaped to spare organs while retaining tumor coverage (23, 24). As a result, H&N cancer emerged as one of the first standard indications of IMRT/VMAT when these techniques became widely available in most modern radiotherapy systems (17). However, the optimum fractionations of

radiotherapy are still being defined, and there exists few studies which evaluates patterns of recurrences (25, 26).

2.2.3.1 Target volume definition and treatment planning

During target volume definition, different volumes are drawn and set to receive their respective radiation dose. For H&N cancer, several guidelines for target volume definition exists. An example of a widely accepted guideline is made by the Danish head and neck cancer group (DAHANCA). They define three different standardized clinical target volumes. These are named CTV1, CTV2 and CTV3 (27).

CTV1 is the innermost volume. Its borders conform around the tumor and is drawn by adding a 5 mm margin to the gross tumor volume (GTV-T) and lymph nodes with metastasis (GTV-N). This volume typically receives a dose of 68-70 Gray (Gy). Patients who have undergone incomplete surgery with residual tumor, including microscopic positive surgical margins, or those that are treated with radiotherapy without prior surgical resection, are treated with CTV1 doses. The 5 mm margin can be decreased to avoid unaffected bone or air. The margins can be increased if the tumor borders are unclear (27).

CTV2 includes high risk areas and consists of gross tumor with a margin of 10 mm, accounting for potential cancer not visible on the CT. This volume is typically treated with 60-64 Gy. For patients that have undergone successful radical surgery, CTV2 represents the highest dose given (27).

CTV3 includes low risk areas such as elective lymph nodes and is treated with a dose of 46-48 Gy without margin. The scope of elective treatment is determined by extent and localization of primary cancer and lymph node status. The volumes are layered in such a way that CTV3 contains CTV2 which contains CTV1. MR and PET imaging can be used as additional aid when drawing the areas that should be treated (14, 27, 28).

In addition, to account for uncertainties in the delivery of the radiation dose, a small additional margin is added to the clinical target volumes. This final volume is called the planned target volume (PTV) (27).

2.2.3.2 Planning CT acquisition

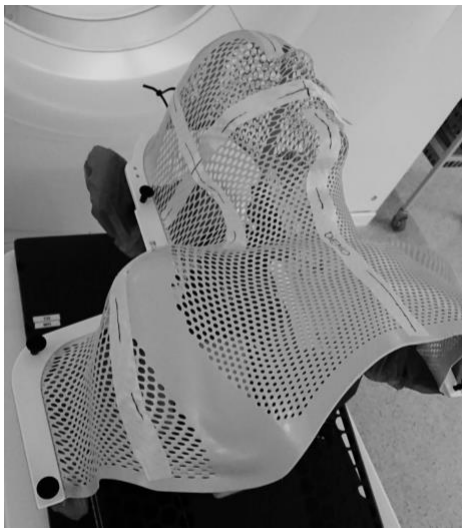


Figure 6: *Example of a mask used for immobilization.*

Before each course of radiotherapy, a planning CT must be acquired. These are almost without exception done with contrast. It is important to immobilize the patient both during the planning CT, and during each subsequent therapy session, the position from the planning CT is reproduced to minimize errors in delivery. To achieve this, the patient is covered in a stiff anatomically shaped mask which also covers the shoulders, such as the one seen in figure 4. Additional imaging is often done. PET-CT can be used to examine potential lymph node metastasis. MRI can be used for additional delineation of soft tissue structures when CT provides inadequate detail, or there are artifacts in the CT-scan from implants or amalgam dental fillings (27, 29).

2.2.3.3 Treatment evaluation

Patients receiving radiotherapy for head and neck cancer are at a particularly high risk of tumor movement. This is partly because the neck and jaw are a series of joints that may move interdependently of each other if not sufficiently immobilized and because the pharynx contains movable structures. Another potential reason for tumor movement is weight loss during the treatment, which is common in H&N cancer patients (30). To avoid errors in delivery, daily online scans are performed using either cone beam CT (CB-CT) or conventional kilovoltage X-rays in two planes (kv-kv) before each treatment session. Images must include both the target volume and critical organs in close proximity. Anatomical landmarks that does not move such as the cervical spine act as landmarks, while movable structures such as the hyoid bone are avoided as reference points. If there is too much deviation the target volumes must be delineated again to ensure acceptable tumor coverage. Weekly systematic “offline” reviews of the pictures are also performed to see tendencies or progressions during the treatment period. If the fields are not within tolerance, new planning CT and re-planning has to be performed. Extensive use of imaging is normally avoided, but exposure is relatively small compared to the treatment, and the consequences of missing the target justifies frequent imaging (31, 32).

2.2.3.4 Hypoxic radiosensitizers

Large tumors can outgrow their oxygen supply and become ischemic. Ionizing radiation produces free radicals in cell DNA, but for the DNA to break, oxygen must bind to the ionized sites. This makes oxygen an important determinant of how susceptible a cell is to radiation. To counteract this, oxygen analogs such as Naxogin® (Nimerazole) can be used as a radiosensitizer when treating a macroscopic tumors, effectively taking oxygens place in the biochemical processes leading to cell death (33).

2.2.3.5 Chemoradiotherapy

To further improve sensibility to radiation and tumor control, the cytotoxic agent cisplatin can be given concomitant with radiotherapy (34). It is often indicated in cases where there are nodal metastases present or fast growing tumors, such as head and neck squamous cell carcinoma or undifferentiated nasopharynx carcinoma (35). It acts by binding to guanine and adenine bases, promoting DNA-strand breaks which leads to apoptosis (36).

