TOMSK POLYTECHNIC UNIVERSITY ТОМСКИЙ ПОЛИТЕХНИЧЕСКИЙ УНИВЕРСИТЕТ

Министерство науки и высшего образования Российской Федерации
федеральное государственное автономное
образовательное учреждение высшего образования
«Национальный исследовательский Томский политехнический университет» (ТПУ)

School: School of Nuclear Science and Engineering
Field of training (Specialty): 14.04.02. Nuclear Physics and Technology
Division: Nuclear Fuel Cycle

MASTER'S GRADUATION THESIS

Topic of research work
Dosimetric and radiobiological evaluation of combined course of radiation therapy for locally advanced cervical cancer based on different techniques for dose delivery

UDC: 615.849: 618.146-006.6

Student

Group	Full name	Signature	Date
0AM8M	**Ahmed Ramadan Abdelrahman Salem**		

Scientific supervisors

Position	Full name	Academic degree, academic rank	Signature	Date
Associate professor	Evgeniia Sukhikh.	PhD		
Professor	Dr. Hatem Mohamed	MD		

Adviser

Position	Full name	Academic degree, academic rank	Signature	Date
Radiation Oncologist	Alexander Taletsky			

ADVISERS:

Section "Financial Management, Resource Efficiency and Resource Saving"

Position	Full name	Academic degree, academic rank	Signature	Date
Associate professor	Menshikova E.V.	PhD		

Section "Social Responsibility"

Position	Full name	Academic degree, academic rank	Signature	Date
Senior lecturer	Verigin D.A	Cand.of Sc		

ADMITTED TO DEFENSE:

Director of the programme	Full name	Academic degree, academic rank	Signature	Date
Nuclear medicine	Cherepennikov Yu.M.	PhD		

Tomsk – 2020

TOMSK POLYTECHNIC UNIVERSITY ТОМСКИЙ ПОЛИТЕХНИЧЕСКИЙ УНИВЕРСИТЕТ

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Division: Nuclear Fuel Cycle

APPROVED BY:
Director of the programme
_____CherepennikovYu.M.
«____» _____ 2020

ASSIGNMENT
for the Graduation Thesis completion

In the form:

Magister's Dissertation

For a student:

Group	Full name
0AM8M	**Ahmed Ramadan Abdelrahman Salem**

Topic of research work:

Dosimetric and radiobiological evaluation of combined course of radiation therapy for locally advanced cervical cancer based on different techniques for dose delivery	
Approved by the order of the Director of School of Nuclear Science & Engineering (date, number):	

Deadline for completion of Master's Graduation Thesis:	

TERMS OF REFERENCE:

Initial date for research work: *(the name of the object of research or design; performance or load; mode of operation (continuous, periodic, cyclic, etc.); type of raw material or material of the product; requirements for the product, product or process; special requirements to the features of the operation of the object or product in terms of operational safety, environmental impact, energy costs; economic analysis, etc.)*	Using Monaco software to create radiotherapy plans for patients with cervical cancer to compare between two different techniques in second stage of radiotherapy.

List of the issues to be investigated, designed and developed *(analytical review of literary sources with the purpose to study global scientific and technological achievements in the target field, formulation of the research purpose, design, construction, determination of the procedure for research, design, and construction, discussion of the research work results, formulation of additional sections to be developed; conclusions).*	1. Literature review about cervical cancer (risk factor, diagnosis, staging, pathology, treatment) 2. Literature review about different techniques of radiotherapy and radiobiological evaluation. 3. Create radiotherapy plans for selected patients and analysis the data.

Advisors to the sections of the Master's Graduation Thesis
(with indication of sections)

Section	Advisor
1. Literature review	Evgeniia Sukhikh/ Hatem Mohamed /Alexander
2. Practical part	Evgeniia Sukhikh/ Hatem Mohamed /Alexander
3. Financial management	Menshikova E.V.
4. Social Responsibility	Verigin D.A

Date of issuance of the assignment for Master's Graduation Thesis completion according to the schedule	

Assignment issued by a scientific supervisors/advisors:

Position	Full name	Academic degree, academic status	Signature	Date
Associate professor	Evgeniia Sukhikh	PhD		
Professor	Dr. Hatem Mohamed	MD		
Radiation Oncologist	Alexander Taletsky			

Assignment accepted for execution by a student:

Group	Full name	Signature	Date
0AM8M	Ahmed Ramadan Abdelrahman Salem		

Tomsk – 2020

TASK FOR SECTION
«FINANCIAL MANAGEMENT, RESOURCE EFFICIENCY AND RESOURCE SAVING»

To the student:

Group	Full name
0AM8M	Ahmed Ramadan Abdelrahman Salem

School	Nuclear Science & Engineering	**Division**	Nuclear-Fuel Cycle
Degree	Master	**Specialization**	14.04.02 Nuclear physics and technology / Nuclear medicine

Input data to the section «Financial management, resource efficiency and resource saving»:	
1. *Resource cost of scientific and technical research (STR): material and technical, energetic, financial and human*	– Salary costs – 859,803; – STR budget – 287,340;
2. *Expenditure rates and expenditure standards for resources*	– Electricity costs – 5,8 rub per 1 kW
3. *Current tax system, tax rates, charges rates, discounting rates and interest rates*	– Labor tax – 27,1 %; – Overhead costs – 30%;
The list of subjects to study, design and develop:	
1. *Assessment of commercial and innovative potential of STR*	– comparative analysis with other researches in this field;
2. *Development of charter for scientific-research project*	– SWOT-analysis;
3. *Scheduling of STR management process: structure and timeline, budget, risk management*	– calculation of working hours for project; – creation of the time schedule of the project; – calculation of scientific and technical research budget;
4. *Resource efficiency*	– integral indicator of resource efficiency for the developed project.
A list of graphic material *(with list of mandatory blueprints):*	
1. *Competitiveness analysis* 2. *SWOT- analysis* 3. *Gantt chart and budget of scientific research* 4. *Assessment of resource, financial and economic efficiency of STR* 5. *Potential risks*	

Date of issue of the task for the section according to the schedule	

Task issued by adviser:

Position	Full name	Scientific degree, rank	Signature	Date
Associate professor	E.V. Menshikova	PhD		

The task was accepted by the student:

Group	Full name	Signature	Date
0AM8M	Ahmed Ramadan Abdelrahman Salem		

Tomsk – 2020

Task for section
«Social responsibility»

To student:

Group	Full name
0AM8M	Ahmed Ramadan Abdelrahman Salem

School	Nuclear Science and Engineering	Department	Nuclear fuel cycle
Degree	Master programme	Specialization	14.04.02 Nuclear physics and technology / Nuclear medicine

Title of graduation thesis:

Dosimetric and radiobiological evaluation of combined course of radiation therapy for locally advanced cervical cancer based on different techniques for dose delivery	
Initial data for section «Social Responsibility»:	
1. Information about object of investigation (matter, material, device, algorithm, procedure, workplace) and area of its application	– Effect of exposure to ionizing radiation in radiation oncology centers on patients and health care workers due to exposure to radiation machines (e.g Elekta machine). – Application area: radiation oncology centers.
List of items to be investigated and to be developed:	
1. Legal and organizational issues to provide safety: – Special (specific for operation of objects of investigation, designed workplace) legal rules of labor legislation; – Organizational activities for layout of workplace.	– Labour code of Russian Federation #197 from 30/12/2001 GOST 12.2.032-78 SSBT – Sanitary Rules 2.2.2/2.4.1340-03. Hygienic requirements for PC and work with it
2. Work Safety: 2.1. Analysis of identified harmful and dangerous factors 2.2. Justification of measures to reduce probability of harmful and dangerous factors	– Enchanced electromagnetic radiation level – Insufficient illumination of workplace – Excessive noise – Deviation of microclimate indicators – Electric shock – Ionizing radiation
3. Ecological safety:	– Indicate impact of linear accelerator on hydrosphere, atmosphere and lithosphere
4. Safety in emergency situations:	– Fire safety;

Assignment date for section according to schedule	

The task was issued by consultant:

Position	Full name	Scientific degree, rank	Signature	date
assistant professor	Verigin D.A.	Cand.of Sc.		

The task was accepted by the student:

Group	Full name	Signature	date
0AM8M	Ahmed Ramadan Abdelrahman Salem		

Expected learning outcomes

Learning outcome (LO) code	Learning outcome (a graduate should be ready)	Requirements of the FSES HE, criteria and / or interested parties
Professional competencies		
LO1	To apply deep mathematical, scientific, socio-economic and professional knowledge for conducting theoretical and experimental research in the field of the use of nuclear science and technology/	FSES HE Requirements (PC-1,2, 3, 6, UC-1,3), Criterion 5 RAEE (p 1.1)
LO2	To demonstrate ability to define, formulate, and solve interdisciplinary engineering tasks in the nuclear field using professional knowledge and modern research methods.	FSES HE Requirements (PC-2,6,9,10,14, UC-2,3,4, BPC1,2), Criterion 5 RAEE (p 1.2)
LO3	To plan and conduct analytical, simulation and experimental studies in complex and uncertain conditions using modern technologies, and to evaluate critically research results.	FSES HE Requirements (PC-4,5,6,9,22, UC-1,2,5,6), Criterion 5 RAEE (p 1.3)
LO4	To use basic and special approaches, skills and methods for identification, analysis, and solution of technical problems in the field of nuclear science and technology.	FSES HE Requirements (PC-7,10,11,12,13, UC-1-3,BPC1,3), Criterion 5 RAEE (p 1.4)
LO5	To operate modern physical equipment and instruments, to master technological processes in the course of preparation for the production of new materials, instruments, installations, and systems.	FSES HE Requirements (PC-8,11,14,15, BPC-1), Criterion 5 RAEE (p 1.3)
LO6	To demonstrate ability to develop multi-option schemes for achieving production goals with the effective use of available technical means and resources.	FSES HE Requirements (PC-12,13,14,16, BPC-2), Criterion 5 RAEE (p 1.3)
Cultural competencies		
LO7	To demonstrate ability to use a creative approach to develop new ideas and methods for designing nuclear facilities, as well as to modernize and improve the	FSES HE Requirements (PC-2,6,9,10,14, UC-1,2,3), Criterion 5 RAEE (p

	applied technologies of nuclear production.	1.2,2.4,2.5)
Basic professional competencies		
LO8	To demonstrate skills of independent learning and readiness for continuous self-development within the whole period of professional activity.	FSES HE Requirements (PC-16,17,21, UC-5,6, BPC-1), Criterion 5 RAEE (p 2.6) coordinated with the requirements of the international standard EURACE & FEANI
LO9	To use a foreign language at a level that enables a graduate to function successfully in the international environment, to develop documentation, and to introduce the results of their professional activity.	FSES HE Requirements (BPC-3, UC-2,4), Criterion 5 RAEE (p 2.2)
LO10	To demonstrate independent thinking, to function efficiently in command-oriented tasks and to have a high level of productivity in the professional (sectoral), ethical and social environments, to lead professional teams, to set tasks, to assign responsibilities and bear liability for the results of work.	FSES HE Requirements (PC-18,20,21,22,23, UC-1,4, BPC-2), Criterion 5 RAEE (p 1.6,2.3) coordinated with the requirements of the international standard EUR-ACE & FEANI

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«Национальный исследовательский Томский политехнический университет» (ТПУ)

School School of Nuclear Science & Engineering
Field of training (specialty) 14.04.02 «Nuclear Physics and Technology»
Level of education Master Degree Program
Division Division for Nuclear-Fuel Cycle
Period of completion 2018/2019 and 2019/2020 academic years
Form of presenting the work:

Master's Thesis

SCHEDULED ASSESSMENT CALENDAR
for the Master's Graduation Thesis completion

Deadline for completion of Master's Graduation Thesis:	

Assessment date	**Title of section (module) / type of work (research)**	**Maximum score for the section (module)**
27.01.2020	1. Preparation of technical specifications and selection of research areas	
24.02.2020	2. Development of a common research methodology	
23.03.2020	3. Selection and study of materials on the topic	
13.04.2020	4. Obtaining necessary data and verification of the obtained results	
27.04.2020	5. Processing received data	
18.05.2020	6. Registration of the work performed	
29.05.2020	7. Preparation for defending a dissertation	

COMPILED BY:
Scientific supervisors:

Position	**Full name**	**Academic degree, academic rank**	**Signature**	**Date**
Associate professor	Evgeniia Sukhikh	Ph.D		
Professor	Dr. Hatem Mohamed	MD		

Adviser

Position	**Full name**	**Academic degree, academic rank**	**Signature**	**Date**
Radiation Oncologist	Alexander Taletsky			

AGREED BY:
Director of the programme

Position	**Full name**	**Academic degree, academic rank**	**Signature**	**Date**
Associate Professor	Cherepennikov Yu.M.	Ph.D		

Table of Contents

1. Introduction:

Gynecologic cancers are leading causes of death in women worldwide. Collectively labeled as gynecologic cancer, ovarian, uterine cervix, uterine corpus, vaginal, and vulvar cancers are leading causes of cancer death in women around the world.(1)

2. Incidence and Epidemiology:

Cervical cancer remains the 4th most often diagnosed cancer and therefore the 4th leading cause of death due to cancer in women worldwide.(2)

Worldwide, 1.1 million women were diagnosed with a gynecologic cancer and an estimated 513,000 (47%) died of their disease.(3)

Cervical cancer remains the most common cancer in women in Eastern and Middle Africa.(3)

3. Risk Factors:

Human papillomavirus (HPV) infection is the most significant risk factor for cervical cancer, as there's a really strong link between HPV infection and cervical cancer.(4)

Other risk elements for cervical cancer encompass the subsequent: cigarette smoking, high parity, long-term use of oral contraceptives, Immunosuppression, multiple sexual partners, but smoking appeared to be the most significant environmental risk factor.(5)

Cancer Cervix risk is six times higher in females with HIV versus females in the general population.(6)

Females whose food do not contain enough fruits and vegetables could be at greater hazard for cancer cervix.(7)

In 2020, an estimated about 13,800 cases of cervical cancer are getting to be diagnosed and about 4,290 deaths will occur in the US. The incidence rate has

dropped by more than half since the mid-1970s, largely due to the widespread of screening with the Pap test. Studies suggest that may be due to HPV vaccine uptake. Moreover, death rate has also dropped by more than half since the mid-1970s due to declines in incidence and the early detection of cancer through screening.[8]

Risk of cancer cervix may be decreased by regular cervical cancer screening tests. A pap test is used to screen for cervical cancer. After certain positive pap test results, HPV test may be done.[9]

4. Diagnosis:

- ✓ **Symptoms:** Early stages are asymptomatic (underscoring the importance of screening)….
  1. Bleeding (most common presentation)
     - Contact bleeding (always suspect cancer cervix).
     - Postmenopausal bleeding (always suspect endometrial cancer)
  2. Discharge: serosanginous or offensive (infected)
  3. Pain (late): low back pain radiating to back of lower extremities
  4. Bowel or urinary symptoms, such as pressure-related complaints, hematuria, bleeding per rectum, or vaginal passage of urine or stool.
- ✓ **Signs:**
  1. General: Cachexia - Anemia - Uremia in advanced cases
  2. Abdominal: No pelviabdominal mass (except if pyometra or metastasis)
  3. Local:
     - Per Vaginal examination (P/V): any of the pathologic forms of ectocervix or endocervix is seen
     - Per Rectal examination (P/R): is the only way to assess cervical size and the best way to assess the degree parametrial infiltration.[10-11]

5. Clinical staging & Investigations:

a) Physical examination: (by an experienced examiner under anesthesia)

- Speculum, bimanual, and rectovaginal.
- Palpation of groin and supraclavicular LNs

b) Cervical biopsy:

- Direct or colposcopic.
- Endocervical curettage if no lesion is colposcopically detected
- Conization: in highly suspicious cases with negative gross and colposcopic findings, as well as, when microinvasion is suspected.

c) Endoscopy

- Hysteroscopy: for uterine spread.
- Cystoscopy: for bladder spread (finger like projections and not bullous edema)
- Proctoscopy: for rectal spread.

d) Imaging studies:

- CT or MRI for accurate assessment of tumor spread.
- Intravenous pyelogram (IVP) for ureteric extension.
- Chest and Abdomen radiograph for evaluation for distant metastases.[11]

6. Staging:

(FIGO) “the International Federation of Gynecology & obstetrics” decided those analysis procedures for staging can be confined to colposcopy, biopsy, conization of cervix, cystoscopy, & procto-sigmiodoscopy. More complicated radiological & surgical techniques aren't presented in the FIGO classification. However in the United States of America computed tomography (CT), magnetic

resonance imaging (MRI), Combined Positron emission tomography/computed tomography (PET/CT), and surgical staging are used to guide treatment options.[12]

Once cancer cervix is diagnosed, radiological imaging is indicated to know how far the cancer has spread. Recommended radiological imaging are chest x-ray, CT, MRI & combined PET/CT. Cystoscopy and proctoscopy are only recommended if urinary bladder or rectal extension is suspected.[13]

(AJCC) "American Joint Committee on Cancer" -8th edition- is the most widely used system for cancer cervix staging. Which is based on the tumor size (T), nodal involvement (N) & presence of distant metastasis (M).[14]

The staging system suggested by FIGO is widely followed and correlate well with the prognosis.[15]

Briefly stage I consists of disease limited to the cervix (IA: microscopic and IB: clinically apparent lesion). Stage II disease extends beyond the cervix reaching upper third of the vagina or parametrium. Stage III disease involvement of pelvic side wall or lower third of vagina including hydronephrosis or non-functioning kidney. Stage IV disease extends beyond the pelvis or involves the mucosa of the rectum or urinary bladder.[15]

TNM Categories		FIGO Stages	Definition
TX			Primary tumour cannot be assessed
T0			No evidence of primary tumour
Tis			Carcinoma in situ (preinvasive carcinoma)
T1		I	Tumour confined to the cervix[a]
	T1a[bc]	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximal depth of 5.0.mm measured from the base of the epithelium and a horizontal spread of 7.0.mm or less[d]
	T1a1	IA1	Measured stromal invasion 3.0.mm or less in depth and 7.0.mm or less in horizontal spread
	T1a2	IA2	Measured stromal invasion more than 3.0.mm and not more than 5.0.mm with a horizontal spread of 7.0.mm or less
	T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
	T1b1	IB1	Clinically visible lesion 4.0.cm or less in greatest dimension
	T1b2	IB2	Clinically visible lesion more than 4.0.cm in greatest dimension
T2		II	Tumour invades beyond uterus but not to pelvic wall or to lower third of vagina
	T2a	IIA	Tumour without parametrial invasion
	T2a1	IIA1	Clinically visible lesion 4.0.cm or less in greatest dimension
	T2a2	IIA2	Clinically visible lesion more than 4.0.cm in greatest dimension
	T2b	IIB	Tumour with parametrial invasion
T3		III	Tumour, involves lower third of vagina, or extends to pelvic wall, or causes hydronephrosis or non.functioning kidney
	T3a	IIIA	Tumour involves lower third of vagina
	T3b	IIIB	Tumour extends to pelvic wall, or causes hydronephrosis or non. functioning kidney
T4		IVA	Tumour invades mucosa of the bladder or rectum, or extends beyond true pelvis[e]

Figure (1) –TNM & FIGO Staging of Cervical Cancer (AJCC Cancer Staging Manual. 8th edition 2018)

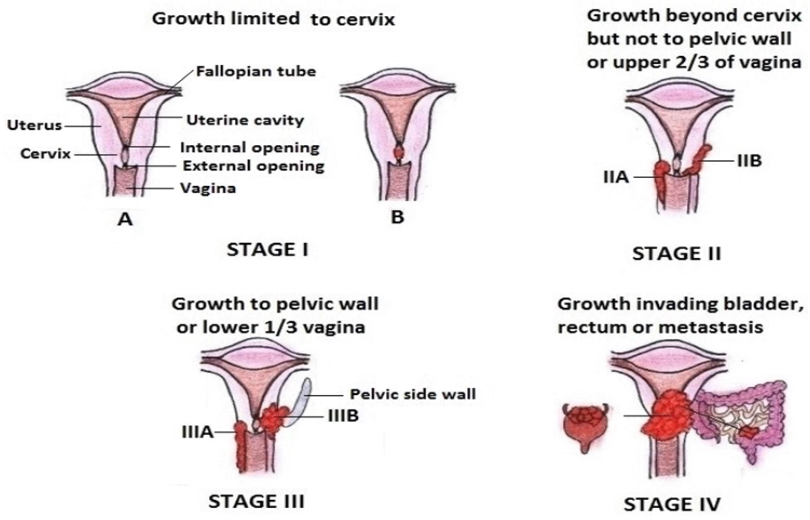

Figure (2) – Cervical Cancer Stages (AJCC Cancer Staging Manual. 8th edition 2018).

Table (1) – FIGO staging according to AJCC 8th edition[16]

FIGO Stage
I: Carcinoma is strictly limited to the cervix.
-IA: Invasive carcinoma diagnosed microscopically. Stromal invasion is restricted to measured maximum depth of 5 mm & in horizontal spread not more than 7 mm.
-IA1: Stromal invasion is 3 mm or less in depth and in horizontal spread 7 mm or less.
-IA2: Stromal invasion more than 3 mm and not more than 5 mm in depth and in horizontal spread less than or equal 7 mm.
-IB: Visible lesions clinically confined to the cervix, or microscopic lesion greater than stage IA.
-IB1: Lesions are less than or equal 4 cm in size clinically in greatest dimension.
-IB2: Lesions are more than 4cm in size clinically in greatest dimension.
II: Tumor extends beyond the cervix, but not extended to the lower third of vagina or onto the pelvic wall.
-IIA: Involvement of upper two-thirds of the vagina. Without invasion of parametrium.
-IIA1: Lesion is visible clinically but in greatest dimension is less than or equal 4 cm in size.
-IIA2: Lesion is visible clinically and size in greatest dimension is more than 4 cm.
-IIB: Parametrial invasion but not to the pelvic side wall.
III: Tumor involves the lower 1/3 of the vagina OR tumor has extended to the pelvic side wall.
-IIIA: Involvement of the lower vagina without extension to pelvic side wall.
-IIIB: Pelvic extension, or hydronephrosis/non-functioning kidney.
IVA: Carcinoma invades mucosa of the rectum or the urinary bladder or extends beyond true pelvis

Pelvic examination under anesthesia (EUA) should be carried out for cervical cancer patients who presented with a clinically visible lesion, after obtaining a careful clinical history & performing a general physical examination for them. Pelvic examination under anesthesia should include inspection of the external genitalia, vagina, uterine cervix, rectal examination & bimanual palpation of the pelvis. Pelvic examination under anesthesia is widely accepted component in the clinical staging & evaluation of patients in order to provide a pain free examination that allows a clearer assessment of parametrial or sidewall tumor extension.[17]

Speculum examination and thorough vaginal & rectal examination will give the exact clinical staging. Lesions may appear as exophytic or endophytic growth, as a polypoid mass, papillary tissue, or barrel shaped cervix, as a cervical ulceration or granular mass, or as necrotic tissue with purulent or bloody discharge.[18]

A significant number of doctors prefer CT for the evaluation of cancer patients, because of its wide availability.[19]

Currently, in cancer cervix cases, MRI is used primarily for the evaluation of cancer morphology & local extent; it accurately evaluates cancer features of a significant prognostic value, like size, endo-cervical growth, parametrial invasion and pelvic side wall or adjacent organ involvement (urinary bladder, rectum). Reported MRI accuracy values for determining cancer stage (operable versus advanced disease) range from 75 to 96 percent.[20]

Hybrid imaging (PET-MRI or PET-CT) is better than conventional cross-sectional methods for the identification of metastatic LNs, with excellent diagnostic accuracy, ranging from 85 to 99 percent.[21]

7. Pathological Types

a) Cervical Intraepithelial Neoplasia (CIN):

Intraepithelial changes begins with minimal atypia and progresses through stages of greater intraepithelial abnormalities in conformity with invasive squamous cell carcinoma. The phrases CIN, dysplasia, carcinoma in situ (CIS) and squamous intraepithelial lesion (SIL) could be used interchangeably.[22]

CIN is usually a disease of meta-plastic squamous epithelium within the transformation zone. The usual process by which cervical squamous epithelium matures is disturbed in Cervical Intraepithelial Neoplasia, as proved morphologically by modifications within nuclear features, cellularity, polarity, differentiation, and mitotic activity. CIN 3 is synonymous with severe dysplasia and carcinoma in situ.[22]

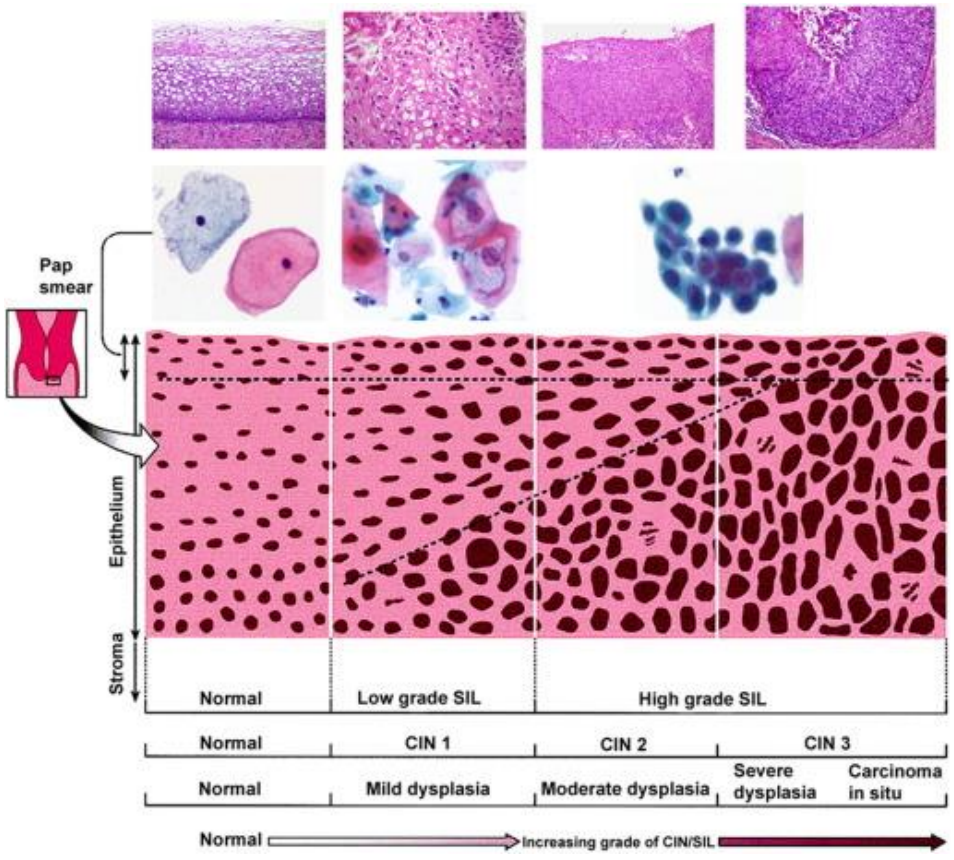

Figure (3) Sequence of histological changes from CIN 1 to CIN 3.[22]

When Cervical Intraepithelial Neoplasia is detected, colposcopy, along side a Schiller test, delineates the extent of the lesion suggests areas to be biopsied. Diagnostic endo-cervical curettage also can help in figuring out the extent of endo-cervical involvement. Females with CIN 1 are regularly observed conservatively (i.e. close follow-up with repeated Pap smears). High grade lesions are treated consistent with the extent of disease. Loop electrosurgical eradication process (LEEP), cervical conization (removal of a cone of tissue round the external os), laser ablation, electro-coagulation diathermy, cryosurgery, & hardly ever hysterectomy could also be done.[22]

b) Microinvasive squamous cell carcinoma:

The earliest invasive changes (early stromal invasion or ESI) show up as small irregular epithelial buds arising from the bottom of CIN 3 lesions. These tiny (b1 mm) tongues of neoplastic epithelial cells don't have an effect on the prognosis of CIN 3 lesions, so both are often treated in a similar fashion with conservative surgery. Within the 2009 FIGO classification, ESI was trimmed from stage IA1. Some oncologists moreover confine micro-invasive carcinoma to tumors without lympho-vascular invasion (LVI). Stage IA2 tumors are associated with lymph node metastases in around 8 percent of cases, Though those that invade ≤ 3 mm (stage IA1) have only a 1 - 2 percent risk of lymph node metastases. Conization or simple hysterectomy generally cures micro-invasive cancers < 3 mm deep.[22]

c) Invasive squamous cell carcinoma:

Early stages of cervical cancer are frequently poorly defined lesions or exophytic and nodular masses. If the tumor is in the endo-cervical canal, it’s often an endophytic mass, which will invade the cervical stroma and cause

diffuse cervical enlargement. Most tumors are non-keratinizing, have solid nests of huge malignant squamous cells and no more than individual cell keratinization. Most remaining cancers show nests of keratinized cells within concentric whorls, therefore known as keratin pearls. Cancer cervix spreads by direct extension or through lymphatic vessels & only rarely through blood vessels. Local extension into surrounding tissues (parametrium) leads to ureteral compression (Stage IIIB). The corresponding clinical problems are hydronephrosis, hydroureter, and renal failure due to ureteric obstruction which is that the commonest explanation for death (50 % of patients). Urinary bladder or rectal invasion (Stage IVA) may cause fistula formation. Metastases to regional LNs involve para-cervical, external iliac, and hypogastric nodes. However, tumor spread are fairly slow, considering the fact that since the typical age for patients with CIN 3 is 35 - 40 years, for stage IA carcinoma, 43 years, & for stage IV, 57 years.[23]

d) Verrucous carcinoma:

A variant of a very well differentiated squamous cell carcinoma that is characterized by having a tendency to recur locally but not to metastasize. Mitotic activity is extremely low. It may be difficult to differentiate verrucous carcinoma from a giant condyloma with cytologic atypia or from a well differentiated invasive squamous carcinoma. Microscopically, verrucous carcinoma is exophytic, with an undulating, hyperkeratotic surface, the deep margin is composed of huge, bulbous masses that invade along a wide front in a pushing fashion.[24]

e) Endocervical adenocarcinoma:

Adeno-carcinoma in situ generally arises within the squamo-columnar junction and extends into the endo-cervical canal. Associated high-grade

squamous cell CIN presents in 40% of cases of AIS. Invasive aden-ocarcinoma commonly takes place as a polypoid or papillary mass.[22]

f) Other rare pathological types:

- **Adeno-squamous carcinoma:** represents about 2 percent -5 percent of cervical cancer & consists of intermingled epithelial cell cores with squamous features & glandular structures. The squamous component is frequently non keratinizing.[25]
- **Basaloid carcinoma or adenoid basal carcinoma:** a very rare tumor which is characterized by nests or cords of small basaloid cells, prominent peripheral palisading of cells in the tumor nests, no significant stromal reaction or capillary space invasion, and an infiltrating growth pattern. Also characterized by its slow growth pattern with limited local invasiveness & low probability of LNs metastases.[22]
- **Adenoid cystic carcinoma:** a rare variant of cervical adenocarcinoma represents about less than 1percent. It is composed of nests and nodules of small carcinoma cells with a few characteristic cribriform patterns. It is locally aggressive with a high probability to metastasize.[26]
- **Clear cell carcinoma:** represents about 2 percent of cervical carcinomas. These tumors are submucosal, composed of clear cells & may grow in a tubular, glandular, papillary, or solid pattern. They appear at any age, with one third occurring in females younger than 30 years of age.[27]
- **Small cell carcinoma:** is also a rare type of cervical cancer which is characterized by nuclear molding, absence of nucleoli, cell necrosis, and high mitotic activity. One third to one half stain positively for neuroendocrine markers like chromogranin, synaptophysin, somatostatin

or serotonin. Lympho-vascular invasion is significantly common in small cell carcinomas HPV 18 has been detected in most of these tumors.[28]

- **Malignant lymphoma:** can be 1ry or 2ry in the cervix, and treated as other lymphomas.[29]

8. Prognostic and Predictive factors

a) Patient Related Factors:

- **Age:** Is not a prognostic factor for cervical cancer as suggested by some reports, However some authors reported decreased survival in females younger than 35 or 40 years, In contrast, 2 European studies noted improved outcome for younger patients.[30]
- **Socio-Economical, Racial and Regional Factors:** Patients with lower socioeconomic status may present at advanced stages & may often not have the capacity to bear the cost of the standard of care.[31]
- **Anemia and Tumor Hypoxia:** Anemia is common in cancer patients. Lower pre-treatment hemoglobin (Hb) level or anemia before treatment has been reported as an independent prognostic factor for poor prognosis in locally advanced cervical cancer (LACC).[32]
- **Medical Co-Morbidities:** Co-morbid as diabetes, hypertension & cardiopulmonary diseases may lead to higher risk of mortality often by themselves. Uncontrolled medical conditions compromise the patient's likelihood of tolerating the concurrent chemo-radiotherapy (CCRT) course.[33]
- **Human immunodeficiency virus (HIV) status:** Women who are +ve for HIV have more aggressive and advanced sickness and a worse prognosis.[34]

b) <u>Tumor Factors:</u>

- **HPV Subtype:** HPV 18 DNA has been determined to be an independent unfavorable molecular prognostic factor. Two research proved a worse outcome when HPV 18 was identified in cancer cervix patients undergoing radical hysterectomy and pelvic lymphadenectomy.[35]
- **Histology:** A few retrospective studies showed a worse outcome for patients with adenocarcinoma, with a noted tendency for distant metastasis, when compared with those with squamous pathology. Suggesting that any adenomatous differentiation may confer a bad prognosis.[36]
- **Grade of Differentiation:** Tumor grade is a prognostic factor for squamous cervical cancer, particularly early-stage disease. Higher tumor grade is associated with decreased survival. Routine evaluation of tumor grade with synoptic description is therefore highly recommended in daily practice[37]. Advanced stage along with poor histopathological differentiation influences the aggressiveness of the tumor responsible for distant relapse.[38]
- **Staging:** The Gynecologic Oncology Group (GOG) reported during a large surgico-pathological staging study on cases with clinical stage IB, that the factors which near prominently expected for metastases to lymph node and a reduction in disease-free survival when capillary-lymphatic space involved by cancer, large tumor size, & increasing depth of stromal infiltration, with the last being the most significant and reproducible.[39]

Table (2) – survival rates for cervical cancer[40]

Stage	5-year survival rate
Stage 0	93 percent
Stage IA	93 percent
Stage IB	80 percent
Stage IIA	63 percent
Stage IIB	58 percent
Stage IIIA	35 percent
Stage IIIB	32 percent
Stage IVA	16 percent
Stage IVB	15 percent

- **Nodal Status:** LN involvement is considered as the single most significant determinant of adverse prognosis, even more than FIGO stage.[41]

c) <u>Biochemical markers:</u>

- **Squamous cell carcinoma antigen (SCC Ag):** Pretreatment (SCC Ag) has shown value as a predictor of lymph node involvement and treatment outcome. Also Post treatment measurements are predictive of relapse free survival. If (SCC Ag) was more than 30ng/mL at diagnosis there was significant lymph node involvement. The most significant of their finding was that the progression free survival (PFS) was significantly better in patients having normal levels of (SCC Ag) after concurrent chemo-radiotherapy in comparison to those in whom (SCC Ag) levels failed to normalize.[42-43]
- **Epidermal Growth Factor (EGFR):** (EGFR) is over expressed in 50 to70 percent of cervical squamous cell carcinoma, with lower expression among adeno & adeno-squamous carcinomas (44). Over expression of (EGFR) membrane staining was associated with an increase in radio resistance. The cytoplasmic staining of phosphorylated (EGFR) "the activated form" & the membrane staining of EGFR are both independent factors predictive of poor response to concurrent chemo-radiotherapy.[45]

- **Carcino-embyrionc antigen(CEA):** Prior to the discovery of SCC Ag, the foremost repeatedly measured tumor marker in cancer cervix was (CEA). Pre-treatment (CEA) >10ng/mL is taken into consideration a risk factor for relapse after concurrent chemo-radiotherapy.[46]
- **CA-125:** Pre-treatment CA-125 is high in 20 - 75 % of cases with cervical adeno-carcinomas, & that is often related to increased risk of lymph node metastasis & an overall poor outcome. Elevated CA-125 post treatment could possibly indicate recurrence of cervical adeno-carcinoma.[47]

9. Overview of Treatment

A. Prophylactic:

1. Avoid the risk factors: (Primary prevention)
   - HPV vaccine (FDA approved 2006).
   - Avoid early sexual exposure: especially with multiple / uncircumcised partners.
   - Use of condom.
   - Limitation of cigerate smoking.
   - Special care for immunocompromised patients.
   - Hysterectomy better to be total & not subtotal.[48-49]
2. Proper treatment of the risk factors: (Secondary prevention)
   - Early detection of CIN by regular Pap smears for asymptomatic high risk patients.
   - Treatment of CIN: lesions by ablation or excision.
   - Strict follow up: by colposcopy & smear for all treated cases.[50-51]

B. Curative:

❖ **local/locoregional disease:** Common types of treatments include

- ➢ **Surgery**
- ➢ **Radiotherapy**
- ➢ **Chemotherapy (chemo)**
- ➢ **Targeted therapy**

Some cases may need more than one kind of treatment. For early stages of cervical cancer, either surgical operation or radiotherapy combined with chemotherapy might be used. For late stages, radiotherapy combined with chemotherapy is mainly the treatment of choice. Chemotherapy is mostly used to treat advanced cervical cancer.[52]

Specialists on cervical cancer treatment team may include; a gynecologist, a gynecologic oncologist, a radiation oncologist, & a medical oncologist. Other specialists might be part of the treatment team including physician assistants, nurse practitioners, nurses, psychologists, rehabilitation specialists, social workers, & other health professionals.(52)

The main therapy of early stage cancer cervix is either surgery or radiotherapy. Surgery is typically done for small lesions & for the early stages of cervical cancer, like stage IA, IB1, & selected IIA1.(53)

Treatment alternatives for cervical cancer

Stage of cancer cervix is the most important factor in choosing of treatment, but other elements can also affect on choosing of treatment, as the type of tumor (squamous cell carcinoma or adenocarcinoma), the exact position of the tumor in the cervix, age of the patient and overall health, and whether she wants to keep her fertility or not.(10)

- Stage 0 (Carcinoma in situ) "CIS":