2.2.3.6 Fractions

Cells have different vulnerability to radiation in different part of the cell cycle. To overcome this, the dose is delivered over time as multiple smaller doses or “fractions”. If a tumor is to receive 70 Gy, this is typically divided into 2 Gy fractions 5 times per week until a total dose of 70 Gy is achieved. This has shown to increase death of tumor cells and decrease damage to non-malignant cells, compared with giving the full treatment in one session.

Some recent studies have shown better outcomes with altered fraction plans. For example, the 2 Gy dose can be given more than 5 times per week (accelerated), thus completing the treatment over a shorter time period. Another possibility is to deliver smaller (hyperfractionated) doses that are less than 2 Gy, but delivered more frequently. Accelerated and hyperfracionated therapy can be useful in the treatment of aggressive tumors that have increased potential for repopulation between sessions (37). There is still ongoing research regarding the optimal fraction interval and dosage (38, 39).

3 Methods

3.1 Patient inclusion and exclusion criteria

The inclusion criteria were patients that completed definitive radiotherapy for H&N cancer at the Department of Oncology at UNN Tromso between 2005-2015. Those who, in addition to radiotherapy, received surgical treatment or chemotherapy, were included as well.

Initially 488 patients were identified in the radiotherapy system (Aria OIS, Varian Medical Systems). 65 was tagged as palliative and therefore excluded. Of the remaining 423, 5 patients were excluded because of aborted treatment, 2 was excluded because they had been treated with radiotherapy previously. 1 was excluded because the intention of treatment was unclear and 1 was excluded because the treatment was for another anatomical area. This left 414 patients. Furthermore, to achieve more similar and comparable groups, those with sinus and larynx cancer where excluded as well. This left us with 292 patients for statistical analysis. The selection process is shown in figure 5.

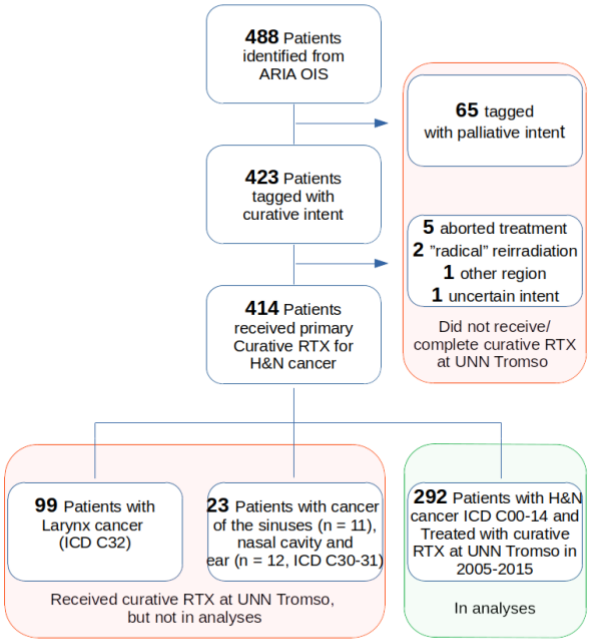


Figure 7: *Flowchart showing which patients where included.*

3.2 Data acquisition

We systematically reviewed the outcomes 292 patients whom received definitive radiotherapy. Clinical information regarding treatment and outcomes was retrieved through the DIPS electronic journals (DIPS AS). Data retrieval took place during the 25th of March 2020 until the 5th of May 2020. Treatment plans were compared with patient outcomes to determine in which degree the treatment had been successful, and if we could observe a pattern in how the treatment had failed in recurrent cases. The main endpoints are differences in infield and distant recurrences and in mortality.

We retrieved the following data for use in statistical analysis:

- TNM-staging.
- Cancer type and location according with ICD-10.
- Age and gender.
- Dates of referral, biopsy, treatment start, recurrences and/or death.
- Disease specific survival. (Was death most likely caused by the cancer that was treated with radiotherapy?)
- The prescribed radiation dosage for CTV1, CTV2 and CTV 3, and wich lymph node areas was assigned for CTV3 in relevant cases.
- HPV status.
- Surgical treatment, and whether or not full resection was achieved.
- Use of chemotherapy.
- Use of radiosensitizers such as Naxogin®.
- Involved lymph node areas.

3.3 Statistics

Groups were defined according to single most advanced radiotherapy technology available in the treatment period. Analysis of overall survival, disease specific survival, recurrence free survival and metastasis free survival was done using Kaplan-Meyer estimates and log ranks-test. Chi-square and Fischer tests were done for categorical data. Continuous variables were analyzed using one-way ANOVA.

3.4 Ethical approval and confidentiality

The author and supervisor had full access to the patient data for this thesis. To ensure confidentiality, patient data were stored on a secure server in the hospital network. During data acquisition patients were linked with their ID in the database. After data acquisition and throughout the project period all patients were de-identified. A key file linking patient ID with patient data was be kept on a separate domain in case additional data from the patient journals was needed. After the project period the data was anonymized. The study was approved by personvernombudet (PVO). Application to the National committee for medical and health research ethics (NEM) was, after consulting with PVO, not deemed necessary.

4 Results

4.1 Study population

As seen in table 1, there are 97, 86 and 109 patients in the IGRT, IMRT and VMAT group respectively. Patient age spanned from 10 to 80 and was comparable between groups (p=0.166). Average tumor size was also comparable (p=0.480). There is an apparent significant increase in N2 staged cancer in the VMAT with 61 patients compared to 41 and 31 in the IGRT and IMRT group (p=0.021). Diagnosis distribution was similar between the groups (p=0.461).