  (AJCC) "American Joint Committee on Cancer" staging system had classified carcinoma in situ as the earliest type of cancer cervix & medical doctors usually consider it as a pre cancer. That is due to the cancer cells within CIS present only within the superficial layer of the cervix, and don't grow into deeper layers. All patients with CIS are often cured with the proper treatment. However, pre-cancerous changes can sometimes come back within the cervix or vagina, so it's vital to closely observe patient after therapy. This consists of follow up with regular Pap tests and with colposcopy in some cases.(10)

- **Treatment alternatives for squamous cell carcinoma in situ:**
  - **Cryosurgery:** It is a relatively simple procedure that takes around 15 minutes

and is performed as an outpatient procedure. It eliminates precancerous lesions on the cervix by freezing[55]. Cryotherapy is a highly effective treatment option for the small and superficial lesions, but for larger and deeper lesions the cure rate < 80 percent. Since the cervical area has very few nerve endings, therefore cryosurgery is generally associated with mild cramping and/or pain. So, it can be performed without anesthesia. But the absence of histo-pathological specimen for further evaluation of the extent of the disease and margins status is considered an important disadvantage of cryotherapy.[56]

- **Laser surgery:** A focused laser beam is directed through the vagina to burn off abnormal cells or to get rid of a little piece of tissue and send to the histo-pathology for tests. This can be performed in a doctor's clinic and is done with local anesthesia.[10]
- **Loop electrosurgical excision procedure (LEEP):** It is the use of a thin heated wire for the removal of abnormal areas from the cervix. It needs an electrosurgical unit which produces a steady low voltage and transfers it to the wire loop device that is used to remove the abnormal tissue. The removed tissues should be sent for the examination to assess the extent of the lesion. So LEEP serves a double purpose, it treats the lesion and at the same time produces a specimen for histo-pathological examination. The procedure can be done under local anesthesia in an outpatient clinic. It is successful in eliminating pre-cancer in > 90 percent of cases. Treatment failure (i.e. persistent lesions at 6 or 12 months of follow up) is seen in < 10 percent of patients. [57]
- **Cold knife conization:** It is the removal of a cone shaped volume of cervical tissue including portions of the ecto-cervix & endo-cervix. Conization is recommended in cases of dysplasia when outpatient treatment isn't accessible

or feasible & to exclude invasive carcinoma. It is an extensive operation involving removal of a large area of the cervix with a scalpel, & is often done under general or regional (spinal/epidural) anesthesia. It takes around 30 minutes. Cold knife conization should be reserved for cases that can't be resolved with cryotherapy or LEEP excision due to possible side effects. The extent of the conization will depend on the size of the lesion and the probability of finding invasive cancer. The patient's desire to have a child must be considered, as conization may lead to cervical stenosis or incompetence in few females. The cone specimen is sent to lab for pathological diagnosis and to ensure complete removal of the abnormal tissue.(56)

- **Simple (total) hysterectomy:** In simple hysterectomy the cervix and the body of the uterus are removed but the parametrium & uterosacral ligament are preserved. Also the vagina and the pelvic lymph nodes aren't removed. Ovaries & fallopian tubes are kept in place except if there is another cause to remove them.(56)

- **Treatment alternatives for adenocarcinoma in situ include:**
  - **Hysterectomy:** The same as in SCC.
  - **Cone biopsy:** It is a possible option for females who wish to have children. The edges of the cone specimen must not have cancer cells & the patient must be closely monitored after treatment. Once the woman has no desire to reproduce, a hysterectomy is recommended.(56)

a) Surgery for invasive cervical cancer

Many females with cancer cervix will have some form of surgery. First surgery is often used to diagnosis cervical cancer. Second it helps to know the extent of the cancer. Also it helps in therapy, especially for earlier stages. Several types of surgery may be used in treatment of cervical cancer, although a number of these destroy cervical tissue (with a laser or with cold) instead of removing it.[52]

Definitive surgical management is feasible only in early stages of the disease, such as stages IA, IB1, and IIA1, when the vaginal involvement does not extend beyond 2 cm.[58]

The extent of surgery will be managed according to the tumor stage, the age of the patient & co-morbidities. The patient's desires regarding fertility and management options need to be considered for example:

1. **In Stage IA1:**

   Treatment for this stage relies upon whether or not patient wants to maintain fertility & whether the cancer has spread to blood or lymph vessels or not, which is termed lympho-vascular invasion.[52]

   - **Fertility sparing:** For cases who need preservation of fertility, cone biopsy ± pelvic LNs dissection is required.[59] For cases with clear margins after cone biopsy, if fertility preservation is desired observation could also be a choice. For cases with positive margins after cone biopsy, options are either a radical hysterectomy or repeat the cone biopsy.[60] For cases with stage IA1 disease with lympho-vascular invasion, radical hysterectomy and pelvic LNs dissection is suggested ± para-aortic LNs sampling.[61]
   - **Non fertility sparing:** A simple hysterectomy could also be a choice if cervical cancer shows no lympho-vascular invasion. If tumor has grown within blood or lymph vessels, removal of the pelvic lymph nodes is need beside radical hysterectomy.[62]

2. **In stage IA2 disease:**

   Local excision can be offered to preserve fertility or extra-fascial hysterectomy. But there is a risk of pelvic lymph node invasion of about 5 percent & bilateral pelvic lymph node dissection is usually recommended.(62)

   - **Radical trachelectomy (cervicectomy):** It is the treatment of choice in females with early stage cancer cervix desiring to preserve fertility. Radical trachelectomy can be done with a vaginal, abdominal or laparoscopic/robotic approach.(63) Intra-operative and postoperative complication rates are identical to radical hysterectomy. About 15 percent of patients develop cervical stenosis and this can lead to dysmenorrhoea or infection.(64)
   - **Laparoscopic hysterectomy and lymph node dissection:** It is offered to females not desiring to retain their fertility. The presence of +ve lymph nodes indicates the need for adjuvant chemo-radiotherapy.(62)

3. **Stages IB and IIA cervical cancer:**

   It can be cured by radical surgery including pelvic lymph node dissection or radiotherapy. The two options are equally effective but differ in terms of morbidity and type of complications.(65)

   - **Radical (Wertheim's) hysterectomy:** This aims to provide definitive treatment for invasive & early metastatic cervical cancer. It involves excision of the primary tumor with a one cm margin of healthy tissue and resection of the main pelvic lymph node areas. It may involve removal of the upper third of the vagina & utero-vesical & utero-sacral ligaments. Urinary bladder function returns slowly and chronic retention may occur. Sometimes painful lymphocytes develop and their drainage may be required.(65)
   - **Anterior, posterior or total pelvic exenteration:** Involve removal of pelvic adnexae with removal of the urinary bladder and/or recto-sigmoid, with possible creation of one or two stoma. The patient should be relatively fit and

can hold out very destructive surgery.[65]

- **Neoadjuvant chemotherapy to surgery:** The purpose for the use of Neoadjuvant chemotherapy (NACT): (i) reduction of the primary tumor size, allowing operability; (ii) eradication of micro-metastatic disease; and (iii) potential increase in tumor vascularization and reduction of the number of hypoxic cells.[66-67] In a meta-analysis, NACT followed by radical surgery showed a significant 35 percent reduce in the risk of death compared with radiotherapy alone, with an absolute improvement of 14% in survival at 5 years, increasing from 50% to 64%.[68]
- **Adjuvant treatment:** Women with risk factors on the pathology specimen should receive adjuvant therapy following hysterectomy. Two classes of risk are defined: Major risk factors and Minor risk factors.
  - **Major RF:**
    - Status of resection margins.
    - Status of parametria and vaginal cuff.
    - Number and status of lymph nodes.
  - **Minor RF "Sedli's criteria":**
    - Lympho-vascular space invasion.
    - Size of the tumor (> 4 cm).
    - Stromal invasion/depth of the wall involved (> 1/3).

✓ If women has one of major risk factors on the pathology specimen should receive adjuvant Concurrent Chemo & Radiotherapy following hysterectomy.

✓ If she has No major risk factors but has 2 of 3 minor she should receive only adjuvant Radiotherapy alone (without chemotherapy).

✓ The most commonly used regimen is weekly cisplatin 40 mg/m2.[69-70]

b) Radiotherapy (RT) for invasive cancer cervix

Radiotherapy uses radioactive particles or high energy x rays to damage cancer cells. Radiotherapy is also used for cancer cervix, for few stages of cancer cervix the preferred therapy is radiotherapy alone or surgery then followed by radiotherapy. For other stages, radiotherapy & chemotherapy given together & that's called concurrent chemo-radiation which is the preferred therapy. The chemotherapy helps the radiation to work better .Also radiotherapy may be used in treatment of metastatic cancers that have spread to other organs or tissues.(52)

There are two types of radiotherapy usually used to treat cancer cervix which are **external beam radiotherapy** & **brachytherapy**.(52)

Radiotherapy is generally used for cervical cancer either as definitive therapy for cases with locally advanced cancer or for cases who are not fit for surgery, as adjuvant therapy following radical hysterectomy for cases who have one or more pathological risk factors for example: +ve lymph nodes, parametrial invasion, +ve surgical margins, large tumor size, deep stromal infiltration, and lympho-vascular invasion.(52)

A study review discovered insufficient evidence that hysterectomy with radiotherapy, with or without chemotherapy improves the survival of females with locally advanced cancer cervix who are treated with radiotherapy or chemo-radiotherapy alone.(71)

The combination of two consecutive stages of irradiation with different dose delivery techniques, i.e., external beam radiotherapy (EBRT) and intracavitary high-dose-rate brachy-therapy (HDR-BT) is called combined RT.(72)

At the first stage of combined RT, the clinical tumor volume and regional lymph nodes are irradiated in total doses up to 44-50 Gy with fraction dose equal to 2 Gy depending on the widespread nature of the process. At the second stage of

the combined RT, the clinical tumor volume is irradiated in the mode of dose boost when the dose per fraction is increased to 6-7.5 Gy delivered in 4 or 5 fractions resulting in the total dose equal to 28-30 Gy. The goal of the total combined RT course is to achieve a total EQD2 dose equal to 90 Gy delivered to the clinical tumor volume in less than 50 days of treatment.[73-74]

A. External beam radiotherapy:

External beam radiotherapy (EBRT) may be routinely administered to cancer cervix female patients with stages IB2 - IVA aiming a curative intent. Females with stages IA - IB1 may also receive external beam treatment if they are inoperable or prefer to avoid surgery. Patients with stage IVB disease may receive palliative radiotherapy to the pelvis for selected indications for example, to relieve pain, stop vaginal bleeding, or relieve urethral obstruction from extrinsic compression. External beam radiotherapy covers the 1ry cervical tumor, treats any adjacent parametrial or utero-sacral, uterine, or vaginal extension, & most essential microscopic disease present in pelvic LNs.[52]

The usage of CT based therapy planning & conformal blockage is taken into account the standard of care for external beam radiotherapy. MRI is that the superior imaging modality for identifying parametrial & soft tissue infiltration in cases with advanced cancers, PET imaging is beneficial to assist outline the nodal volume of coverage, in cases who aren't surgically staged.[52]

Coverage regarding microscopic nodal disease requires a dose of about 45 Gy of an EBRT (in fractionation of 1.8 - 2.0 Gy daily). Most of the patients who receive EBRT for cancer cervix, concurrent chemotherapy (either Cisplatin only, or Cisplatin with 5-fluorouracil) is given during EBRT.[75]

Intensity modulated radiation therapy (IMRT) can help in reducing the dose to the bowel & other vital organs within the post hysterectomy setting & in

treating the para-aortic nodes. Also these methods are beneficial when excessive doses are desired to treat gross disease within regional LNs.[75]

- **Parametrial boost:** This is optional; it is used in stage FIGO IIb patients & above (ie any patient with parametrial extension). The Dose required for parametrial boost is 5.4Gy in 3 daily fractions over 3 days. Parametrial boost is a debatable topic & must be assessed on a patient to patient basis. A retrospective study conducted to validate the practice of not treating clinically infiltrated parametrium by parametrial boost & to validate the adequacy of nodal boost in node positive patients regardless the status of parametrium. Results showed that cervical cancer with clinically infiltrated parametrium can be treated without parametrial boost.[76]
- **Complications of EBRT for cervical cancer:**
  - Early:
    - Fatigue
    - Stomach upset
    - Diarrhea
    - Skin changes: because the radiation crosses via the skin to the tumor, it may affect the skin cells causing changes ranging from mild redness to sever peeling. Also the skin might release fluid which will cause infection thus the area exposed to radiotherapy must be cleaned & protected carefully.
  - Late:
    - The rate of major late side effects of radiotherapy for stages I & IIA cervical cancer ranges from 3-5 percent & for stages IIB & III between 10-15 percent. Injury to the gastrointestinal tract usually appears within the 1st 2 years after therapy, while that of the urinary tract are seen more frequently 3-5 years after therapy.[77]
    - Anal incontinence is observed occasionally from the late side effects of radiation therapy. Study investigated radiotherapy effects on ano-rectal function using manometry in twenty four patients with cervical cancer

who had late radiation proctitis. These data were compared with those from 24 age-matched non-irradiated female volunteers. Regardless of the severity of proctitis symptoms, 75 percent of irradiated patients exhibited abnormal manometric parameters for motor or sensory functions. Radiation damage to the external sphincter muscle & to nerves was considered to be an essential cause of motor dysfunction.[78]

- Ureteral stricture was found in 2.5 % of 1,784 cases with stage IB cervical cancer treated with radiation. Flank pain and urinary tract infection were the commonest presenting symptoms. Ureteral stricture in 5 cases was complicated by a vesico-vaginal fistula.[78]
- Urinary tract infections development. Study collected two hundred and sixth-teen urine samples from thirty six patients receiving pelvic irradiation, twelve of them had urinary tract infection. The most common organisms isolated were Escherichia coli, & Enterococcus species. Proper urine bacterial studies & cultures are indicated in patients suspected of having superimposed urinary tract infection during the course of radiotherapy.[80]
- Radiation to the pelvis can irritate the urinary bladder which is called radiation cystitis causing discomfort & a usual urge to urinate. Study identified 116 of 1,784 patients (6.5 %) with stage IB cervical carcinoma treated with radiotherapy in whom hemorrhagic cystitis developed, 23 % was grade 2 (repeated minor bleeding) & 18 % was grade 3 (hospitalization required for medical management). The onset of hematuria median interval was 35.5 months. The risk of severe hematuria requiring surgical intervention was 1.4 % at ten years & 2.3 % at twenty years.[81]
- Radiation can make the vulva & vagina more sensitive that may lead to vaginal pain & occasionally causes a discharge.[75]
- Pelvic radiation can affect the ovaries that may lead to menstrual changes & even early menopause. Radiation causes ovarian failure with a cessation of menses over a six month - one year period after treatment. Radiation also causes uterine fibrosis in a dose dependent fashion.[82]
- Low blood counts: such as anemia, leucopenia which increases the risks of serious infection.[75]

B. Brachytherapy:

Brachytherapy is short wave radiation therapy delivered by the insertion of applicators into the uterus via the vagina. The American Brachytherapy Society indicates that brachytherapy should be considered an essential component of definitive radiotherapy treatment.(83)

Brachytherapy or internal radiotherapy is putting a radiation source within or near the tumor. This kind of radiotherapy travels a brief distance. The sort of brachytherapy frequently used in therapy of cervical cancer is intracavitary brachytherapy. The radiation source is placed in a device into the vagina & may be into the cervix. And often additionally employed to external beam radiotherapy as a part of the most essential therapy for cervical cancer.(84)

Brachytherapy is an essential part of definitive radiotherapy shown to improve Overall survival.(84)

- **Types of brachytherapy:** High dose rate (HDR), Medium dose rate (MDR), pulsed dose rate (PDR), and Low dose rate (LDR) brachytherapy are considered equivalent in terms of outcome and complication risk when carefully applied and individualized based on the need of the patient and pertinent clinical history.(85)
  - **Low-dose rate brachytherapy (LDR-BT)** is fulfilled over some days. During these days, the treated person stays in a private room in the health center with devices holding the radioactive material within place. While the radiotherapy is being given, the health center staff will care for the patient, but also take precautions to minimize their own radiation exposure. (LDR) brachytherapy delivers radiation at a dose of 0.4-2 Gray (Gy)/hour.(86)
  - **High-dose rate brachytherapy (HDR-BT)** is performed as an outpatient over radioactive material is inserted for some minutes & then removed. The advantage of HDR therapy is that you simply don't need to stay for long periods of your time in the hospital. HDR brachytherapy delivers a dose more than12 Gy/hour.(86)

- **Medium-dose rate brachytherapy (MDR-BT)** is to deliver a dose of 2-12 Gy/h, & it is not in common use. In those few cases in which it has been used, the treatment results have been rather poor compared with LDR or HDR treatments.[86]
- **Pulsed Dose Rate brachytherapy (PDR-BT)** is a recent brachytherapy modality that combines physical advantages of high-dose-rate (HDR) technology (isodose optimization, planning flexibility and radiation safety) with radiobiological advantages of low-dose-rate (LDR) brachytherapy (repair advantages).[86]

Outcomes after LDR and HDR brachytherapy have been compared in different number of retrospective, institutional studies as well as in prospective randomized trials that noted same survival outcomes for both.[86]

A Cochrane review has recommended the use of high dose rate intracavity brachytherapy for all clinical stages of cervical cancer.[86]

- **Brachytherapy applicators:** they are medical devices that guide the radioactive source to be near to the tumor for a therapy time.

Brachytherapy is an essential component of definitive therapy for all cases with 1ry cervical cancer who aren't candidates for surgical treatment. This is often performed using an intra-cavitary approach, with an intrauterine tandem & vaginal colpostats. According to the patient anatomy & the tumor, the vaginal component of brachytherapy could be delivered using ovoids, ring, or cylinder (combined with the intrauterine tandem) in cases with an intact cervix. MRI imaging immediately preceding brachytherapy may be helpful in delineating residual tumor geometry. When combined with EBRT, brachytherapy is usually initiated for the therapy of the residual tumor. In early disease like, stage IA2, brachytherapy alone without EBRT may be an option.[87]

Since HDR contact therapy exhibits steep dose fall-off around the source, the role of the brachytherapy applicator is crucial: inappropriate placement of the source results in ‘‘hot” and ‘‘cold” spot in the dose distribution.[88]

➢ Two applicator types: standard and 3D printed.

- Standard applicators have a poor ability to comply to the patient anatomy variability & have big air gaps between the applicator and the skin standard.[89]

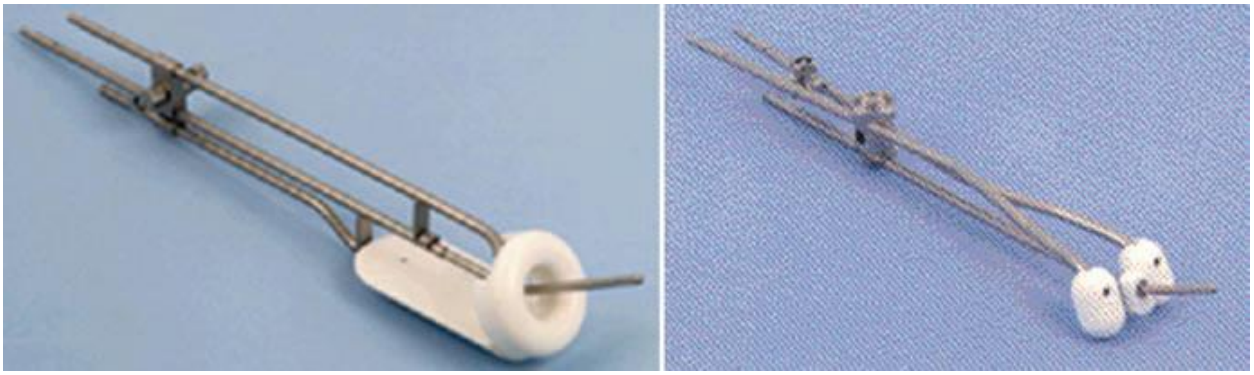

Figure (4) – Ring–tandem & ovoid–tandem “standard” applicators.[90]

- 3D printed applicators by using 3D printers is a new technique that utilizes patient CT information to create an applicator that conforms to the curvature of the patients anatomy for treatment of various types of cancers. Applicators printed using acrylonitrile butadiene styrene (ABS) plastic. That would offer comparable dose distributions, reproducibility, and conformity with the patient leading to smaller air gaps between applicator and treatment site, and decrease the applicator errors. Also offer better patient conformity, reduced air gap, and convenience to both patient and therapist.[88]

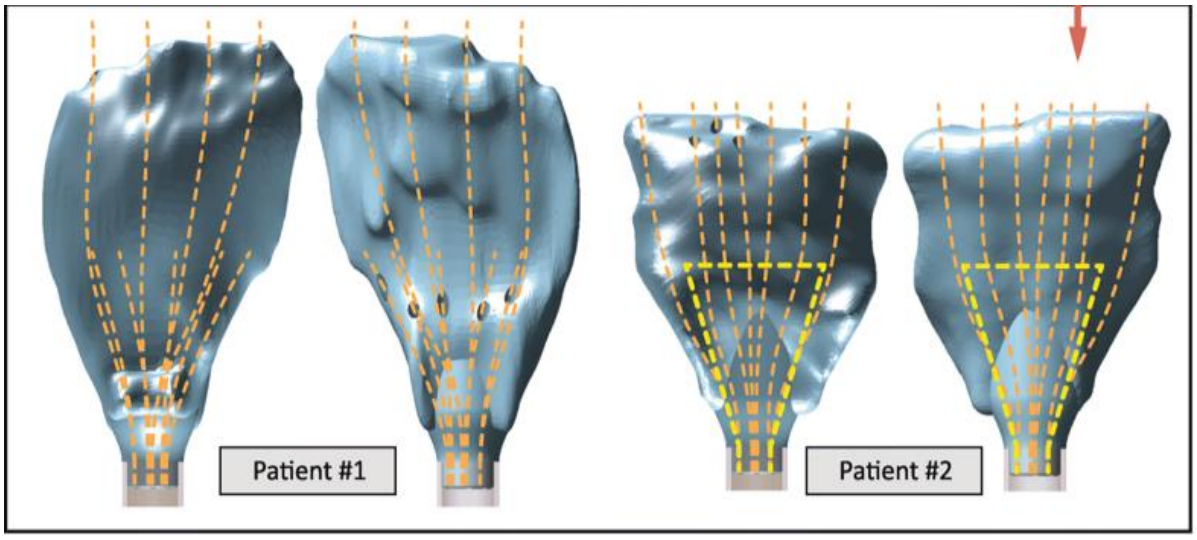

Figure (5) – 3D printed vaginal applicator with catheter tunnels.[88]

- **<u>Possible short-term side effects of brachytherapy:</u>**
  - The radiation with brachytherapy only travels a short distance so the main outcomes of the radiation are on the cervix & the walls of the vagina, including:
    - Vaginal irritation (commonest). It becomes red, sore & there may be a discharge.
    - Vulvar irritation
    - Pain and discomfort at the site of the applicator.
    - General feeling of fatigue
    - Short term urinary symptoms including urinary retention, pain on urination, incontinence and inability to urinate.
  - Brachytherapy may also cause many of the same outcomes as EBRT, for example diarrhea, nausea & low blood counts.
  - The side effects usually resolve within a few days following the completion of treatment. However, severe bleeding, pain and infection are side effects that require immediate medical attention.
  - Usually brachytherapy is given after EBRT before the outcomes can go away so it is difficult to know which type of radiotherapy is the cause of the complications.[91-92]

c) Chemotherapy for cervical cancer

Many patients with cervical cancer receive chemotherapy, either adjuvant, concurrent with radiation or palliative.[93]

For few stages of cancer cervix, the preferred therapy is radiotherapy & chemotherapy given together which is called concurrent chemo-radiation. The chemotherapy helps the radiation work better.[52]

- **Choices for concurrent chemo-radiation include:**
  - Cisplatin given weekly during radiation given intravenous (IV) about 4 hours before the radiotherapy.
  - Cisplatin + 5-fluorouracil (5-FU) given every 4 weeks during radiotherapy.
  - Carboplatin has been added to the guidelines as a preferred radio-sensitizing agent for patients who are Cisplatin intolerant.[52]
  - Chemotherapy can be used for cancers that have spread to other organs & tissues. Also It can be helpful when cancer recurs after treatment with chemo-radiation.[52]

- **The chemotherapy drugs usually used to treat advanced cancer cervix:**
  - Cisplatin.
  - Carboplatin.
  - Paclitaxel "Taxol".
  - Topotecan.
  - Gemcitabine "Gemzar".

Combinations of these chemotherapy drugs are usually used. Others can be used also, for example, Ifosfamide "Ifex", Docetaxel "Taxotere", 5- fluorouracil "5-FU", Mitomycin & Irinotecan "Camptosar". Also Bevacizumab "Avastin" the targeted drug could be added to chemotherapy.[52]

Chemotherapy is usually recommended for patients with recurrent disease or extra-pelvic metastases who aren't candidates for radiotherapy or surgery. Patients whose disease responds to chemotherapy may have relief from their symptoms. If Cisplatin was previously administrated as a radio-sensitizer, combination platinum

based regimens are favored over single agents in the metastatic cases which is based on few randomized phase III trials. But responses to chemotherapy are usually of short duration and survival is rarely increased.[94-95]

Cisplatin has been considered the most efficient agent for metastatic cancer cervix. Most patients who develop metastatic disease receive concurrent Cisplatin/ plus radiotherapy as primary therapy & may no longer be sensitive to single platinum based chemotherapy. Cisplatin based combination chemotherapy protocols like Cisplatin/Paclitaxel /Bevacizumab, Cisplatin/Paclitaxel & Cisplatin/Topotecan, have been widely investigated in clinical studies.[94-95-96]

Study compared (Cisplatin/Paclitaxel) versus Cisplatin alone for metastatic, recurrent, or persistent cervical cancer. Females receiving the two drug combination had a higher response rate (36 percent versus 19 percent) and improved Progression free survival (4.8 months versus 2.8 months) compared to single agent Cisplatin, but no improvement was viewed in median survival. Also patients who responded to Cisplatin/Paclitaxel had a significant improvement in quality of life.[95]

In Another study patients investigated for Cisplatin alone versus (Cisplatin/Topotecan) for recurrent or persistent cancer cervix. The single agent Cisplatin was shown to be inferior to Topotecan combination regimen with respect to overall response rate, Progression free survival, & median survival.[94]

(FDA) “the Food and Drug Administration” has approved (Cisplatin/Topotecan) for advanced cancer cervix. But the (Cisplatin/Paclitaxel) or (Carboplatin/Paclitaxel) protocols are less toxic & easier to be used than protocol (Cisplatin/Topotecan).[97]

Generally Cisplatin is considered as the most active agent and is usually recommended as a 1st line single agent chemotherapy choice for recurrent or

metastatic cancer cervix, reported response rates are about 20-30 percent with an occasional complete response (CR).[98-99]

Overall survival (OS) with Cisplatin is about 6 - 9 months. Both Carboplatin & Paclitaxel have been reported to be tolerable and effective & are also possible 1st line single agent chemotherapy. So palliation with single agents Cisplatin, Carboplatin, or Paclitaxel could be a reasonable strategy in cases with recurrent disease not candidate for surgery or radiotherapy.[100]

- **Targeted therapy for cervical cancer:** These are newer drugs that specifically target changes in cancer cells & nearby cells that help them grow. These work differently from standard chemotherapy drugs & usually have different complications. For an example, tumors must form new blood vessels to supply them by nourishment to grow. This process is named angiogenesis. Some drugs arrest this vessels growth & these drugs are known as angiogenesis inhibitors.

- **Bevacizumab (Avastin®)** is an angiogenesis inhibitor drug which could be used in treatment of advanced cancer cervix. It's a monoclonal antibody which targets vascular endothelial growth factor (VEGF), a protein that helps in formation of new blood vessels. This drug is usually used with chemotherapy for a period. And if the cancer responds, the chemotherapy may be stopped & Avastin given by itself till the cancer starts growing again.[96]
- **Pazopanib** is a potent selective multi targeted receptor (Tyrosine kinase inhibitors (TKI)s of VEGFR-1,VEGFR-2,VEGFR-3), that blocks tumor growth and inhibits angiogenesis.[101]
- **Gefitinib** is TKIs against endothelial growth factor receptor (EGFR), which have been evaluated as single agents in patients with cancer cervix.[102]
- **Temsirolimus** is a mTOR (is a key protein kinase controlling signal transduction from various growth factors and upstream proteins to the level of mRNA and ribosome with regulatory effect on cell cycle progression, cellular proliferation & growth) inhibitor used in patients with cancer cervix.[103]

❖ **Advanced/metastatic disease:**

- **<u>Stages IIb-Iva:</u>** (parametrial extension up to lesions involving nearby organs such as the bladder and the rectum)
  - External beam radiotherapy & concurrent chemotherapy (cisplatin) with brachytherapy is the core treatment in patients with advanced cancer.[104-105]
  - The combination of 5-fluorouracil & cisplatin has been used as concurrent chemotherapy also. They are both radiosensitisers & are associated with a longer period of disease remission and reduced disease progression.[106]
- **<u>Stage IVb:</u>** (distant metastasis)
  - There is no standard treatment but it is mainly palliative with a multidisciplinary approach, including gynaecological surgeons, oncologists, a palliative care team, nurse specialists & occupational therapists. Optimal pain control should be readily achievable. Palliative doses of radiotherapy may be given to achieve reasonable bleeding control if this becomes a major issue.[107]

❖ **Recurrent cancer cervix:**

- Management is multidisciplinary and depends on the type of recurrence, mode of primary therapy & the woman's fitness. If there's local pelvic recurrence following primary therapy together with radiotherapy, the lady could also be appropriate for pelvic exenterative surgery. Exenterative surgery in carefully selected cases could provide a 5-year survival of 40-60 percent.[108]
- The standard therapy is radiotherapy with or without platinum-based chemotherapy, if there's recurrence after surgery. The role of chemotherapy is mainly for palliation to relieve symptoms as well as to prolong survival.[109]
- Radical hysterectomy & pelvic exenterative surgery involving partial resection of the bladder, bowel and/or ureter may be performed in carefully selected women with persistent disease following primary radiotherapy. The morbidity from such extensive surgery is high & only few women are suitable for this procedure; however, some may be cured & thus have a good quality of life.[107]

10. Techniques delivery of prescription dose (3DCRT, IMRT, VMAT)

(**3DCRT**) “Three-dimensional conformal radiotherapy” is a method where the beams of radiation utilized in therapy are shaped to suit the cancer. Conformal radiotherapy uses the targeting information of CT image to focus exactly on the cancer while avoiding the healthy tissue. This made it feasible to use high levels of radiation in therapy, which are more effective in killing and shrinking cancers.[110]

While 3DCRT planning & delivery approves for correct dose conformity to irregular shapes, there are still obstacles within the corrections which might be made. As its name implies, (**IMRT**) “intensity-modulated radiotherapy” allows the modulation of the intensity or fluency of every radiation beam, so every field might have certain or many areas regarding high-intensity radiation & some varieties of lower-intensity areas within a similar field, hence allowing higher control regarding the dose distribution within the target.[111]

IMRT utilizes specific beam modifiers to differ or modulate the radiation intensity over the field of delivery. The aim is to control the beam hence that when the whole radiation delivery is taken into account, the dose conforms intently according to the cancer or target volume within the patient. IMRT can additionally utilizes more radiation beams of various sizes & various intensities to irradiate a cancer with precision & accuracy. The intensity of radiation of every portion of the beam is controlled, & the beam shape can alternate or multiple beams used during every treatment. The aim of IMRT is to shape the radiation dose to avoid or

minimize exposure of normal tissue & reduce the complications of therapy while delivering a therapeutic dose to the tumor.[112]

(**VMAT**) "Volumetric arc therapy" is a sort of IMRT in which the therapy is delivered in certain or more dynamically modulated arcs. Because the gantry rotates, the MLCs move, giving a special aperture form for every angle of the gantry. The speed of rotation of the gantry & the LINAC dose rate could be modulated during therapy to give the desired delivered dose for every gantry angle. The standard of the planned dose distributions which may be achieved is such as those that can be done with other varieties of IMRT. The plan quality relies upon attainable modulation, which, in turn, relies upon the gantry speed, number of arcs, or both. The main advantage concerning VMAT is the whole therapy is often completed shortly. This advantage is important, so we anticipate that VMAT will be the IMRT delivery technique of choice for many treatments.[113-114]

11. VMAT boost for 2nd stage of RTH replacing brachytherapy

The second stage of combined RT is usually implemented using intracavitary HDR-BT based on gamma-emitting radionuclides 60-Cobalt or 192-Iridium.[73]

The advantage of Brachytherapy over external beam is the possibility of delivering a high dose to a clinical tumor volume with a relatively low dose load on organs at risk (bladder and rectum). However, Brachytherapy has several significant drawbacks compared with external beam radiotherapy (EBRT). The main one is the substantial heterogeneity of the coverage of the clinical target volume, where doses in the range from 90% to 300% of the prescribed dose are delivered.[74]

Brachytherapy is also a less comfortable procedure for patients because they experience painful sensations when inserting applicators into the uterine cavity, which sometimes requires anesthesia.[115]

On the other hand, with Brachytherapy, no additional margin from the clinical tumor volume (CTV) is required, which should consider the inaccuracy of dose delivery from fraction to fraction, i.e., creating a planned target volume (PTV), which is mandatory for EBRT. Because irradiation occurs from inside and not from the outside, in the case of movement of the organ with the implant inserted, the implant will move along with the organ.[74-116]

Volumetric arc therapy (VMAT) shows great potential for producing highly conformal doses to treatment volumes while sparing organs at risk (OARs). VMAT was successful in duplicating the high-dose volumes (200%-75%) of the brachytherapy treatment plans, as well as delivering a homogenous dose distribution of 6 Gy to the PTV. VMAT could potentially be an alternative option for duplicating traditional brachytherapy dose distributions for patients in need of brachytherapy who are unable to undergo the treatment modality.[117]

The first investigations devoted to the study of the possibility of replacing Brachytherapy with external beam radiotherapy (EBRT) during the second stage of combined radiotherapy started in 2012. The goal of such investigations was to change Brachytherapy with external beam radiotherapy (EBRT) in hypofractionation mode for patients for whom Brachytherapy was not possible for various reasons.[118]

Also Brachytherapy (BT) is a major component in radiotherapy of locally advanced cancer cervix, but it is impractical for some patients due to medical, ethical or religious causes. For these patients, only external beam radiotherapy (EBRT) is used, so this study aiming to carry out a dosimetric and radiobiological planning of the replacement of traditional combined radiation therapy [3D

conformal radiotherapy (3D-CRT) + high-dose-rate brachy-therapy (HDR-BT)] by combinations of [(3D-CRT) + (VMAT)] or [(VMAT) + (VMAT)] while preserving the value of the total dose delivered and the number of fractions to detect the best technique among russian patients at Tomsk Regional Oncology Center, Tomsk Polytechnic University. This will be aid to improve the radiation planning and delivery to cervical cancer patients in the Russian & Egyptian population.

12. Patient positioning and immobilization Devices

Variation in the patient positioning is major problem during radiotherapy for pelvic malignancies. Higher patient setup errors will compel Radiation oncologist to give a larger planning target volume (PTV) margins, i.e. irradiate more normal tissues. Smaller PTV margins may lead to potential geographic miss of the target volume and, hence, may lead to recurrence.[119]

All the patients were positioned in a supine position with hands above the head or akimbo on the chest based on the patient comfort. Immobilization objectives to supply reproducible patient positioning with little patient movement, also patient comfort should be considered; there should keep a balance between the 2 aims. Various immobilization devices to be used on the linac couch are available; these encompass:

- **Vacuum bag cushion(VBC):**
  - Whole body VBCs are nylon mattress filled with tiny polyurethane beads. Patient is made to lie down in a supine position. A comfortable cradle is formed around to conform to the body contours of the patient by using a vacuum pump for 10 min. After the VBC achieved the desirable firm consistency, the self-sealing quick release valve was used to seal the mattress. The laser marks are placed on the VBC, corresponding to indexer

and on the patient's body for daily setup reproducibility. These minimize pelvic tilt, which may occur after the 1st few fractions when the person tend to be more relaxed during therapy.[120-121]

Figure (6) – vacuum bag cushion[121]

- **<u>Knee & ankle supports:</u>**
  - Usually utilize in combination with other fixation devices to confirm reproducible leg position, which, by the way, stabilizes setup in the trunk region.[120]

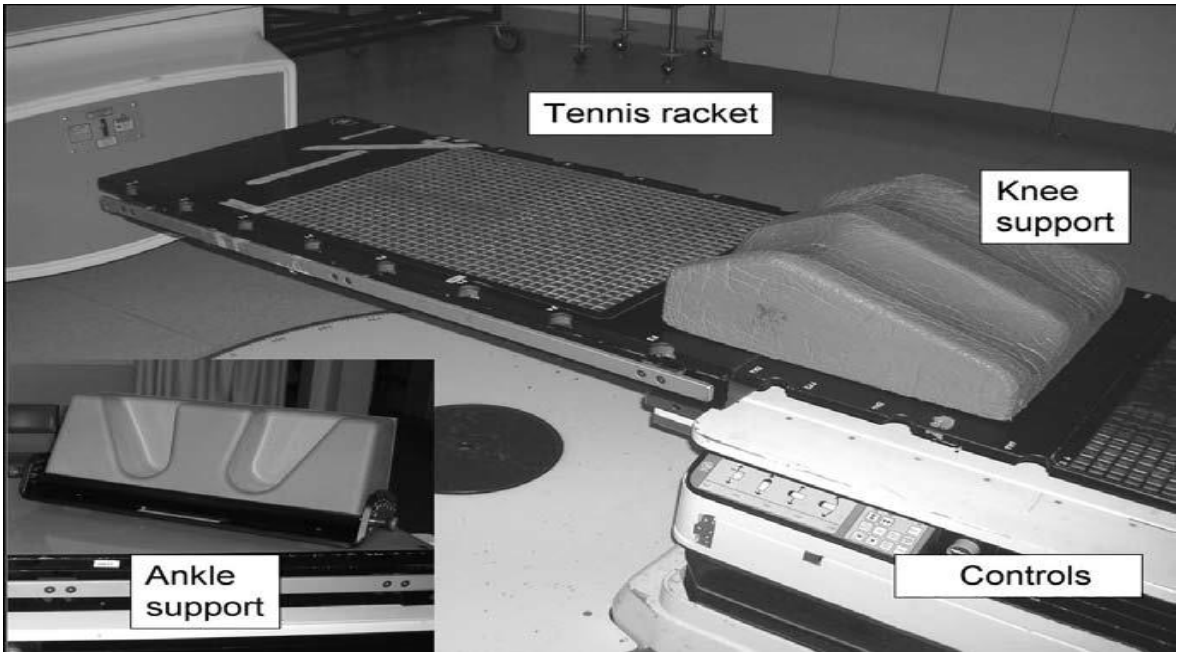

Figure (7) – Knee & ankle supports[120]