Table 1: *A summary of clinical variables for H&N patients treated with IGRT, IMRT and VMAT at Kreftavdelingen UNN Tromso from 2005-2015 (chi square test and Fisher's Exact test for categorical data and one-way ANOVA for continuous variables).*

	IGRT	IMRT	VMAT	
Total number	97	86	109	
				P
Age, median (range)	59 (14-78)	62 (16-80)	61 (10-80)	0.166
Follow-up of survivors in months, median (range)	150 (117-186)	111 (82-137)	71 (54-115)	
Size (mm), median (range)*	25 (2-70)*	24 (1-60)*	27 (8-63)*	
tStage				0.480
I	16	21	19	
II	41	29	41	
III	6	5	13	
IV	30	27	35	
nStage				**0.021**
0	34	31	25	
1	18	19	14	
2	41	31	67	
3	1	1	2	
Diagnosis				0.461
C00	0	3	0	
C01	12	4	12	
C02	16	12	18	
C03	3	2	2	
C04	8	6	3	
C05	4	4	3	
C06	5	5	2	
C07	1	6	3	
C08	3	2	4	
C09	30	27	40	
C10	5	5	12	
C11	5	5	3	
C12	1	1	0	
C13	3	3	6	
C14	1	1	1	

4.2 IGRT, IMRT and VMAT and their associations with clinical and treatment variables

In table 2, we see that all but 2 patients received CT scans prior to treatment. There was a significant increase in the use of MRI ($p<0.001$) and PET-CT ($p=0.007$) in the VMAT group over IMRT over IGRT. Surgery was used slightly more in the IMRT group ($p=0.099$). Resection margins were similar ($p=0.963$), whereas Naxogin and Chemotherapy had increased usage ($p=0.03$ and $p<0.001$).

Table 2: *A summary of the diagnostic work-up, treatment and treatment outcomes for H&N patients treated with IGRT, IMRT and VMAT at Kreftavdelingen UNN Tromso from 2005-2015 (chi square test Fisher's Exact tests for categorical data).*

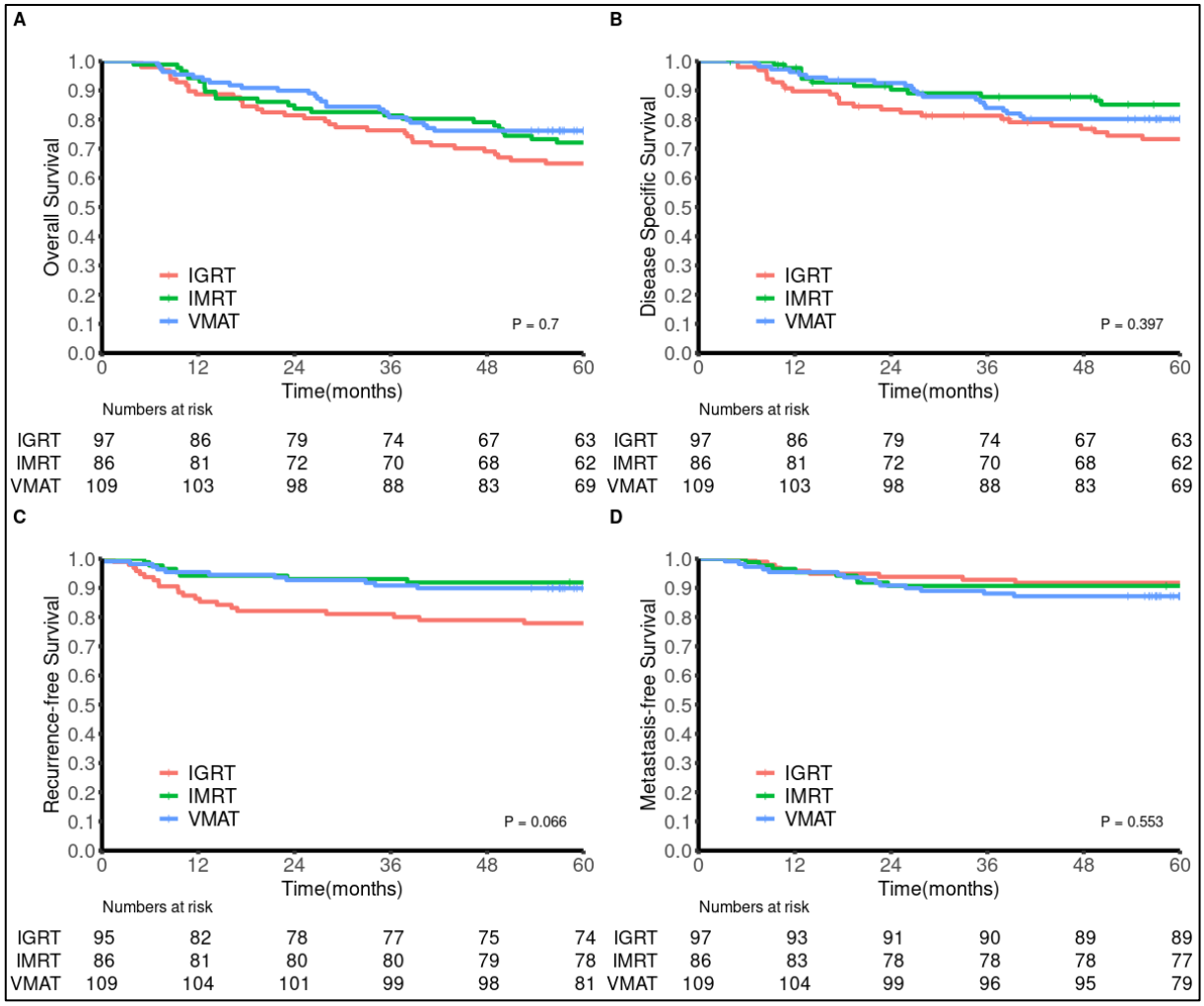
	IGRT	IMRT	VMAT	
Total number	97	86	109	
Diagnostic work-up				
CT				0.540
No	1	1	0	
Yes	96	85	109	
MRI				**<0.001**
No	68	46	38	
Yes	29	40	71	
PET				**0.007**
No	95	80	94	
Yes	2	6	15	
Treatment				
Surgery				0.099
No	42	31	56	
Yes	55	55	53	
Resection margins				0.963
R0	27	26	30	
R1	9	10	11	
R2	13	13	11	
Naxogin				**0.030**
No	51	38	39	
Yes	43	48	70	
Chemotherapy				**<0.001**
No	68	45	32	
Yes	26	41	77	
Treatment outcome				
Loco-regional failure				**0.008**
No	71	75	96	
Yes	26	11	13	
Time to loco-regional failure in months, median (range)	11 (2-136	23 (5-124)	22 (0-77)	
Metastasis				0.899
No	84	76	94	
Yes	13	10	15	
Time to metastasis in months, median (range)	33 (7-96)	19 (6-129)	21 (3-68)	