➢ **External & Internal Markers:**

- Cases are usually aligned to external markers either positioned on the top cast or located at patient tattoo position. External marker positions are commonly defined at CT simulation time, whereby external fiducial markers are positioned with regard to isocenter. Unfortunately, there's internal organ mobility so external markers can at the best only guide the initial therapy setup. While some structures like the pelvic LNs may follow the bony anatomy quite nicely.[120]
- Consider using vaginal, anal, & cervical markers to delineate normal tissue structures.[122]

13. Equipment

➢ **Elekta Synergy accelerator:**

- Elekta Synergy accelerator is produced by Elekta (Elekta Oncology Systems, Crawley, UK). A few hundred of such accelerators are now used clinically. The Elekta Synergy can deliver photon and electron beams. The accelerator may be used to irradiate complex targets in 3D conformal and Intensity Modulation mode. Before first clinical use according to international recommendations the acceptance and commissioning tests have to be performed. Later the quality control tests have to be performed regularly. The Synergy is reportedly an advanced digital linear accelerator and first platform to enable clinicians to image and treat patients simultaneously. The combination of high-resolution imaging, taken in 3D and at the time of treatment, combined with workflow solutions developed to be applicable on a routine basis, is described as '4D Adaptive,' said Elekta.[123]

Figure (8) – Elekta synergy linear accelerator(123)

- **Multileaf collimators (MLCs):**
  - Multileaf collimator is becoming the main tool for beam shaping on the linear accelerator. It is a simple and useful system in the preparation and performance of radiotherapy treatment. Multileaf collimators are reliable, as their manufacturers developed various mechanisms for their precision, control and reliability, together with reduction of leakage and transmission of radiation between and through the leaves. Multileaf collimator is known today as a very useful clinical system for simple field shaping, but its use is getting even more important in dynamic radiotherapy, with the leaves moving during irradiation. This enables a precise dose delivery on any part of a treated volume. Intensity modulated radiotherapy (IMRT), the therapy of the future, is based on the dynamic use of MLCs.[124]

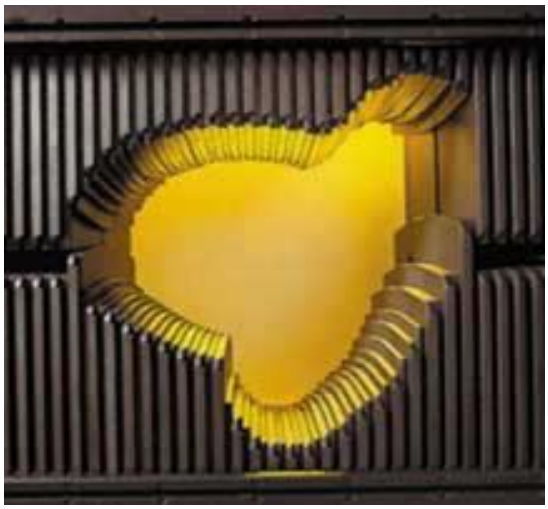

Figure (9) – Multileaf Collimator [124]

14. Treatment planning system

- **Monaco:**
  - Monaco is a comprehensive treatment planning solution for 3D, IMRT, VMAT and stereotactic techniques that uses the gold-standard Monte Carlo dose calculation algorithm to deliver highly accurate dose distributions. With a suite of optimization tools, the Monaco software is designed to generate plans that spare as much healthy tissue as possible, while maximizing dose to the target.[125]
  - The Monaco Treatment Planning System supported a virtual energy fluency model of the photon beam tip elements of the linac & a dose count machine done together with Monte Carlo algorithm X-Ray Voxel MC (XVMC), has been examined before being put into clinical use. An Elekta Synergy together with 6 MV was characterised the use of routine equipment. After the machine's model was installed, a group of functionality, geometric, dosimetric & information transfer tests have been performed. The dosimetric tests included dose calculations in water, heterogeneous phantoms and Intensity Modulated Radiotherapy (IMRT) verifications. Data transfer

checks have been run for each imaging device, TPS and the electronic medical history connected to Monaco.[126]

15. MultiSource HDR & HDRplus for brachytherapy

- **MultiSource HDR:**
  - The MultiSource radiation unit is a remote-controlled automatic afterloading device for gamma radiation and can be used with a Co-60 or an Ir-192 source. It is used for interstitial, intracavitary, intraluminal and intraoperative brachytherapy. Radiation of the skin surface is also possible.[127]
  - The radiation unit must only be used by trained qualified staff under the instruction of a specialist doctor who is familiar with the kind of therapy. The pertinent accident prevention regulations, radiation protection regulations, occupational health regulations and other generally accepted occupational health and safety regulations must be needed. Proper use covers working with the MultiSource radiation unit for measuring and testing purposes in compliance with the safety regulations stated above.[127]

Figure (10) – MultiSource HDR[127]

- **HDRplus:**
  - The HDRplus software is a radiation therapy planning system to perform high dose rate and pulse dose rate brachytherapy planning in combination with the appropriate afterloader device. With this software package, you may perform studies based on one or two co-registered image sequences, isocentric orthogonal x-ray films, isocentric semi-orthogonal x-ray films, non-isocentric x-ray films using a Reco-Box or even without images.
  - You first will need to enter general data on the patient and the study.
  - The images must be loaded into to the study by using one of several methods available for image sequences and orthogonal image plans (scanner, video frame grabber, network supporting DICOM file transfer, or image files on data carrier, i.e. CD, DVD, memory stick, etc.),
  - Then reconstructing the applicators, for image sequence based studies drawing the contours for the planned target volume (PTV) and the organs at risk (OARs) and generating the dose description points for image sequences automatically or placing groups of dose control points with the mouse for orthogonal image based plans. After editing the desired dose constraints for the various groups of dose description points the dwell times may be calculated automatically.
  - The results of the planning process may then be viewed in two-dimensional or three-dimensional representations. You may inspect each image slice as well as the standard views in patient space: sagittal, coronal, and transversal.
  - With the three-dimensional depiction, you may view the displayed organs, applicators, dose control points etc. in any orientation and view the scene from different angles. You may also display an isodose surface for a selectable dose value. Using the color coded surface dose feature, the current dose levels are displayed in color-coded form with pre-selected colors on the

structures' surfaces.

- For evaluation of the planning results, HDRplus calculates and displays the various Dose Volume Histograms DVH (Cumulative DVH, Differential DVH and Natural DVH) as well as histogram parameters like Dxx, Vxx, COIN, etc.
- After finishing the planning task, the report needs to be checked thoroughly. If desired, the study may be saved into an archive for later recalling. You may use the Patient Manager to save and retrieve studies.
- Using the highest quality ultrasound, CT, X-Ray or MR images yields the best study results. Check the integrity of the imaging equipment before using its images for creating a new study.[128]

16. How to do a treatment planning with the Reco-Box

1. Image acquisition: Place the Reco Box around the patient.
   - Make sure that both plates are placed in the same position.
   - Make sure that you use the correct orientation of the box and make sure that the side where you usually place the film is close to image intensifier.
   - In order to be able to be able to do a correct calibration of the images in the TPS, place a wire with a known length (e.g. 10cm) on the image intensifier.
2. Take two images: one PA and one lateral
   - Make sure that you use the correct orientation of the box.
   - Make sure that ALL markers are visible on the images
   - Make sure the wire is visible
   - Make sure that you can see as much of the applicator as possible on the images. At least you have to see ALL tips of the applicators.
   - Do NOT move the box without the patient while taking the images
3. Transfer the images to the TPS: either by DICOM transfer or by scanning the xray films.
   - When scanning the images a resolution of not more than 150dpi is recommended.
   - Make sure that you scan the images in the correct orientation.
4. Create a new patient and a new study in HDRplus:
   - Choose the correct reconstruction method.
5. Load both images into the HDRplus:
   - Choose the correct view/orientation for the loaded images (PA, Lat RL or Lat LR)
6. Select the correct Reco Box file at Setup:
   - Choose the correct file depending on the position of the lateral markers (A, B

or C) and the orientation of the lateral image (LR for lateral left to right and RL for lateral right to left images)

- At Setup Planning choose if the Reco Box to Film distance is variable or fixed. Choose Fixed if you are using x-ray films which were put in the correct place on the Reco box. Use Variable if you are using a digital c-arm with a variable distance between Reco Box and image intensifier.

7. Calibrate the Pixel size of the images:
   - Use either the line that you have drawn on the x-ray film before scanning or the wire on the image intensifier to draw a line with a known length on the images.
   - Make sure that you select Projection from the Pulldown menue before drawing the line on the images.
   - Do the pixel size calibration for BOTH images.
8. Calibrate the Reco Box:
   - Press the Reco Box Calibration button to start the calibration of the Reco Box.
   - Match the red cross with the big markers and the blue cross with the small markers. Calibration of the Reco Box has to be done in BOTH images.
   - Finish the calibration by clicking on the Reco Box Calibration button again.
9. Check the calibration:
   - Place the mouse on a point which you can identify on both images, for example the tip the intrauterine tube. In the second image the corresponding orange line has to cross this point as well.
   - If it doesn't match, please check if you have selected the correct Reco Box file check if you have done the pixel size calibration and the Reco Box calibration correctly and if the orientation of the images (AP/PA,Lat RL/Lat LR) is correct.[(129)]

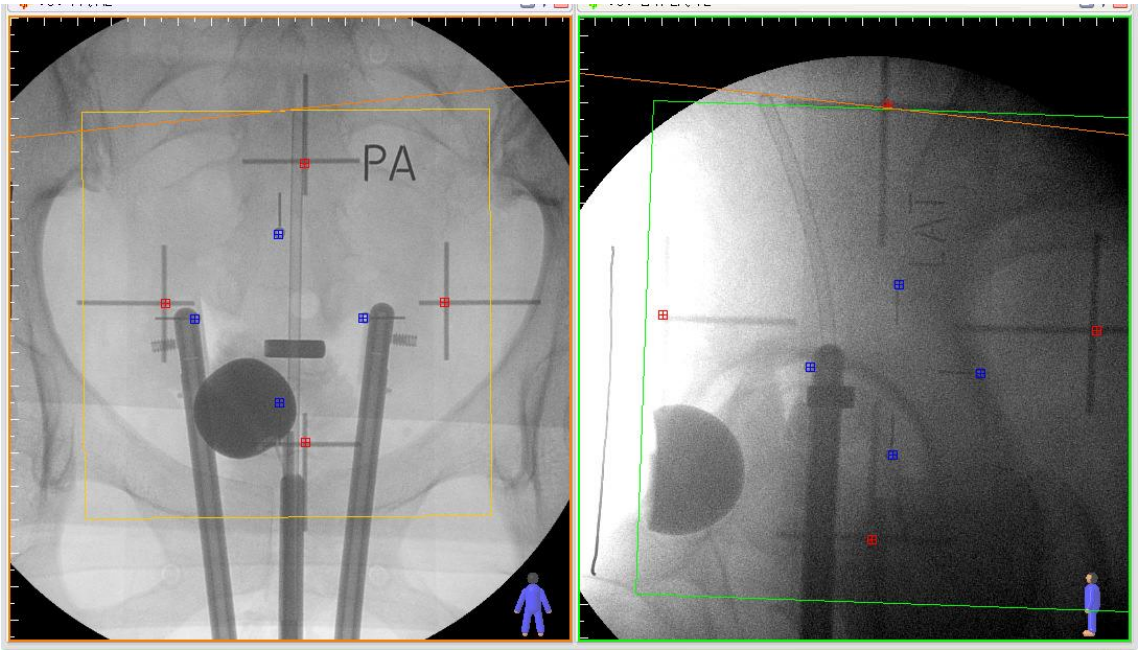

Figure (11) – Treatment planning with the Reco-Box[129]

17. Carrying out measurements and processing of received data

Data of twelve patients with cervical cancer (ten patients of squamous carcinoma and two of adenocarcinoma) stages T2bNxM0 (four patients) and T3NxM0 (eight patients) were randomly selected between the patients who have received combined radiotherapy at Tomsk Regional Oncology Center.

Patients' age was in the range from 42 to 58 years. Patients had received courses of standard combined radiotherapy using EBRT with 3D-CRT (Elekta Synergy linac, 10 MeV, AB Elekta) or conventional radiotherapy based on 60Co (Theratron Equinox 100) followed by HDR BT (Multisource HDR, Bebig). The prescribed dose for first-stage EBRT was 50 Gy given in 25 fractions (2 Gy/fr). All patients received concomitant cisplatin chemotherapy weekly with the first-stage EBRT.

Different irradiation techniques were compared for the second-stage of Radiotherapy (boost), either Brachytherapy or VMAT-boost. The first six patients

have received second-stage by HDR BT by dose of 30 Gy in 5 fractions (6 Gy/fr). The other six patients couldn't receive second-stage by HDR BT and have intolerance to procedure due to anatomical causes like pronounced narrowing of the vagina, the inability to place applicators, perforation risk, and personal or religious reasons to avoid the BT procedure. So they have received second-stage by EBRT (VMAT-boost) by dose of 30 Gy in 5 fractions (6 Gy/fr). We will compare tumor coverage and doses of organs at risk (OARs) included bladder and rectum in the two different techniques.

- **First group (HDR-BT for the second stage):**
  - Six patients were scanned using the CT scanner in a supine position with inserted Manchester-type CT-compatible implants that were fixed well. No additional safety margins are needed to take into account internal movement during BT because the applicator moves together with the CTV.[115]
  - Contouring for both CTV and OARs was performed for each fraction after insertion of implant of BT applicators. The whole organs were contoured based on CT images without division on parts. As seen in Figure (12).

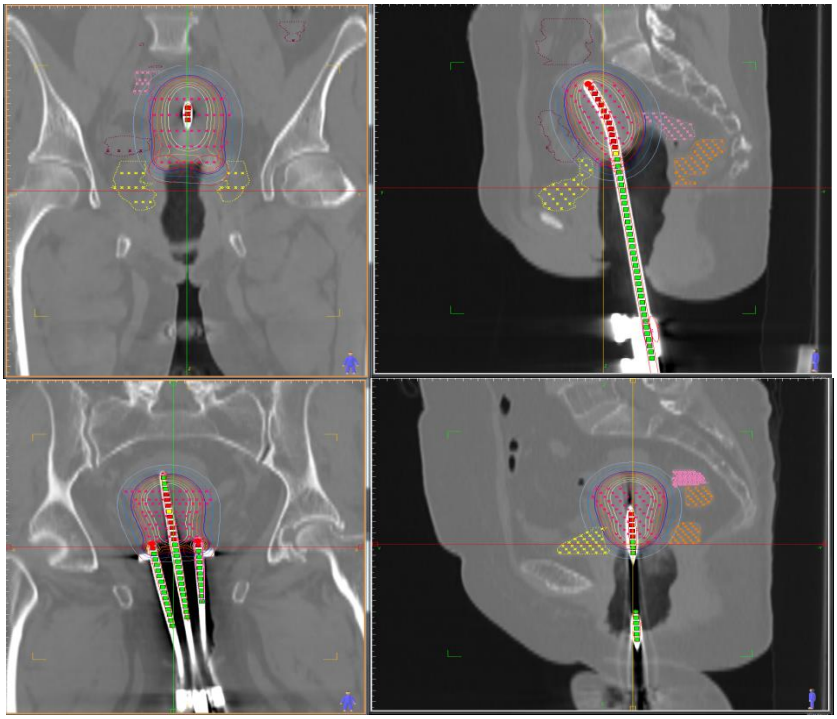

Figure (12) – Contouring for both CTV and OARs in BT.

- The treatment planning goal for HDR BT was prescribed to deliver more than 90% of the dose to 90% of the volume (D90% ≥ V90%). Dose-Volume Histograms (DVHs) were used for the analysis of the planning results, as seen in figure (13)
- The dosimetric planning of the HDR BT of the second stage was carried out using the HDRplus 3D BT dose-planning system (version 3.4) for the MultiSource HDR apparatus with 60Co source (Bebig, Germany).

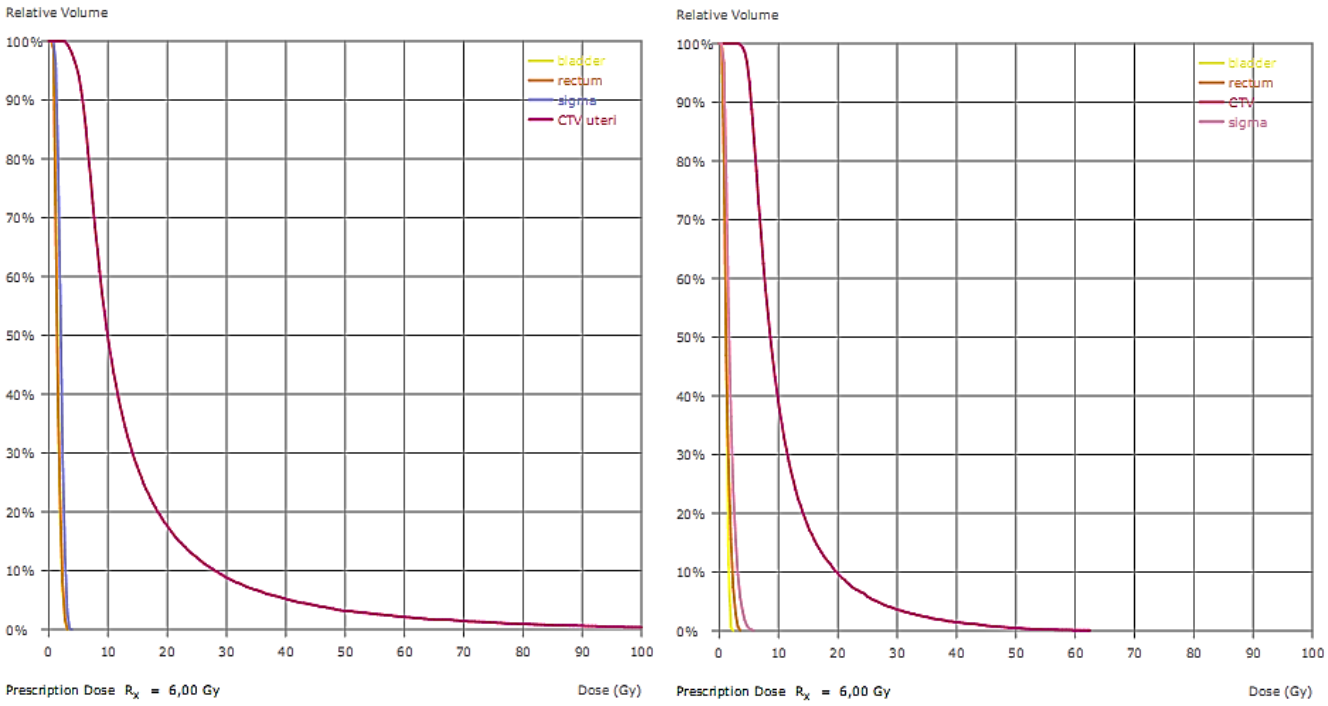

Figure (13) – DVHs of some patients of BT in one fraction for each

- For OAR, it was important to specify the position of the hot spots in the bladder and rectum (D2cc) as this small volume may cause an impact on the clinical outcome. We detected dose of 2cc volume of the bladder and 2cc of the rectum for each patient per fraction and calculate total dose. [130-131]
- Then we calculate Biologically Equivalent Dose (BED) which is derived from the Linear-quadratic model and defined as:

$$\mathbf{BED = nd\ [\ 1 + \ d\ /\ (\alpha/\beta)\ ]}\ ^{(132)}$$

As n: number of equal fractions, d: dose per fraction, (α/β) is 3 Gy for the bladder and 3,9 Gy for the rectum.[131] Then we calculated "EQD2" (equivalent dose in 2 Gy/fr) by equation:

$$\mathbf{EQD2= BED\ /\ [\ 1 + 2\ /\ (\alpha/\beta)\ ]}\ ^{(132)}$$

Results are seen in table (3).