4.3 IGRT, IMRT and VMAT and their associations with treatment outcomes

As seen in figure 8, there is a tendency for better recurrence free survival associated with conventional IMRT and VMAT compared to IGRT (p=0.066). Overall survival, disease specific survival and metastasis free survival was comparable between the groups (p=0.7, p=0.397 and p=0.553 respectively).

In table 2 we see that IMRT and VMAT are associated with fewer loco-regional failures compared with IGRT (p=0.008). Metastasis was comparable between the groups (p=0.899)

Figure 8: *Kaplan-Meyer estimates of outcomes. A) Overall survival. B) Disease specific survival. C) Recurrence free survival. D) Metastasis free survival.*



4.4 Clinical variables and their associations with outcomes

As we see in table 3 and table 4, advanced tumor stage was associated with poor prognosis. Additional diagnostic work-up with CT and MRI were also associated with worse outcomes, most likely because additional imaging was done more frequently for the advanced staged cases. Naxogin® was associated with worse outcomes, likely because it is not used in freely resected cases or microscopic cancers.

Table 3: *Clinical variables as predictors of (A) overall and (B) disease specific survival (univariate analyses, log-rank test).*

	A) Overall Survival					**B)** Disease Specific Survival				
	N(%)	5 Year	Median	HR(95%CI)	P	N(%)	5 Year	Median	HR(95%CI)	P
tStage					**<0.001**					**<0.001**
I	56(19)	82	NA	1.000		56(19)	93	NA	1.000	
II	111(38)	81	156	1.02(0.64-1.62)		111(38)	89	NA	1.44(0.79-2.64)	
III	24(8)	62	94	1.9(0.89-4.06)		24(8)	69	94	4.26(1.62-11.2)	
IV	92(32)	53	90	2.25(1.36-3.75)		92(32)	60	99	5.23(2.71-10.07)	
Missing	9(3)					9(3)				
nStage					**0.012**					0.774
0	90(31)	73	118	1.000		90(31)	85	NA	1.000	
1	51(17)	76	129	0.96(0.58-1.6)		51(17)	84	NA	1.09(0.56-2.11)	
2	139(48)	68	156	0.92(0.61-1.37)		139(48)	74	NA	1.27(0.75-2.13)	
3	4(1)	50	43	4.35(0.54-35.13)		4(1)	67	NA	1.96(0.15-25.95)	
Missing	8(3)					8(3)				
MRI					0.07					**0.011**
No	152(52)	76	156	1.000		152(52)	86	NA	1.000	
Yes	140(48)	66	117	1.38(0.96-1.96)		140(48)	72	NA	1.79(1.13-2.84)	
PET					**0.042**					**0.049**
No	269(92)	73	154	1.000		269(92)	81	NA	1.000	
Yes	23(8)	52	75	1.8(0.86-3.74)		23(8)	58	NA	1.98(0.79-4.98)	
Naxogin					0.093					**0.002**
No	128(44)	75	178	1.000		128(44)	86	NA	1.000	
Yes	161(55)	68	118	1.35(0.95-1.93)		161(55)	74	NA	2.12(1.35-3.35)	
Missing	3(1)					3(1)				
Chemotherapy					0.151					0.492
No	145(50)	68	117	1.000		145(50)	81	NA	1.000	
Yes	144(49)	74	NA	0.77(0.54-1.1)		144(49)	77	NA	1.17(0.74-1.85)	
Missing	3(1)					3(1)				
Radiation technique					0.7					0.397
IGRT	97(33)	65	129	1.000		97(33)	73	NA	1.000	
IMRT	86(29)	72	NA	0.9(0.59-1.37)		86(29)	85	NA	0.68(0.39-1.19)	
VMAT	109(37)	76	NA	0.84(0.55-1.3)		109(37)	80	NA	0.83(0.47-1.44)	

Table 4: *Clinical variables as predictors of (A) loco-regional recurrence-free survival and (B) metastasis-free survival (univariate analyses, log-rank test).*

	Loco-regional Recurrence Free Survival					Metastasis Free Survival				
	N(%)	5 Year	Median	HR(95%CI)	P	N(%)	5 Year	Median	HR(95%CI)	P
tStage					**<0.001**					**0.021**
I	56(19)	96	NA	1.000		56(19)	93	NA	1.000	
II	111(38)	91	NA	3.36(1.56-7.22)		111(38)	95	NA	0.88(0.37-2.1)	
III	24(8)	88	NA	4.96(1.55-15.81)		24(8)	83	NA	1.97(0.53-7.4)	
IV	90(31)	73	NA	10.02(4.43-22.63)		92(32)	82	NA	2.6(1.04-6.46)	
Missing	11(4)					9(3)				
nStage					0.932					0.335
0	90(31)	91	NA	1.000		90(31)	93	NA	1.000	
1	51(17)	84	NA	1.19(0.51-2.74)		51(17)	96	NA	1.17(0.47-2.93)	
2	137(47)	85	NA	1.16(0.61-2.21)		139(48)	84	NA	1.82(0.88-3.75)	
3	4(1)	75	NA	1.75(0.14-21.26)		4(1)	100	NA	0(0-0)	
Missing	10(3)					8(3)				
MRI					0.338					0.232
No	152(52)	88	NA	1.000		152(52)	93	NA	1.000	
Yes	138(47)	85	NA	1.32(0.75-2.32)		140(48)	86	NA	1.47(0.78-2.79)	
Missing	2(1)									
PET					**0.002**					0.129
No	267(91)	88	NA	1.000		269(92)	91	NA	1.000	
Yes	23(8)	65	NA	3.07(0.94-10.02)		23(8)	78	NA	2.04(0.58-7.13)	
Missing	2(1)									
Naxogin					**0.048**					**0.005**
No	127(43)	91	NA	1.000		128(44)	95	NA	1.000	
Yes	160(55)	84	NA	1.84(1.03-3.26)		161(55)	86	NA	2.78(1.47-5.25)	
Missing	5(2)					3(1)				
Chemotherapy					0.844					0.09
No	144(49)	87	NA	1.000		145(50)	92	NA	1.000	
Yes	143(49)	87	NA	0.94(0.53-1.67)		144(49)	87	NA	1.74(0.92-3.29)	
Missing	5(2)					3(1)				
Radiation technique					0.066					0.553
IGRT	95(33)	78	NA	1.000		97(33)	92	NA	1.000	
IMRT	86(29)	92	NA	0.5(0.25-1.01)		86(29)	91	NA	0.92(0.43-2)	
VMAT	109(37)	90	NA	0.55(0.28-1.08)		109(37)	87	NA	1.36(0.63-2.94)	

5 Discussion

5.1 Main findings

As described in our results, the Kaplan-Meyer estimates suggest a slightly longer recurrence free survival with IMRT/VMAT compared to 3D-IGRT, approaching statistically significant levels (p=0.066). We also described significantly fewer loco-regional failures in IMRT and VMAT compared with 3D-IGRT (p=0.008). Overall survival, disease specific survival, and metastasis free survival was comparable between the 3D-IGRT, IMRT and VMAT group.

The results seem to indicate better loco-regional tumor control with IMRT and VMAT than IGRT. However, the results should be interpreted with caution as confounding factors exist. We know, for example, that HPV associated tumors are contributing to an increasingly larger proportion of cancer cases and have more favorable prognostics. If there are more HPV tumors in the VMAT and IMRT group, this might be a confounder mimicking better loco-regional tumor control. Another confounder, that may reduce the differences, is that modern techniques with organ sparing possibilities may lead to more ambitious treatment plans of patients that otherwise would have received palliative care only. There are also other uncertainties which are discussed later in the discussion.

The findings in our study support the continued use and research of VMAT and IMRT against cancer and suggests a longer recurrence free survival and fewer loco-regional failures compared with conventional techniques.

5.2 Similar studies

By searching Pubmed with the criteria; *"(IMRT) AND (radiotherapy) AND (head and neck) AND (conventional) AND ((vs) OR (comparison))"*, we found 13 studies that compared the outcomes of patients treated with IMRT to those who had received conventional radiotherapy. Some of these studies suggests better loco-regional control and lower toxicities with the use of IMRT compared to conventional radiotherapy. Some found no discernible difference between groups. None reported inferiority of IMRT/VMAT compared with IGRT (40-46). Some systematic reviews and meta analyses have also been done. They report better outcomes and fewer unwanted side effects with IMRT compared to conventional radiotherapy (15, 16, 47, 48). The findings in other research are comparable to our findings and strengthens the credibility of our results.

5.3 Methods

5.3.1 Lifestyle factors

Retrieval of lifestyle factors such as obesity, habitual smoking or ingestion of alcohol was not deemed possible within the time frame of this study. If there is an uneven distribution of smokers and drinkers between the two therapy groups, this might be a confounding factor. By including all patients treated, the study population is varied in regard to socioeconomic background, age and lifestyle. Not randomizing patients might have created unknown confounding factors, should the groups be different. However, no selection of patients to either treatment group has been done by the authors.

5.3.2 Uncertainties in data collection

The data stored in the hospital journal system is tremendous. It is plausible that some information that existed "somewhere" was sometimes missed. It is also important to note that there was some difference in which details where recorded in 2005 compared with 2015. Newer journals generally had more complete journals. This might be caused by some documentation still being written on physical paper in 2005. It seemed in some cases that documents where simply missing among the older journals. Death date was however very certain, because all deaths are registered and the date which it occurred is easily available.

There is also some level of uncertainty when trying to translate qualitative terms into quantitative terms. This should especially be noted for the evaluation DSS, which was

evaluated by the author by reading the final journal written before death. DSS was therefore, in some cases, interpreted by the author. If the patient was diagnosed with recurrent cancer and had associated symptom such as trouble breathing or severe malnutrition, this was plotted as disease specific non-survival.

It was originally planned to gather data on-site at the Department of Oncology, but the 2020 COVID-19 pandemic made it impossible for students to enter the hospital. Thus, data gathering had to be done through a hospital proxy service from a home office. The data sets might have been more accurate and easily complete, if the author had possibility to collect data on-site, with the supervisor and radiotherapy staff more freely available. Regardless, important problems that arose were successfully solved through digital meetings between the author and supervisor.

5.3.3 Uncertain distinction of treatment groups

To separate the different treatment groups, a date approach was used. It was assumed that IMRT and VMAT was used consistently from the moment it became available in February 2009 and January 2012 respectively. It was later discovered a minor mixing of patients between the 3D-IGRT, IMRT and VMAT group, because the transition was not as immediate as originally thought. In regard to this, it could be more accurate to say that our study investigates the effects of availability of IMRT and VMAT.