Table (3) – Physical doses, BED & EQD2 of OARs (bladder & rectum) in BT.

HDR BT	Urinary bladder (2cc)				Rectum (2cc)			
	Dose/fr	total	BED	EQD2	Dose/fr	total	BED	EQD2
Patient 1	4.272	21.36	51.8	31.1	2.472	12.36	15.7	10.4
Patient 2	1.48	7.4	11.1	6.6	2.25	11.25	17.7	11.7
Patient 3	4.6	23	58.3	35	3.62	18.1	34.9	23.1
Patient 4	3.55	17.75	38.8	23.3	2.82	14.1	24.3	16.1
Patient 5	2.27	11.35	19.9	12	2.37	11.85	19.1	12.6
Patient 6	3.8	19	43.1	25.8	1.32	6.6	8.8	5.8

- DVHs of six patients received HDR BT were used to know coverage of clinical target volume (CTV) by different percentage of prescribed dose e.g. dose 90%, 95%, 98%...etc. And results were collected in table (4).

Table (4) – Coverage of (CTV) at different percentage of prescribed dose in BT.

HDR BT	Dose 90%	Dose 95%	Dose 98%	Dose 99%	Dose 100%	Dose 109%	Dose 110%	Dose 150%	Dose 200%	Dose 250%
Pt 1 CTV%	91.7	89.1	87.9	87.2	86.9	82.1	81.6	59.4	37.5	25.1
Pt 2 CTV%	96.3	95.3	92.6	91.9	91.4	85.8	85.2	57.9	36.2	24.3
Pt 3 CTV%	92.2	89.4	88.3	88	87.7	82.1	81.5	57	38.3	27.5
Pt 4 CTV%	89.7	85.6	83.8	82.9	82	74.2	73.3	46.4	27.5	17.6
Pt 5 CTV%	90.8	88.2	87.1	86.4	86.1	81.6	81.1	59.7	38.7	27
Pt 6 CTV%	91.7	89.2	86.8	86.3	85.9	79.96	79.3	52.4	30.3	19.8

➢ **<u>Second group (VMAT for the second stage):</u>**

- Other six patients were scanned using the CT scanner in a supine position. Contouring for both CTV and OARs was performed based on CT images as seen in Figure (14).

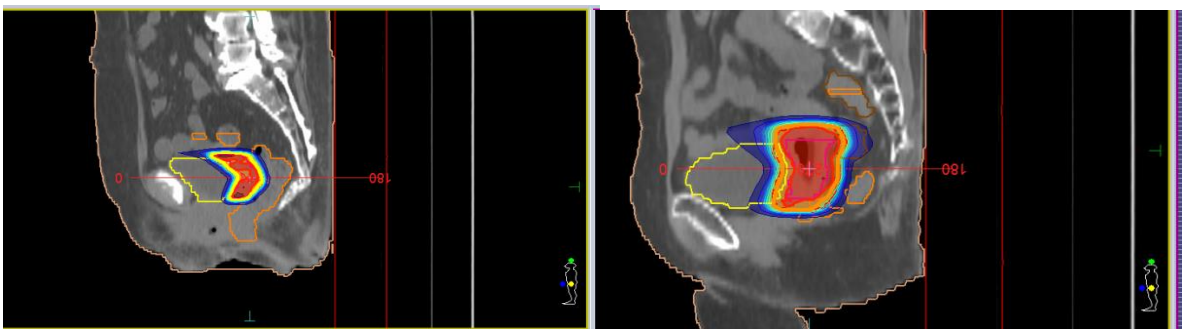

Figure (14) – Contouring for both CTV and OARs in VMAT.

- Planning was carried out using the Monaco planning system (v. 5.10.04, Elekta) at the Elekta Synergy linac of 10 MeV. For the VMAT technique, the inverse algorithms based on the Monte Carlo method were used. Plan example seen in figure (15) and DVH examples seen in figure (16).

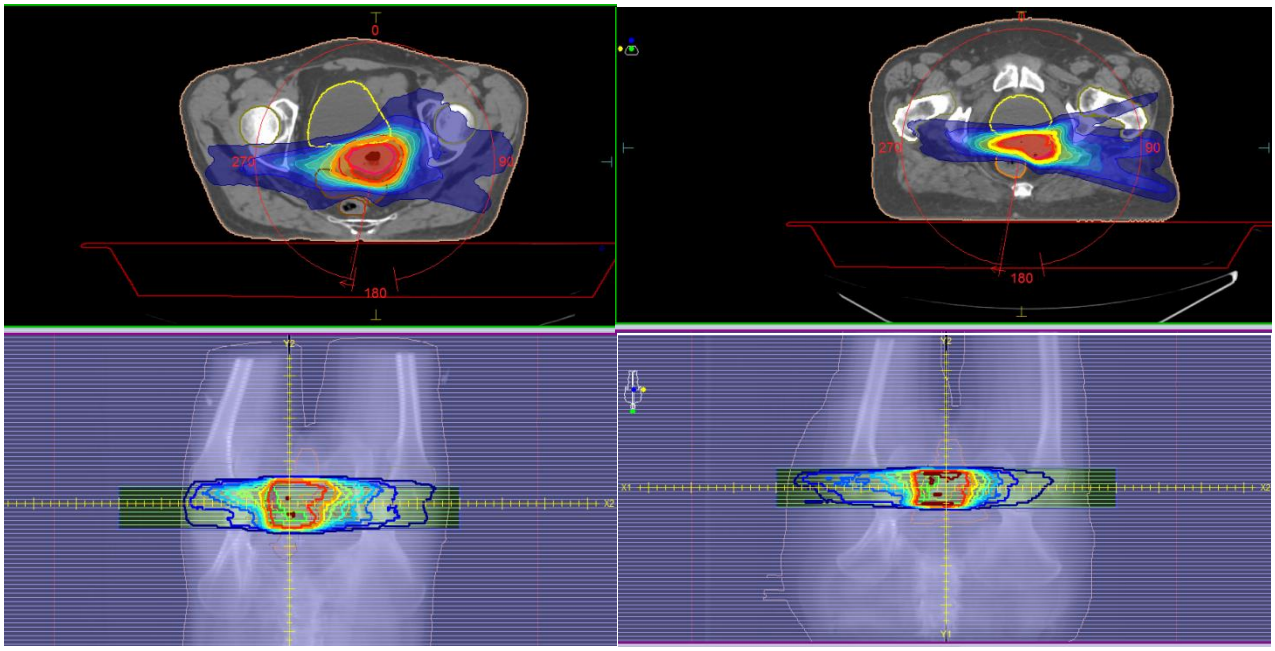

Figure (15) – Plan example of VMAT.

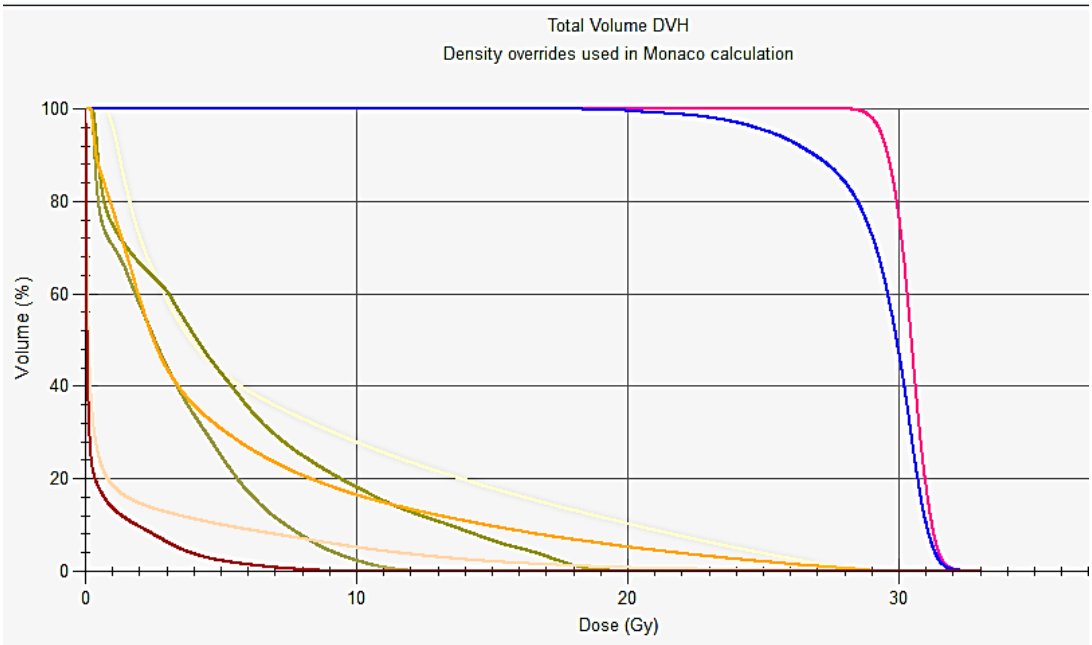

Figure (16) – DVH example of VMAT.

- For OAR, we calculate dose of 2cc volume of the bladder and 2cc of the rectum for each patient per fraction and calculate total dose. Then we calculate BED and EQD2 from equations mentioned before. Results are seen in table (5).

Table (5) – Physical doses, BED & EQD2 of OARs (bladder & rectum) in VMAT.

VMAT boost	Urinary bladder (2cc)				Rectum (2cc)			
	Dose/fr	total	BED	EQD2	Dose/fr	total	BED	EQD2
Patient 1	5.42	27.1	76.1	45.6	5.47	27.35	65.7	43.3
Patient 2	4.76	23.8	61.6	36.9	2.9	14.5	25.3	16.7
Patient 3	5.16	25.8	70.2	42.1	3.89	19.45	38.9	25.7
Patient 4	5.28	26.4	72.9	43.7	4.48	22.4	48.1	31.8
Patient 5	5.16	25.8	70.2	42.1	4.01	20.05	40.7	26.9
Patient 6	4.68	23.4	59.9	35.9	4.38	21.9	46.5	30.7

- DVHs of six patients received VMAT boost were used to know coverage of target volume (CTV) by different percentage of prescribed dose e.g. dose 90%, 95%, 98%...etc. And results were collected in table (6).

Table (6) – Coverage of (CTV) at different percentage of prescribed dose in VMAT.

VMAT boost	Dose 90%	Dose 95%	Dose 98%	Dose 99%	Dose 100%	Dose 109%	Dose 110%	Dose 150%	Dose 200%
Pt 1 CTV%	100	100	99.6	97.9	94.6	2.03	1.03	----	----
Pt 2 CTV%	100	100	98.4	95.9	91.4	3.1	1.44	----	----
Pt 3 CTV%	100	99.88	95.2	91	81	8.05	4.5	----	----
Pt 4 CTV%	100	99.6	93	86.2	79.4	0.98	0.94	----	----
Pt 5 CTV%	100	99.79	96.5	89	82.5	0.61	0.56	----	----
Pt 6 CTV%	100	99.57	95	89.2	83.3	1.08	0.87	----	----

18. Discussion of results

Microsoft Excel 2010 and IBM SPSS Version 20 were used for calculations and for descriptive statistics. Descriptive statistics of the data are presented as mean ± standard deviation (SD) regarding total physical dose, BED & EQD2 received by 2 cm3 of OARs including Bladder & Rectum in both techniques (VMAT & Brachherapy). Parameters are in Table (7) and figure (17).

Table (7) – Comparison between VMAT & Brachytherapy in total physical dose, BED & EQD2 received by OARs (mean ± SD)

		Brachytherapy	VMAT
Urinary Bladder	**Total**	18.375 ± 6.05	25.8 ± 1.47
	BED	40.95 ± 18.31	70.2 ± 6.39
	EQD2	24.55 ± 11	42.1 ± 3.84
Rectum	**Total**	12.11 ± 3.76	20.98 ± 4.21
	BED	18.4 ± 8.84	43.6 ± 13.27
	EQD2	12.15 ± 5.86	28.8 ± 8.74

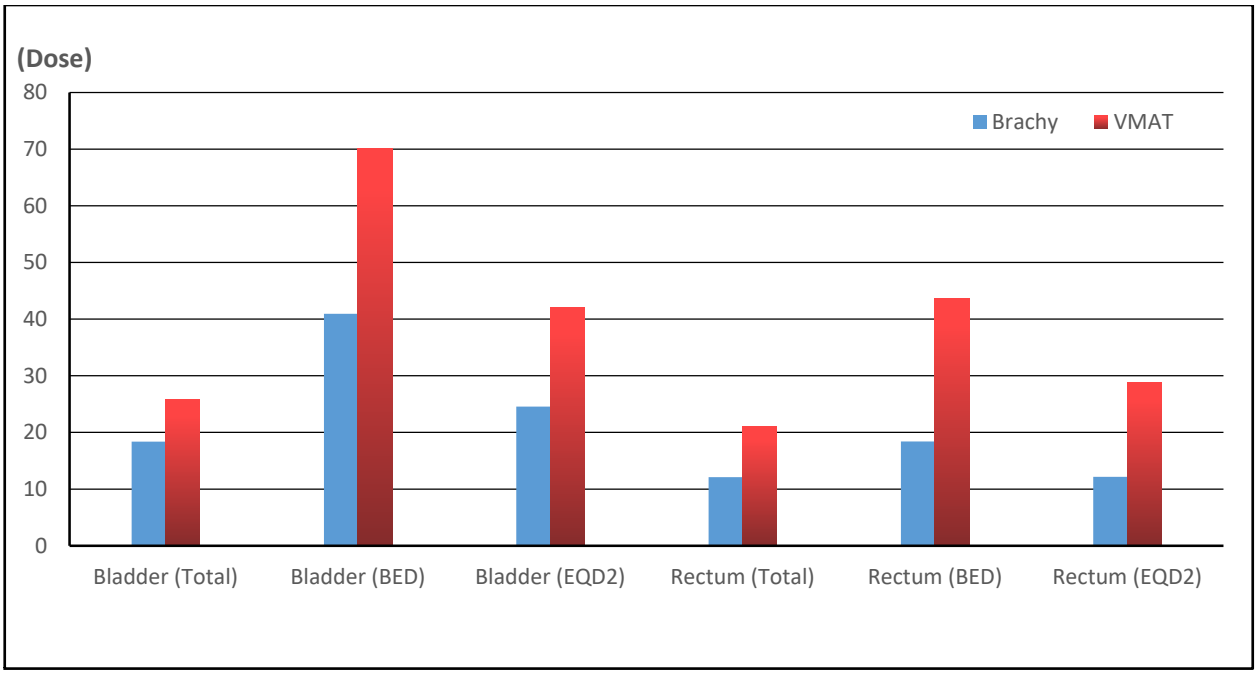

Figure (17) – Comparison between VMAT & Brachytherapy in mean of total physical dose, BED & EQD2 received by OARs

Our study showed that the mean physical dose received by 2cm3 of Bladder and Rectum in Brachytherapy (18.375 ± 6.05 Gy and 12.11 ± 3.76 Gy) and in VMAT (25.8 ± 1.47 Gy and 20.98 ± 4.21 Gy), respectively. BEDs were calculated for 2cm3 of Bladder and Rectum in Brachytherapy (40.95 ± 18.31 Gy and 18.4 ± 8.84 Gy) and in VMAT (70.2 ± 6.39 Gy and 43.6 ± 13.27Gy), respectively. Also EQD2 were calculated for 2cm3 of Bladder and Rectum in Brachytherapy (24.55 ± 11 and 12.15 ± 5.86) and in VMAT (42.1 ± 3.84 and 28.8 ± 8.74), respectively. We found that doses received by 2cm3 of Bladder & Rectum in Brachytherapy lesser than doses received in VMAT. As we know that Brachytherapy is kind of radiotherapy that travels a brief distance[(84)], so the dose fall off after small distance from source and that make dose received by OARs lower.

DVHs were used to detect coverage of target volume of patients at different variants of percentage of prescribed dose in both techniques (VMAT & Brachytherapy). Microsoft Excel 2010 was used for calculations of descriptive

statistics and plot of results in histogram. Descriptive statistics of the data are presented as mean ± standard deviation (SD) of CTV coverage% regarding variants of doses. Results are in table (8) and figure (18).

Table (8) – Comparison between VMAT & Brachytherapy in coverage of CTV (mean ± SD) at different percentage of prescribed Doses.

Dose %	CTV coverage % by Brachytherapy	CTV coverage % by VMAT
90%	91.7 ± 2.25	100 ± 0
95%	89.15 ± 3.19	99.84 ± 0.19
98%	87.5 ± 2.86	95.85 ± 2.41
99%	86.8 ± 2.92	90.1 ± 4.48
100%	86.5 ± 3.04	82.9 ± 6.15
109%	81.85 ± 3.82	1.56 ± 2.8
110%	81.3 ± 3.94	0.985 ± 1.47
150%	57.45 ± 5.16	----
200%	36.85 ± 4.7	----
250%	24.7 ± 4	----

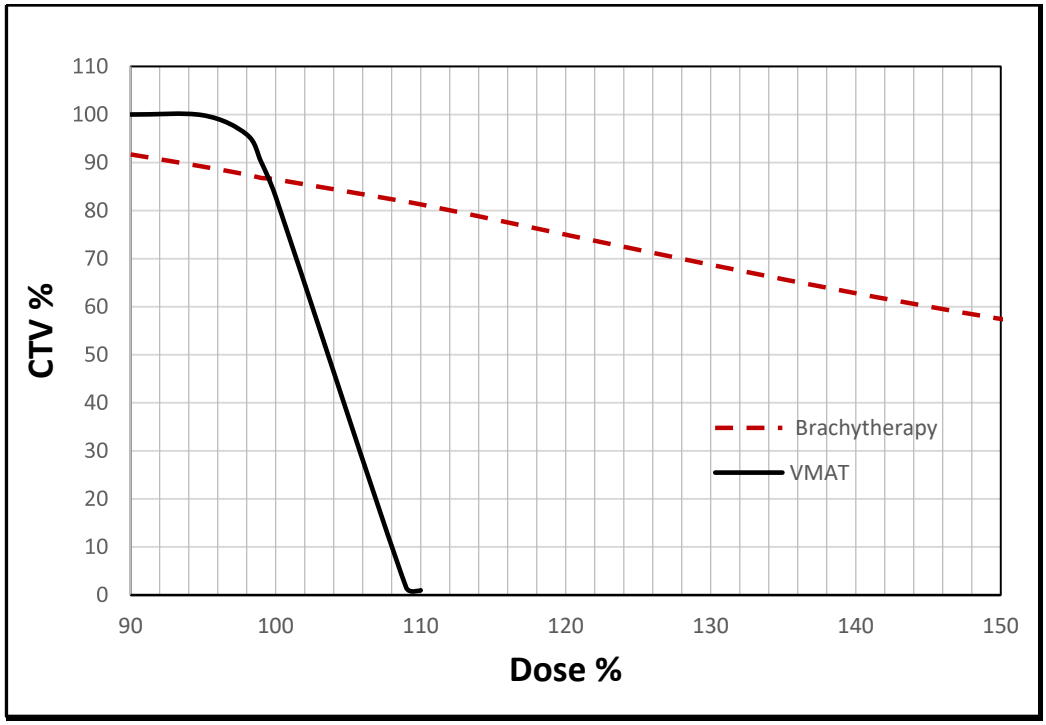

Figure (18) – Comparison between VMAT & Brachytherapy in coverage of CTV (mean ± SD) at different percentages of prescribed Dose.