5.3.4 Different TNM-grading

During the time interval of this retrospective cohort, TNM-6 was replaced with TNM-7. Different criteria might have caused some patients to be staged differently. In this case most of the 3D-IGRT was staged using TNM-6, whereas most of the IMRT/VMAT group was staged using TNM-7. Stage migration might be a confounder in the analysis.

The apparent increase in advanced N-stage in the VMAT group, can likely be explained by the introduction of both clinical and pathological N-staging, as we did not separate between pN-stage and cN-stage in analysis.

5.4 Ethical considerations

Because this is a retrospective study, many of the patients that have undergone radiotherapy are now diseased. This makes a consent for participation in research impossible. Of ethical

reasons we strived to read only the necessary journals for the statistics. However, a lot of information was often read in order to find what was needed. All data was stored in a secure location and strict confidentiality was ensured. We believe that the benefits of assessing the quality of treatment given by doing a quality assurance study for the Department of Oncology, UNN Tromso. Justifies the retrieval of patient data. It is not unthinkable that many patients would have wanted to ensure the quality of the treatment they were given.

6 Conclusion

In this retrospective cohort, we examined how the introduction of 3D-IGRT, IMRT and VMAT affected survival outcomes, patterns of loco-regional and metastatic recurrences among patients treated for (H&N) cancer at the department of Oncology, UNN Tromso in the period from 2005-2015.

We saw that overall survival was similar between the groups (p=0.7). Disease specific survival and metastatic free survival was also comparable (p=0.59 and p=0.39 respectively). Difference in recurrence free survival approached statistically significant differences (p=0.066), slightly in favor of IMRT/VMAT over 3D-IGRT. Our findings are strengthened by other studies showing similar results, with either no difference between groups or results in favor of IMRT/VMAT over 3D-IGRT. We found no higher risk of local failure with IMRT compared to conventional radiotherapy, even if the conformality was higher.

Other outcomes and details regarding treatment could have been included. We did, for example, not include side effects, which can cause patients to abort treatment. Neither did we account for lifestyle factors such as obesity, smoking and alcohol consumption. Conducting a randomized controlled trial is difficult, as it would be unethical to designate patients to an outdated treatment. However, a large retrospective cohort, where groups are properly matched for lifestyle and age, could provide more certain results.

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Appendix: GRADE evaluations

Referanse: Kong M, Hong SE, Choi J, Kim Y. Comparison of survival rates between patients treated with conventional radiotherapy and helical tomotherapy for head and neck cancer. Radiat Oncol J. 2013;31(1):1-11.			Studiedesign: Retrospektiv Kohortestudie Grade - kvalitet Very weak
Formål	Materiale og metode	**Resultater**	**Diskusjon/kommentarer/sjekkliste**
Compared to conventional radiotherapy (RT), intensity-modulated radiotherapy (IMRT) significantly reduces the rate of treatment-induced late toxicities in head and neck cancer. However, a clear survival benefit of IMRT over conventional RT has not yet been shown. This study is among the first comparative study to compare the survival rates between conventional RT and helical tomotherapy in head and neck cancer.. **Konklusjon** This study showed the locoregional recurrence-free survival benefits of helical tomotherapy in the treatment of head and neck cancers. **Land** **År data innsamling**	From January 2008 to November 2011, 37 patients received conventional RT and 30 patients received helical tomotherapy for management of head and neck cancer. We retrospectively compared the survival rates between patients treated with conventional RT and helical tomotherapy, and analyzed the prognostic factors for survival.	The 1- and 2-year locoregional recurrence-free survival rates were 61.2% and 58.1% for the conventional RT group, 89.3% and 80.3% for the helical tomotherapy group, respectively. The locoregional recurrence-free survival rates of the helical tomotherapy group were significantly higher than conventional RT group (p = 0.029). There were no significant differences in the overall and distant metastasis-free survival between the two groups. RT technique, tumor stage, and RT duration were significant prognostic factors for locoregional recurrence-free survival.	**Sjekkliste:** • Formålet klart formulert? • Er gruppene rekruttert fra samme populasjon/befolkningsgruppe? (seleksjons bias) • Var gruppene sammenliknbare i forhold til viktige bakgrunnsfaktorer? (seleksjons bias)* • Var de eksponerte individene representative for en definert befolkningsgruppe/populasjon?* • Ble eksposisjon og utfall målt likt og pålitelig (validert) i de to gruppene? (Classification bias) ** • Er den som vurderte resultatene (endepunkt- ene) blindet for gruppetilhørighet?** • Var studien prospektiv? • Ble mange nok personer i kohorten fulgt opp? (Attrition bias/follow-up-bias) • Er det utført frafallsanalyser? (Eval. attrition bias) • Var oppfølgingstiden lang nok til å påvise positive og/eller negative utfall? • Er det tatt hensyn til viktige konfunderende faktorer i design/ gjennomføring/analyser? • Tror du på resultatene? -Bradford Hills criteria (time sequence, dose-response gradient, biological plausibility, consistency….) • Kan resultatene overføres til den generelle befolkningen? • Annen litteratur som styrker/svekker resultatene? • Hva betyr resultatene for endring av praksis? **Hva diskuterer forfatterne som:** • **Styrke** • **Svakhet**

Referanse:Lin CS, Chen YW, Liu SC, Tsao CC, Lin KT, Lee SP, et al. Treatment outcomes with whole-field versus split-field intensity-modulated radiotherapy for patients with nasopharyngeal carcinoma. Head & neck. 2019;41(3):598-605.			Studiedesign: Retrospektiv Kohortestudie Grade - kvalitet Weak
Formål	Materiale og metode	**Resultater**	**Diskusjon/kommentarer/sjekkliste**
The purpose of this study was to present our comparison of the clinical outcome of patients with nasopharyngeal carcinoma (NPC) treated with whole-field intensity-modulated radiotherapy (whole-field-IMRT) or split-field-IMRT. **Konklusjon** **Conclusion:** Our study shows that whole-field-IMRT using a lower dose/fraction for the lower neck results in at least comparable locoregional control and less fibrosis compared to conventional fraction with split-field-IMRT. **Land** **År data innsamling**	**Methods:** We retrospectively studied 388 patients with M0 NPC. The median lower neck doses were 50 Gy in 1.35 Gy/fractions for the 240 whole-field-IMRT patients, and 50.4 Gy in 1.8 to 2.0 Gy/fractions for the 148 split-field-IMRT patients.	**Results:** The IMRT technique did not affect the overall survival (OS; P = .077) and locoregional control (P = .231) rates. However, the split-field-IMRT group had more locoregional recurrences at the whole neck (P = .005) but not at the nasopharynx (P = .968) or the lower neck (P = .485). The patients treated with split-field-IMRT (43.2%) had more grade III neck fibrosis than the patients who received whole-field-IMRT (18.3%; P < .001). Only 1 patient had temporal lobe necrosis in our study.	**Sjekkliste:** • Formålet klart formulert? • Er gruppene rekruttert fra samme populasjon/befolkningsgruppe? (seleksjons bias) • Var gruppene sammenliknbare i forhold til viktige bakgrunnsfaktorer? (seleksjons bias)* • Var de eksponerte individene representative for en definert befolkningsgruppe/populasjon?* • Ble eksposisjon og utfall målt likt og pålitelig (validert) i de to gruppene? (Classification bias) ** • Er den som vurderte resultatene (endepunkt- ene) blindet for gruppetilhørighet?** • Var studien prospektiv? • Ble mange nok personer i kohorten fulgt opp? (Attrition bias/follow-up-bias) • Er det utført frafallsanalyser? (Eval. attrition bias) • Var oppfølgingstiden lang nok til å påvise positive og/eller negative utfall? • Er det tatt hensyn til viktige konfunderende faktorer i design/ gjennomføring/analyser? • Tror du på resultatene? -Bradford Hills criteria (time sequence, dose-response gradient, biological plausibility, consistency….) • Kan resultatene overføres til den generelle befolkningen? • Annen litteratur som styrker/svekker resultatene? • Hva betyr resultatene for endring av praksis? **Hva diskuterer forfatterne som:** • **Styrke** • **Svakhet**

Referanse: Lohia S, Rajapurkar M, Nguyen SA, Sharma AK, Gillespie MB, Day TA. A comparison of outcomes using intensity-modulated radiation therapy and 3-dimensional conformal radiation therapy in treatment of oropharyngeal cancer. JAMA Otolaryngol Head Neck Surg. 2014;140(4):331-7.			Studiedesign: Retrospektiv Kohortestudie Grade - kvalitet Weak
Formål	Materiale og metode	**Resultater**	**Diskusjon/kommentarer/sjekkliste**
To determine whether IMRT improves percutaneous endoscopic gastrostomy (PEG) tube and treatment-related toxicity outcomes compared with 3D-CRT in patients with oropharyngeal squamous cell carcinoma. **Konklusjon** The use of IMRT significantly improves PEG tube and toxicity-related outcomes compared with 3D-CRT in the treatment of oropharyngeal primary cancers. Given the association between mucosal toxic effects, PEG tube dependence, and dysphagia, these findings may be an indication of improved swallowing outcomes with IMRT. **Land** **År data innsamling** 2000 -2009	**Design, setting, and participants:** Retrospective review of 159 patients with oropharyngeal primary tumors with no history of chemotherapy, radiation therapy, or surgery of the head and neck who underwent definitive treatment with radiotherapy for oropharyngeal squamous cell carcinoma at the Hollings Cancer Center outpatient clinic, Medical University of South Carolina, from 2000 to 2009. **Intervention:** Doses of 70 Gy in 35 daily fractions of radiotherapy delivered via IMRT or 3D-CRT. **Main outcomes and measures:** Primary end points included PEG tube dependence 1 year after radiotherapy start, weight loss during treatment, and change in Eastern Cooperative Oncology Group performance status. Secondary end points included overall and disease-free survival, disease recurrence, and toxic effect profiles.	**Results:** The IMRT group (n = 103) had a significantly lower rate of PEG tube dependence 1 year after treatment initiation than the 3D-CRT group (n = 56) for all patients (P = .02) and for those with advanced T stage (P = .01) and a shorter time to PEG tube removal (P < .001). Acute grade 3 or greater toxic effects to skin and mucous membranes occurred less frequently in the IMRT group (P = .02 and P < .001, respectively). The 2 groups did not differ significantly in weight loss, treatment failure (hazard ratio, 0.82 [95% CI, 0.47-1.41]), overall survival (P = .45), or disease-free survival (P = .26)	**Sjekkliste:** • Formålet klart formulert? • Er gruppene rekruttert fra samme populasjon/befolkningsgruppe? (seleksjons bias) • Var gruppene sammenliknbare i forhold til viktige bakgrunnsfaktorer? (seleksjons bias)* • Var de eksponerte individene representative for en definert befolkningsgruppe/populasjon?* • Ble eksposisjon og utfall målt likt og pålitelig (validert) i de to gruppene? (Classification bias) ** • Er den som vurderte resultatene (endepunkt- ene) blindet for gruppetilhørighet?** • Var studien prospektiv? • Ble mange nok personer i kohorten fulgt opp? (Attrition bias/follow-up-bias) • Er det utført frafallsanalyser? (Eval. attrition bias) • Var oppfølgingstiden lang nok til å påvise positive og/eller negative utfall? • Er det tatt hensyn til viktige konfunderende faktorer i design/ gjennomføring/analyser? • Tror du på resultatene? -Bradford Hills criteria (time sequence, dose-response gradient, biological plausibility, consistency….) • Kan resultatene overføres til den generelle befolkningen? • Annen litteratur som styrker/svekker resultatene? • Hva betyr resultatene for endring av praksis? **Hva diskuterer forfatterne som:** • **Styrke** • **Svakhet**