Our study showed that the mean target coverage at 90% & 95% of the prescribed dose in Brachytherapy is (91.7% ± 2.25 and 89.15% ± 3.19) and in VMAT (100% ± 0 and 99.84% ± 0.19), respectively. Mean target coverage at 100% & 110% of the prescribed dose in Brachytherapy is (86.5% ± 3.04 and 81.3% ± 3.94) and in VMAT (82.9% ± 6.15 and 0.985% ± 1.47), respectively. We found the dose distribution over target volume is non-uniform in Brachytherapy and results in irradiation of significant target volumes by doses higher than prescribed dose, i.e., 150-200% of the prescribed dose was delivered to 57.45% and 36.85% of the target volume, respectively. In VMAT dose distribution over target volume is uniform as 98% of the prescribed dose was delivered to 95.85 of the target volume and hot spots don't exceed 110% of the prescribed dose delivered to about 1% only of the target volume.

19. Conclusion

As mentioned before, there are many patients that couldn't receive second-stage by HDR BT and have intolerance to procedure due to anatomical causes like pronounced narrowing of the vagina, the inability to place applicators, perforation risk, and personal or religious reasons to avoid the BT procedure. The results of our study show that the VMAT could be effective to replace HDR brachytherapy.

Results of our study show that the use of the VMAT technique for the second stage of combined RT of cervical cancer allows a significant increase in the irradiation uniformity, to deliver the prescribed dose to the target with a high coverage level (99% of the target volume can be irradiated with a dose higher than 95% of the prescribed dose), and to minimize overexposure of large volumes with high doses (hot spots don’t exceed 110% of the prescribed dose delivered to about 1% only of the target volume).

20. Social responsibility

20.1 Introduction

Cervical cancer remains the 4th most diagnosed cancer and therefore the 4th leading cause of death due to cancer in women worldwide. Radiotherapy is one of the common types of treatment of cervical cancer and it is applied in two stages, first stage done by EBRT but second stage could be done by different irradiation techniques. Our study has compared BT & VMAT for the second stage of radiation in cervical cancer because some patients couldn't receive second-stage by BT and have intolerance to procedure due to anatomical causes like pronounced narrowing of the vagina, and personal or religious reasons to avoid the BT procedure. So we should be sure if VMAT could replace BT in this situations or not.

20.2 Legal and organizational items in providing safety

Nowadays one of the main way to radical improvement of all prophylactic work referred to reduce Total Incidents Rate and occupational morbidity is the widespread implementation of an integrated Occupational Safety and Health management system. That means combining isolated activities into a single system of targeted actions at all levels and stages of the production process.

Occupational safety is a system of legislative, socio-economic, organizational, technological, hygienic and therapeutic and prophylactic measures and tools that ensure the safety, preservation of health and human performance in the work process.(133)

According to the Labor Code of the Russian Federation, every employee has the right:

- To have a workplace that meets Occupational safety requirements;

- To have a compulsory social insurance against accidents at manufacturing and occupational diseases;

- To receive reliable information from the employer, relevant government bodies and public organizations on conditions and Occupational safety at the

workplace, about the existing risk of damage to health, as well as measures to protect against harmful and (or) hazardous factors;

- To refuse carrying out work in case of danger to his life and health due to violation of Occupational safety requirements;

- Be provided with personal and collective protective equipment in compliance with Occupational safety requirements at the expense of the employer;

- For training in safe work methods and techniques at the expense of the employer;

- For personal participation or participation through their representatives in consideration of issues related to ensuring safe working conditions in his workplace, and in the investigation of the accident with him at work or occupational disease;

- For extraordinary medical examination in accordance with medical recommendations with preservation of his place of work (position) and secondary earnings during the passage of the specified medical examination;

- For warranties and compensation established in accordance with this Code, collective agreement, agreement, local regulatory an act, an employment contract, if he is engaged in work with harmful and (or) hazardous working conditions.

The labor code of the Russian Federation states that normal working hours may not exceed 40 hours per week, The employer must keep track of the time worked by each employee.

Rules for labor protection and safety measures are introduced in order to prevent accidents, ensure safe working conditions for workers and are mandatory for workers, managers, engineers and technicians.

20.3 Basic ergonomic requirements for the correct location and arrangement of researcher's workplace

The workplace when working with a PC should be at least 6 square meters. The legroom should correspond to the following parameters: the legroom height is at least 600 mm, the seat distance to the lower edge of the working surface is at least 150 mm, and the seat height is 420 mm. It is worth noting that the height of the table should depend on the growth of the operator.

The following requirements are also provided for the organization of the workplace of the PC user: The design of the working chair should ensure the maintenance of a rational working posture while working on the PC and allow the posture to be changed in order to reduce the static tension of the neck and shoulder muscles and back to prevent the development of fatigue.

The type of working chair should be selected taking into account the growth of the user, the nature and duration of work with the PC. The working chair should be lifting and swivel, adjustable in height and angle of inclination of the seat and back, as well as the distance of the back from the front edge of the seat, while the adjustment of each parameter should be independent, easy to carry out and have a secure fit.

20.4 Occupational safety:

A dangerous factor or industrial hazard is a factor whose impact under certain conditions leads to trauma or other sudden, severe deterioration of health of the worker.[133]

A harmful factor or industrial health hazard is a factor, the effect of which on a worker under certain conditions leads to a disease or a decrease in working capacity.

20.4.1 Analysis of harmful and dangerous factors that can create object of investigation:

The aim of this study to carry out a dosimetric and radiobiological planning of the replacement of traditional combined radiation therapy [3D conformal

radiotherapy (3D-CRT) + high-dose-rate brachy-therapy (HDR-BT)] by combinations of [(3D-CRT) + (VMAT)] or [(VMAT) + (VMAT)] while preserving the value of the total dose delivered and the number of fractions to detect the best technique among russian patients at Tomsk Regional Oncology Center, Tomsk Polytechnic University

20.4.2. Analysis of harmful and dangerous factors that can arise at workplace during investigation:

The thesis was performed at Tomsk Regional Oncology Center. Work was performed using a PC. Production conditions at the workplace are characterized by the presence of dangerous and harmful factors, which are classified into groups: Elements: physical, chemical, biological, psychophysiological.The main elements of the production process that form dangerous and harmful factors are presented in Table 9.

Table (9) – Possible hazardous and harmful factors

Factors (GOST 12.0.003-2015)	Work stages			Legal documents
	Development	Manufacture	Exploitation	
1. Deviation of microclimate indicators	+	+	+	Sanitary rules 2.2.2 / 2.4.1340–03. Sanitary and epidemiological rules and regulations "Hygienic requirements for personal electronic computers and work
2. Excessive noise		+	+	
3.Increased level of electromagnetic radiation	+	+	+	
4.Insufficient illumination of the working area		+	+	

				organization." Sanitary rules 2.2.1 / 2.1.1.1278–03. Hygienic requirements for natural, artificial and combined lighting of residential and public buildings. Sanitary rules 2.2.4 / 2.1.8.562–96. Noise at workplaces, in premises of residential, public buildings and in the construction area. Sanitary rules 2.2.4.548–96. Hygienic requirements for the microclimate of industrial premises.
5. Abnormally high voltage	+	+	+	Sanitary rules GOST

value in the circuit, the closure which may occur through the human body				12.1.038-82 SSBT. Electrical safety. Maximum permissible levels of touch voltages and currents.
6. Increased levels of ionizing radiation	+	+	+	Sanitary Rules 2.6.1. 2523 -0 9. Radiation Safety Standards (NRB-99/2009).

The following factors effect on person working on a computer:

- physical:
  - temperature and humidity;
  - noise;
  - static electricity;
  - electromagnetic field of low purity;
  - illumination;
  - presence of radiation;
- psychophysiological:
  - psychophysiological dangerous and harmful factors are divided into:
    - physical overload (static, dynamic)
    - mental stress (mental overstrain, monotony of work, emotional overload).

Deviation of microclimate indicators

The air of the working area (microclimate) is determined by the following parameters: temperature, relative humidity, air speed. The optimum and

permissible values of the microclimate characteristics are established in accordance with[134] and are given in Table 10.

Table (10) – Optimal and permissible parameters of the microclimate

Period of the year	Temperature, C	Relative humidity,%	Speed of air movement, m/s
Cold and changing of seasons	23-25	40-60	0.1
Warm	23-25	40	0.1

Excessive noise

Noise and vibration worsen working conditions; have a harmful effect on the human body, namely, the organs of hearing and the whole body through the central nervous system. It result in weakened attention, deteriorated memory, decreased response, and increased number of errors in work. Noise can be generated by operating equipment, air conditioning units, daylight illuminating devices, as well as spread from the outside. When working on a PC, the noise level in the workplace should not exceed 50 dB.

Increased level of electromagnetic radiation

The screen and system blocks produce electromagnetic radiation. Its main part comes from the system unit and the video cable. According to [2], the intensity of the electromagnetic field at a distance of 50 cm around the screen along the electrical component should be no more than:

- in the frequency range 5 Hz - 2 kHz - 25 V / m;
- in the frequency range 2 kHz - 400 kHz - 2.5 V / m.

The magnetic flux density should be no more than:

- in the frequency range 5 Hz - 2 kHz - 250 nT;
- in the frequency range 2 kHz - 400 kHz - 25 nT.

Abnormally high voltage value in the circuit

Depending on the conditions in the room, the risk of electric shock to a person increases or decreases. Do not operate the electronic device in conditions of high humidity (relative air humidity exceeds 75% for a long time), high temperature (more than 35 ° C), the presence of conductive dust, conductive floors and the possibility of simultaneous contact with metal components connected to the ground and the metal casing of electrical equipment. The operator works with electrical devices: a computer (display, system unit, etc.) and peripheral devices. There is a risk of electric shock in the following cases:

- with direct contact with current-carrying parts during computer repair;
- when touched by non-live parts that are under voltage (in case of violation of insulation of current-carrying parts of the computer);
- when touched with the floor, walls that are under voltage;
- short-circuited in high-voltage units: power supply and display unit.

Upper limits for values of contact current and voltage

	Voltage, V	Current, mA
Alternate, 50 Hz	2	0.3
Alternate, 400 Hz	3	0.4
Direct	8	1.0

Insufficient illumination of the working area

Light sources can be both natural and artificial. The natural source of the light in the room is the sun, artificial light are lamps. With long work in low illumination conditions and in violation of other parameters of the illumination, visual perception decreases, myopia, eye disease develops, and headaches appear.

According to the standard, the illumination on the table surface in the area of the working document should be 300-500 lux. Lighting should not create glare on the surface of the monitor. Illumination of the monitor surface should not be more than 300 lux.

The brightness of the lamps of common light in the area with radiation angles from 50 to 90° should be no more than 200 cd/m, the protective angle of the

lamps should be at least 40°. The safety factor for lamps of common light should be assumed to be 1.4. The ripple coefficient should not exceed 5%.

Increased levels of ionizing radiation

Ionizing radiation is radiation that could ionize molecules and atoms. This effect is widely used in energetics and industry. However, there is health hazard. In living tissue, this radiation could damage cells that result in two types of effects. Deterministic effects (harmful tissue reactions) due to exposure with high doses and stochastic effects due to DNA destruction and mutations (for example, induction of cancer).

To provide radiation safety with using sources of ionizing radiation one must use next principles:

a) Keep individual radiation doses from all radiation sources not higher than permissible exposure;
b) Forbid all activity with using radiation sources if profit is low than risk of possible hazard;
c) Keep individual radiation doses from all radiation sources as low as possible.

There are two groups of people related to work with radiation: personnel, who works with ionizing radiation, and population.

Quantity	Dose limits	
	personnel	population
Effective dose	20 mSv per year in average during 5 years, but not higher than 50 mSv per year	1 mSv per year in average during 5 years, but not higher than 5 mSv per year
Equivalent dose per year in eye's lens	150 mSv	15 mSv
skin	500 mSv	50 mSv
Hands and feet	500 mSv	50 mSv

Effective dose for personnel must not exceed 1000 mSv for 50 years of working activity, and for population must not exceed 70 mSv for 70 years of life.

In addition, for women from personnel of age below 45 years there is limit of 1 mSv per month of equivalent dose on lower abdomen. During gestation and breast feeding women must not work with radiation sources.

For students older than 16, who uses radiation sources in study process or who is in rooms with increased level of ionizing radiation, dose limits are quarter part of dose limits of personnel.

20.4.3 Justification of measures to reduce the levels of exposure to hazardous and harmful factors on the researcher

Deviation of microclimate indicators

The measures for improving the air environment in the production room include: the correct organization of ventilation and air conditioning, heating of room. Ventilation can be realized naturally and mechanically. In the room, the following volumes of outside air must be delivered:

- At least 30 m^3 per hour per person for the volume of the room up to 20 m^3 per person;
- Natural ventilation is allowed for the volume of the room more than 40 m^3 per person and if there is no emission of harmful substances.

The heating system must provide sufficient, constant and uniform heating of the air. Water heating should be used in rooms with increased requirements for clean air.

The parameters of the microclimate in the laboratory regulated by the central heating system, have the following values: humidity 40%, air speed 0.1 m / s, summer temperature 20-25 ° C, in winter 13-15 ° C. Natural ventilation is provided in the laboratory. Air enters and leaves through the cracks, windows, doors. The main disadvantage of such ventilation is that the fresh air enters the room without preliminary cleaning and heating.

Excessive noise

In research audiences, there are various kinds of noises that are generated by both internal and external noise sources. The internal sources of noise are working equipment, personal computer, printer, ventilation system, as well as computer equipment of other engineers in the audience. If the maximum permissible conditions are exceeded, it is sufficient to use sound-absorbing materials in the room (sound-absorbing wall and ceiling cladding, window curtains). To reduce the noise penetrating outside the premises, install seals around the perimeter of the doors and windows.

Increased level of electromagnetic radiation

There are the following ways to protect against EMF:

- Increase the distance from the source (the screen should be at least 50 cm from the user);

- The use of pre-screen filters, special screens and other personal protective equipment.

When working with a computer, the ionizing radiation source is a display. Under the influence of ionizing radiation in the body, there may be a violation of normal blood coagulability, an increase in the fragility of blood vessels, a decrease in immunity, etc. The dose of irradiation at a distance of 20 cm to the display is 50 μrem / hr. According to the norms [2], the design of the computer should provide the power of the exposure dose of x-rays at any point at a distance of 0.05 m from the screen no more than 100 μR / h.

Fatigue of the organs of vision can be associated with both insufficient illumination and excessive illumination, as well as with the wrong direction of light.

Increased levels of ionizing radiation

In case of radiation accident, responsible personnel must take all measures to restore control of radiation sources and reduce to minimum radiation doses,

number of irradiated persons, radioactive pollution of the environment, economic and social losses caused with radioactive pollution.

Radiation control is a main part of radiation safety and radiation protection. It is aimed at not exceeding the established basic dose limits and permissible levels of radiation, obtaining the necessary information to optimize protection and making decisions about interference in the case of radiation accidents, contamination of the environment and buildings with radionuclides.

The radiation control is control of:

- Radiation characteristics of radiation sources, pollution in air, liquid and solid wastes.
- Radiation factors developed with technological processes in working places and environment.
- Radiation factors of contaminated environment.
- Irradiation dose levels of personnel and population.

The main controlled parameters are:

- Annual effective and equivalent doses
- intake and body content of radionuclides
- Volume or specific activity of radionuclides in air, water, food products, building materials and etc.
- Radioactive contamination of skin, clothes, footwear, working places and etc.
- Dose and power of external irradiation.
- Particles and photons flux density.

Radiation protection office establish control levels of all controlled parameters in according to not exceed dose limits and keep dose levels as low as possible. In case of exceeding control levels radiation protection officers start investigation of exceed causes and take actions to eliminate this exceeding.

During planning and implementation of radiation safety precautions, taking any actions about radiation safety and analysis of effectiveness of mentioned action and precautions one must value radiation safety with next factors:

- Characteristics of radioactive contamination of the environment;
- Probability of radiation accidents and scale of accidents;

- Degree of readiness to effective elimination of radiation accidents and its aftermathches;
- Number of persons irradiated with doses higher than controlled limits of doses;
- Analysis of actions for providing radiation safety, meeting requirements, rules, standards of radiation safety;
- Analysis of irradiation doses obtained by groups of population from all ionizing radiation sources.

Abnormally high voltage value in the circuit

Measures to ensure the electrical safety of electrical installations:

- Disconnection of voltage from live parts, on which or near to which work will be carried out, and taking measures to ensure the impossibility of applying voltage to the workplace;
- Posting of posters indicating the place of work;
- Electrical grounding of the housings of all installations through a neutral wire;
- Coating of metal surfaces of tools with reliable insulation;
- Inaccessibility of current-carrying parts of equipment (the conclusion in the case of electroporating elements, the conclusion in the body of current-carrying parts).[135]

Insufficient illumination of the working area

Desktops should be placed in such a way that the monitors are oriented sideways to the light openings, so that natural light falls mainly on the left.

Also, as a means of protection to minimize the impact of the factor, local lighting should be installed due to insufficient lighting, window openings should be equipped with adjustable devices such as blinds, curtains, external visors, etc.

20.5 Ecological safety

20.5.1 Analysis of the impact of the research object on the environment

All radiotherapy centers are required to have a containment building in according to international requirements. The walls of containment buildings are several feet thick and made of concrete and therefore can stop the release of any radiation emitted by the reactor into the environment

All possible impact of radiotherapy on environment is greatly reduced in operating regime by many safety precautions means. The most danger of nuclear energy come because of different sorts of disaster

20.5.2 Analysis of the environmental impact of the research process

Process of investigation itself in the thesis do not have essential effect on environment. One of hazardous waste is fluorescent lamps. Mercury in fluorescent lamps is a hazardous substance and its improper disposal greatly poisons the environment.

Outdated devices goes to an enterprise that has the right to process wastes. It is possible to isolate precious metals with a purity in the range of 99.95–99.99% from computer components. A closed production cycle consists of the following stages: primary sorting of equipment; the allocation of precious, ferrous and non-ferrous metals and other materials; melting; refining and processing of metals. Thus, there is an effective disposal of computer devices.

20.5.3 Justification of environmental protection measures

Pollution reduction is possible due to the improvement of devices that produces electricity, the use of more economical and efficient technologies, the use of new methods for generating electricity and the introduction of modern methods and methods for cleaning and neutralizing industrial waste. In addition, this problem should be solved by efficient and economical use of electricity by consumers themselves. This is the use of more economical devices, as well as efficient regimes of these devices. This also includes compliance with production discipline in the framework of the proper use of electricity.