Referanse:Mohamed ASR, Smith BD, Smith JB, Sevak P, Malek JS, Kanwar A, et al. Outcomes of carotid-sparing IMRT for T1 glottic cancer: Comparison with conventional radiation. Laryngoscope. 2020;130(1):146-53.			Studiedesign: Retrospektiv Kohortestudie Grade - kvalitet Weak
Formål	Materiale og metode	**Resultater**	**Diskusjon/kommentarer/sjekkliste**
Sammenlikne IMRT vs konvensjonell stråleterapi for glottiskreft **Konklusjon** These results warrant further prospective evaluation of CS-IMRT for early-stage glottic larynx cancer. **Land** **År data innsamling** 1989-2011	330 consecutive patients with early-stage laryngeal carcinoma were treated from 1/1989 to 5/2011, including 282 CRT and 48 CS-IMRT patients. The median follow-up was 43 (CS-IMRT) and 66 (CRT) months	**Hovedfunn** There was no difference in local failure rates comparing patients undergoing CS-IMRT with CRT, with 3-year local control rates of 88% vs. 89%, respectively (p=0.938). Using a 1cm circumferential margin, the average dose to the left and right carotid arteries was 48.3 and 47.9 Gy, respectively. 88% of locoregional recurrences involved the ipsilateral true vocal cord, including all local recurrences in the IMRT group.	**Sjekkliste:** • Formålet klart formulert? • Er gruppene rekruttert fra samme populasjon/befolkningsgruppe? (seleksjons bias) • Var gruppene sammenliknbare i forhold til viktige bakgrunnsfaktorer? (seleksjons bias)* • Var de eksponerte individene representative for en definert befolkningsgruppe/populasjon?* • Ble eksposisjon og utfall målt likt og pålitelig (validert) i de to gruppene? (Classification bias) ** • Er den som vurderte resultatene (endepunkt- ene) blindet for gruppetilhørighet?** • Var studien prospektiv? • Ble mange nok personer i kohorten fulgt opp? (Attrition bias/follow-up-bias) • Er det utført frafallsanalyser? (Eval. attrition bias) • Var oppfølgingstiden lang nok til å påvise positive og/eller negative utfall? • Er det tatt hensyn til viktige konfunderende faktorer i design/ gjennomføring/analyser? • Tror du på resultatene? -Bradford Hills criteria (time sequence, dose-response gradient, biological plausibility, consistency….) • Kan resultatene overføres til den generelle befolkningen? • Annen litteratur som styrker/svekker resultatene? • Hva betyr resultatene for endring av praksis?

Referanse: Mok G, Gauthier I, Jiang H, Huang SH, Chan K, Witterick IJ, et al. Outcomes of intensity-modulated radiotherapy versus conventional radiotherapy for hypopharyngeal cancer. Head & neck. 2015;37(5):655-61.			Studiedesign: Retrospektiv Kohortestudie Grade - kvalitet Weak
Formål	Materiale og metode	**Resultater**	**Diskusjon/kommentarer/sjekkliste**
Sammenlikne IMRT vs konvensjonell stråleterapi. **Konklusjon** Bedre locoregional kontroll, sammenlignbar overlevelse og fjernmetastaser. **Land** Canada **År data innsamling** 2012	**Populasjon:** 181 pasienter med hypofarynkskarsinom. 90 i konvensjonell gruppe 91 i IMRT. **Hoved utfall:** Overlevelse, locoregional kontroll, fjernmetastaser. **Viktige konfunderende faktorer:** Forskjellige grupper ble behandlet på forskjellige tidspunkt som kan gi forskjeller i andre aspekter ved diagnostikk og behandling. Mer nøyaktig diagnostikk hos IMRT gruppen **Statistiske metoder:** chi-square, fischer, t-test, cox proportional hazard model.	**Hovedfunn** **Betweem exposes/unexposed:** Better locoregional control 75% vs 58%. P.0,003. **Bifunn** Ingen forskjell i overlevelse eller metastaser.	**Sjekkliste:** • Formålet klart formulert? Ja • Er gruppene rekruttert fra samme populasjon/befolkningsgruppe? (seleksjons bias) Ja • Var gruppene sammenliknbare i forhold til viktige bakgrunnsfaktorer? (seleksjons bias)* Ja • Var de eksponerte individene representative for en definert befolkningsgruppe/populasjon?* Ja • Ble eksposisjon og utfall målt likt og pålitelig (validert) i de to gruppene? (Classification bias) ** Ja • Er den som vurderte resultatene (endepunkt- ene) blindet for gruppetilhørighet?** Nei • Var studien prospektiv? Nei • Ble mange nok personer i kohorten fulgt opp? (Attrition bias/follow-up-bias) Trolig • Er det utført frafallsanalyser? (Eval. attrition bias) • Var oppfølgingstiden lang nok til å påvise positive og/eller negative utfall? Ja • Er det tatt hensyn til viktige konfunderende faktorer i design/ gjennomføring/analyser? Ja • Tror du på resultatene? -Bradford Hills criteria (time sequence, dose-response gradient, biological plausibility, consistency….) Ja • Kan resultatene overføres til den generelle befolkningen? Ja • Annen litteratur som styrker/svekker resultatene? Ja, styrker • Hva betyr resultatene for endring av praksis? For IMRT. **Hva diskuterer forfatterne som:** • **Styrke** • **Svakhet**