Simple conclusion is that it is necessary to strive to reduce energy consumption, to develop and implement systems with low energy consumption. In modern computers, modes with reduced power consumption during long-term idle are widely used.

20.6 Safety in emergency

20.6.1 Analysis of probable emergencies that may occur at the workplace during research

The fire is the most probable emergency in our life. Possible causes of fire:

- Malfunction of current-carrying parts of installations;
- Work with open electrical equipment;
- Short circuits in the power supply;
- Non-compliance with fire safety regulations;
- Presence of combustible components: documents, doors, tables, cable insulation, etc.

Activities on fire prevention are divided into: organizational, technical, operational and regime.

20.6.2 Substantiation of measures for the prevention of emergencies and the development of procedures in case of emergencies

Organizational measures provide for correct operation of equipment, proper maintenance of buildings and territories, fire instruction for workers and employees, training of production personnel for fire safety rules, issuing instructions, posters, and the existence of an evacuation plan.

The technical measures include compliance with fire regulations, norms for the design of buildings, the installation of electrical wires and equipment, heating, ventilation, lighting, the correct placement of equipment.

The regime measures include the establishment of rules for the organization of work, and compliance with fire-fighting measures. To prevent fire from short circuits, overloads, etc., the following fire safety rules must be observed:

- Elimination of the formation of a flammable environment (sealing equipment, control of the air, working and emergency ventilation);
- Use in the construction and decoration of buildings of non-combustible or difficultly combustible materials;
- The correct operation of the equipment (proper inclusion of equipment in the electrical supply network, monitoring of heating equipment);
- Correct maintenance of buildings and territories (exclusion of the source of ignition - prevention of spontaneous combustion of substances, restriction of fire works);
- Training of production personnel in fire safety rules;

- The publication of instructions, posters, the existence of an evacuation plan;
- Compliance with fire regulations, norms in the design of buildings, in the organization of electrical wires and equipment, heating, ventilation, lighting;
- The correct placement of equipment;
- Well-time preventive inspection, repair and testing of equipment.

In the case of an emergency, it is necessary to:

- Inform the management (duty officer);
- Call the Emergency Service or the Ministry of Emergency Situations - tel. 112;
- Take measures to eliminate the accident in accordance with the instructions.[136]

20.7 Conclusions:

In this section about social responsibility the hazardous and harmful factors were revealed. All necessary safety measures and precaution to minimize probability of accidents and traumas during investigation are given.

Possible negative effects on environment were given in compact form describing main ecological problem of using nuclear energy.

It could be stated that with respect to all regulations and standards, investigation itself and object of investigation do not pose special risks to personnel, other equipment and environment.

21. Financial management, resource efficiency and resource saving.

The purpose of this section discusses the issues of competitiveness, resource efficiency and resource saving, as well as financial costs regarding the object of study of Master's thesis. Competitiveness analysis is carried out for this purpose. SWOT analysis helps to identify strengths, weaknesses, opportunities and threats associated with the project, and give an idea of working with them in each case. For the development of the project requires funds that go to the salaries of project participants and the necessary equipment, a complete list is given in the relevant section. The calculation of the resource efficiency indicator helps to make a final assessment of the technical decision on individual criteria and in general.

21.1. Competitiveness analysis of technical solutions:

In order to find sources of financing for the project, it is necessary, first, to determine the commercial value of the work. Analysis of competitive technical solutions in terms of resource efficiency and resource saving allows to evaluate the comparative effectiveness of scientific development. This analysis is advisable to carry out using an evaluation card.

First of all, it is necessary to analyze possible technical solutions and choose the best one based on the considered technical and economic criteria.

Evaluation map analysis presented in Table 1. The position of your research and competitors is evaluated for each indicator by you on a five-point scale, where 1 is the weakest position and 5 is the strongest. The weights of indicators determined by you in the amount should be 1. Analysis of competitive technical solutions is determined by the formula:

$$C = \sum W_i \cdot P_i,$$

C - the competitiveness of research or a competitor;

Wi– criterion weight;

Pi – point of i-th criteria.

VMAT: Volumetric modulated arc therapy.

BT: Brachytherapy.

Table (11) – Evaluation card for comparison of competitive technical solutions

Evaluation criteria	Criterion Weight	Points		Competitiveness Taking into account weight coefficients	
		P_{VMAT}	P_{BT}	C_{VMAT}	C_{BT}
Technical criteria for evaluating resource efficiency					
1. Risk of radiotherapy side effects	0.18	4	2	0.72	0.36
2. Dose homogeneity	0.13	5	2	0.65	0.26
3. Dose on organs at risk	0.2	4	2	0.8	0.4
4. Easy planning	0.14	3	5	0.42	0.7
5.Risk of treatment failure	0.1	3	5	0.3	0.5
Economic criteria for performance evaluation					
1. Competitive methods	0.08	5	5	0.4	0.4
2. Power application	0.07	5	5	0.35	0.35
3. Price	0.1	5	4	0.5	0.4
Total	1	34	30	4.14	3.37

21.2. SWOT analysis:

Complex analysis solution with the greatest competitiveness is carried out with the method of the SWOT analysis: Strengths, Weaknesses, Opportunities and Threats. The analysis has several stages. The first stage consists of describing the strengths and weaknesses of the project, identifying opportunities and threats to the project that have emerged or may appear in its external environment. The second stage consists of identifying the compatibility of the strengths and weaknesses of the project with the external environmental conditions. This compatibility or incompatibility should help to identify what strategic changes are needed.

Table (12) – SWOT Analysis.

	Strengths: S1.Increase dose to tumor lead to increase tumor control. S2. Short treatment time	**Weaknesses:** W1. Lack of necessary software in oncology clinics.
Opportunities: O1. Treatment of patients with cervical cancer. O2. Reduction in patient's treatment time	*Strategy which based on strengths and opportunities:* *1. Acceleration of the entire course of Radiotherapy.*	*Strategy which based on weaknesses and opportunities:* 1. Training of medical physicists to work with the inverse planning program
Threats: T1. Lack of commercial interest in the project due to the availability of other VMAT techniques.	*Strategy which based on strengths and threats:* 1. Calculation of biological effective dose (BED) and equivalent dose in 2 Gy/fr (EQD2) for VMAT boost and Brachytherapy boost	*Strategy which based on weaknesses and threats:* 1. Creation of a statistical database showing the comparison between VMAT boost and Brachytherapy boost.

21.3. Project Initiation

The initiation process group consists of processes that are performed to define a new project or a new phase of an existing one. In the initiation processes, the initial purpose and content are determined and the initial financial resources are fixed. The internal and external stakeholders of the project who will interact and influence the overall result of the research project are determined.

21.3.1. Stakeholders of the project

Table (13) – Stakeholders of the project

Project stakeholders	Stakeholder expectations
Russian oncological clinics and patients	Availability of Radiotherapy Equipment.
Medical Physicists	Create radiotherapy plans.
Oncologists	Approve radiotherapy plans.

21.3.2. Purpose and results of the Project

Table (14) – Project purposes and expected results

Purpose of project:	To compare between VMAT boost and Brachytherapy boost in treatment of cervical cancer.
Expected results of the project:	1. VMAT could be effective to replace Brachythrapy 2. VMAT allows a significant increase in the irradiation uniformity,
Criteria for acceptance of the project result:	1. maintenance dose to organs at risk within constraints
Requirements for the project result:	1. The project must be completed by June 1, 2020 of the year. 2. The results obtained must meet the acceptance criteria for

	the project result.

21.3.3. The organizational structure of the project.

Table (15) – The organizational structure of the project.

№	Participant	Role in the project	Functions	Labor time, hours.
1	Supervisor	Head of project	Consultations. Review master's dissertation.	528 hours
2	Master’s student	Executor	Writing master's dissertations. Compare between both techniques based on dose volume histogram. Calculate biological effective dose (BED) and equivalent dose in 2 Gy/fr (EQD2) for both techniques. Statistical analysis of data.	1350 hours

21.3.4. Project limitations

Table (16) – Project limitations.

Factors	Limitations / Assumptions
3.1. Project's budget	310000 rub
3.1.1. Source of financing	TPU
3.2. Project timeline:	22/07/2019 to 14/05/2020
3.2.1. Date of approval of plan of project	20/03/2020
3.2.2. Completion date	1/06/2020

21.3.5. Project Schedule

Table (17) – Project Schedule.

Job title	Duration, working days	Start date	Date of completion	Participants
General Technical supervision	**60 days**	22/07/2019	20/09/2019	Supervisor
Research and analysis of literature	**59 days**	21/09/2019	19/11/2019	Supervisor/ Student
Collection of cases and creating radiotherapy plans	**157 days**	20/11/2019	25/04/2020	Supervisor/ Student
Analysis and evaluation of results	**12 days**	26/04/2020	08/05/2020	Supervisor/ Student
Preparing of dissertation	**26 days**	09/05/2020	04/06/2020	Student

A Gantt chart is a type of bar chart that illustrates a project schedule. This chart lists the tasks to be performed on the vertical axis, and time intervals on the horizontal axis. The width of the horizontal bars in the graph shows the duration of each activity.

Table (11) – Gantt chart of Project Schedule

№	Activities	Participants	T_c, days	Duration of the project											
				July	August	September	October	November	December	January	February	March	April	May	June
1	General Technical supervision	Supervisor	60												
2	Research and analysis of literature	Supervisor / Student	59												
3	Collection of cases and creating radiotherapy plans	Supervisor / Student	157												
4	Analysis and evaluation of results	Supervisor / Student	12												
5	Preparing of dissertation	Student	26												

21.4. Scientific and technical research budget.

The amount of costs associated with the implementation of this work is the basis for the formation of the project budget. This budget will be presented as the lower limit of project costs when forming a contract with the customer.

To form the final cost value, all calculated costs for individual items related to the manager and the student are summed.

In the process of budgeting, the following grouping of costs by items is used:

- Material costs of scientific and technical research;
- Costs of special equipment for scientific work (Depreciation of equipment used for design);
- Basic salary;
- Additional salary;
- Labor tax;
- Overhead.

Name	Material costs	Costs of special equipment	Basic salary	Additional salary	labor tax	Overhead	Total cost
Cost, rubles	8,030	19,000	143,224	10,922	48,521	57,643	287,340

The budget for scientific and technical research is shown in table:

21.4.1. Calculation of material costs.

The calculation of material costs is carried out according to the formula:

$$C_m = (1 + k_T) \cdot \sum_{i=1}^{m} P_i \cdot N_{consi} \quad (2)$$

where m – the number of types of material resources consumed in the performance of scientific research;

N_{consi} – the amount of material resources of the i-th species planned to be used when performing scientific research (units, kg, m, m^2, etc.);

P_i – the acquisition price of a unit of the i-th type of material resources consumed (rub./units, rub./kg, rub./m, rub./m^2, etc.);

k_T – coefficient taking into account transportation costs.

Prices for material resources can be set according to data posted on relevant websites on the Internet by manufacturers (or supplier organizations).

Energy costs are calculated by the formula:

$$C = P_{el} \cdot P \cdot F_{eq} \qquad (3)$$

where P_{el} – power rates (5.8 rubles per 1 kWh);

P – power of equipment, kW;

F_{eq} – equipment usage time, hours.

Table (19) – Material Costs.

Name	Unit	Amount	Price per unit, rub.	Material costs, rub.
Electricity of computer	kWh	150	5.8	870
Papers		300	1	300
Printing on A4 sheet		400	4	1,600
Pen		3	150	450
Transportation and procuring expenses		100	21	2,100
Internet	Month	5	1000	5,000
Total				10,320

21.4.2. Cost of special equipment.

Equipment was not specifically purchased for this work, therefore, it is necessary to calculate costs associated with this special equipment (devices and mechanisms

fixation, special Software necessary to carry out work for example in this work Monaco Treatment Planning System (TPS)) all of those cost about 15,000.

21.5. Basic salary.

This point includes the basic salary of participants directly involved in the implementation of work on this research. The value of salary costs is determined based on the labor intensity of the work performed and the current salary system.

The basic salary (S_b) is calculated according to the following formula:

$$S_b = S_a \cdot T_w \quad (4)$$

where S_b – basic salary per participant;

T_w – the duration of the work performed by the scientific and technical worker, working days;

S_a - the average daily salary of participant, rub.

The average daily salary is calculated by the formula:

$$S_a = S_m \cdot M / F_v \quad (5)$$

where S_m – monthly salary of an participant, rub .;

M – the number of months of work without leave during the year:
at holiday in 48 days, M = 11.2 months, 6 day per week;

$F_{\text{в}}$ – valid annual fund of working time of scientific and technical personnel (251 days).

Table (20) – The valid annual fund of working time

Working time indicators	
Calendar number of days	365
The number of non-working days - weekend - holidays	 52 14
Loss of working time - vacation - sick absence	 48
The valid annual fund of working time	251

Monthly salary is calculated by formula:

$$S_{month} = S_{base} \cdot (k_{premium} + k_{bonus}) \cdot k_{reg} \quad (6)$$

where S_{base} – base salary, rubles;

$k_{premium}$ – premium rate;

k_{bonus} – bonus rate;

k_{reg} – regional rate.

21.5.1. Supervisor base salary.

The basic salary of the supervisor is calculated on the basis of the sectoral labor payment. The sectoral wage system in TPU assumes the following composition of wages. The salary is determined by the enterprise.

In TPU, salaries are distributed in accordance with the positions held. The head of this research work is an employee with the position of an associate professor The salary of the senior teacher is 35120 rubles.

The wage increments are 10000 rubles (surcharges of the academic council), and the district coefficient for Tomsk Region is 1.3.

Basic Salary of Supervisor: 35,120 *1.3 = 45,656 rub

(45,500 * 10.4)/251 = 1,891.7 rub/day

In total of days: 1,891.7 rub/day * 288 days = 544,809.6 rub

21.5.2. Master student salary.

Since master student basic salary is 17,310

Basic Salary of master student: 17,310*1.3 = 22,503 rub

(22,503 *10.4)/251 = 932.4 rub/day

In total of days: 932.4 rub/day * 254 days = 236,829.6 rub

Table (21) – Calculation of basic salary.

Participant	Basic salary, rubles
Head of project	544,809.6
Student	236,829.6
Total	781,639.2

21.5.3. Additional salary.

This point includes the amount of payments stipulated by the legislation on labor, for example, payment of regular and additional holidays; payment of time associated with state and public duties; payment for work experience, etc.

Additional salaries are calculated on the basis of 10-15% of the base salary of workers:

$$W_{add} = k_{extra} \cdot W_{base} \quad (7)$$

where W_{add} – additional salary, rubles;

k_{extra} – additional salary coefficient (10%);

W_{base} – base salary, rubles.

Table (22) – Calculation of Additional Salary.

	Supervisor	Master student
Basic salary, rub/month	544,809.6	236,829.6
Additional salary, rub	54,481	23,683
Total	78,164	

21.5.4. Labor tax.

Tax to extra-budgetary funds are compulsory according to the norms established by the legislation of the Russian Federation to the state social insurance (SIF), pension fund (PF) and medical insurance (FCMIF) from the costs of workers.

Payment to extra-budgetary funds is determined of the formula:

$$P_{social} = k_b \cdot (W_{base} + W_{add}) \quad (8)$$

where k_b – coefficient of deductions for labor tax.

In accordance with the Federal law of July 24, 2009 No. 212-FL, the amount of insurance contributions is set at 30%. Institutions conducting educational and scientific activities have rate - 27.1%.

Table (23) – Calculation of Labor tax.

	Supervisor	**Master student**
Coefficient of deductions	27.1%	
Salary, rubles	544,809.6	236,829.6
Labor tax, rubles	147,643.4	64,180.8
Total	211,824.2	

21.5.5. Overhead costs.

Overhead costs include other management and maintenance costs that can be allocated directly to the project. In addition, this includes expenses for the

maintenance, operation and repair of equipment, production tools and equipment, buildings, structures, etc.

Overhead costs account from 30% to 90% of the amount of base and additional salary of employees.

Overhead is calculated according to the formula:

$$C_{ov} = k_{ov} \cdot (W_{base} + W_{add}) \quad (9)$$

where k_{ov} – overhead rate.

Table (24) – Calculation of Overhead

	Supervisor	**Master student**
Overhead rate	30%	
Salary, rubles	544,809.6	236,829.6
Overhead, rubles	326,885.8	71,048.9
Total	397,934.7	

21.5.6. Formation of budget costs.

The calculated cost of research is the basis for budgeting project costs.

Determining the budget for the scientific research is given in the table.

Table (25) – Budget for scientific and technical research.

	Name	**Cost, rubles**
1.	Material costs	10,320
2.	Costs of special equipment	15,000
3.	Basic salary	781,639.2

4.	Additional salary	78,164
5.	Labor tax	211,824.2
6.	Overhead	397,934.7
Total planned cost		1,494,882.1

21.6. Conclusion

Thus, in this section was developed stages for design and create competitive development that meet the requirements in the field of resource efficiency and resource saving.

These stages includes:

- Development of a common economic project idea, formation of a project concept;
- Organization of work on a research project;
- Identification of possible research alternatives;
- Research planning;
- Assessing the commercial potential and prospects of scientific research from the standpoint of resource efficiency and resource saving;
- Determination of resource (resource saving), financial, budget, social and economic efficiency of the project.

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List of abbreviations

ABS: Acrylonitrile butadiene styrene
AJCC: The American Joint Committee on Cancer
BED: Biological effective dose
CCRT: Concurrent-chemo-radiotherapy
CEA: Carcino-embyrionc antigen
CIN: Cervical intraepithelial neoplasia
CIS: Carcinoma in situ
CR: Complete response
CT: Computed tomography
CTV: Clinical target volume
EBRT: External beam radiation therapy
EGFR: Epidermal Growth Factor
EQD2: Equivalent dose in 2 Gy/fr
EUA: Pelvic examination under anesthesia
FDA: The Food and Drug Administration
FIGO: The International Federation of Gynecology and obstetrics
GOG: The Gynecologic Oncology Group
HDR-BT: High dose rate brachytherapy
HIV: Human immunodeficiency virus
HPV: Human papilloma virus
IMRT: Intensity modulated radiation therapy
IV: Intravenous
IVP: Intravenous pyelogram
LACC: Locally advanced cervical cancer
LDR-BT: Low dose rate brachytherapy
LEEP: Loop electrosurgical excision procedure
LNs: Lymph nodes
LVI: lympho-vascular invasion
MDR-BT: Medium dose rate brachytherapy
MLCs: Multileaf collimators
MRI: Magnetic resonance imaging
NACT: Neoadjuvant chemotherapy
OARs: Organs at risk
OS: Overall survival
PDR-BT: Pulsed dose rate brachytherapy
PET/CT: Combined Positron emission tomography/computed tomography
PFS: Progression free survival

PTV: Planned target volume
P/V: Per Vaginal examination
P/R: Per Rectal examination
RT: Radiotherapy
SCC Ag: Squamous cell carcinoma antigen
SD: Standard deviation
SIL: Squamous intraepithelial lesion
TKIs: Tyrosine kinase inhibitors
VBC: Vacuum bag cushion
VEGF: Vascular endothelial growth factor
VMAT: Volumetric arc therapy
3DCRT: Three-dimensional conformal radiotherapy
5-FU: 5-fluorouracil

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