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THE DEVELOPMENT OF GYNECOLOGICAL RADIOTHERAPY/ONCOLOGY IN SWEDEN

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The development of gynecological radiotherapy and oncology during this century has changed the methods of diagnosis and treatment of cancer and given better results. From the beginning the gynecologist could only palpate and inspect. Later on roentgen examination was introduced and later still microscopic diagnosis, more advanced diagnostic methods, e.g. endoscopy, ultrasound, isotope examination, advanced microscopic diagnosis and computerized tomography. In parallel with the development in diagnosis, treatment has developed. To start with surgery was the only method available. Later on intracavitary radiation, low energy radiation, endocrine therapy, chemotherapy and high energy treatment became available along with some experimental therapies. Today we have a broad range of therapeutic tools to use. In the future we might use profylaxis more than we do today to prevent cancer and when cancer is already there we might enhance the immune defence or introduce specific immunotherapy with clonal antibodies, specially made for the actual tumour, and consequently surgery, radiotherapy and chemotherapy will be often less used.

It is, of course, impossible in a short paper to review fully the development of gynecological radiotherapy/oncology in Sweden. The following is a short review based on my personal selection of some important and interesting developments in the field of gynecological radiotherapy/oncology, especially treatment of cancer of the cervix uteri (1).

Radium treatment

Soon after the discovery of x-rays by Roentgen in 1895 and of radium by Marie Curie in 1898 a fascinating development in radiotherapy started. Dr. Gösta Forsell—radiologist—and dr. Johan Berg—surgeon—in Stockholm started in October 1910 the first small clinic for radiotherapy in an apartment house. It was named Radiumhemmet and had 16 beds; 10 for females and 6 for males. It was equipped with one roentgen apparatus and 120 mg of radium divided into 11 applicators for intracavitary radiation (2).

It soon became obvious that radiotherapy could not be handled on one hand in the whole field of radiotherapy. The service was therefore divided into a general department where Elis Berven was the pioneer and a gynecological department where James Heyman developed the methods. Later on Hans-Ludvig Kottmeier continued to develop methods for the treatment of gynecological cancer by radiotherapy and extended his activities to the international field working for standardized treatment methods and for an internationally accepted staging of gynecological cancer. See below.

When radiotherapy was first used in gynecology the equipment was very primitive. Radiation protection was undeveloped and radiophysics was new. Rolf Sievert, professor of radiophysics, was a pioneer in the development of radiophysics as means to understanding of radiotherapy and in radiation protection. After some decades radiation protection during radium application was fully developed. (3, 4).

Intracavitary radiation of different kinds of cancer of the uterus has been diversified and developed in many

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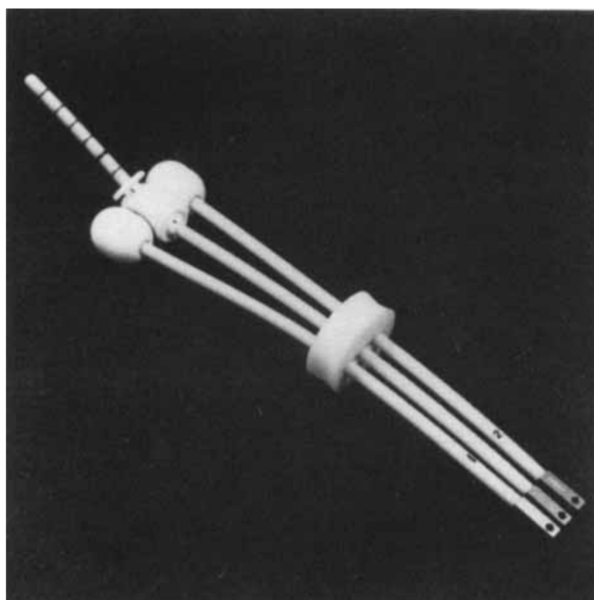

Fig. 1. Amersham System plastic applicators with source trains in position in uterine tube and both vaginal ovoids.

ways. Today we have at our disposal a variety of methods for this treatment. A new kind of intracavitary radiation technique has been developed, first in England and later on in the Nordic countries, namely the afterloading technique. This technique was initiated not to obtain better treatment results, but to improve radiation protection. Different types of applicators can be used. See fig. 1. The applicators are put in place and fixed in the treatment position. The applicators could then be loaded afterwards—mostly with ^{137}Cs -, either manually or by remote control. Treatment with the afterloading system can be given with a high-intensity or low-intensity technique. A variety of systems for the afterloading treatment technique have been developed over the last 20 years. There are still many difficult radiobiological problems involved in this treatment technique given with high dose-rate as the dose is given within a short time. The intestines in the pelvis do not change position during the short treatment time as they do during ordinary radium treatment over a longer time. The dose–time relationship is also altered. There are wide new fields to be explored in this intriguing radiobiological problem. This treatment technique has not yet been fully developed.

External radiation

The original radium treatment method for cancer of the cervix at Radiumhemmet was after some years—in 1929—completed with external radiation to achieve a better dose distribution to different parts of the pelvis. For this type of treatment orthovoltage roentgen rays of approximately 200 KV was used. This roentgen quality has many drawbacks; it had its greatest effect on the skin, the depth dose was low and the absorption in the bone pelvis was high.

The introduction of the teleradium treatment method made the megavoltage technique available. There were, however, many obstacles since radium was very expensive and only small amounts could be placed in the teleradium unit for teletherapy. Thus, only small fields and short treatment distances could be used. No significant development in the treatment of gynecological cancer was achieved by this apparatus.

A most essential step forward came with the introduction of kilocurie telecobalt units, using radioactive ^{60}Co, which had a half-life of 5.3 years and emits two gamma-quanta of approximately 1 MV. A good treatment effect over large fields with long treatment distances, giving better depth doses, could be achieved with these telecobalt unites and a much more adequate dose could be directed to different parts of the pelvis. The radiation from ^{60}Co shows no increased absorption in the bone pelvis, its dose maximum lying beneath the skin, and therefore no skin reactions occurred. One drawback with the cobalt unit is that the radioactive source has such dimensions that penumbra problems appeared. The relatively short half-life of 5.3 years constantly extended the treatment time to give the same dose.

Another significant achievement was the introduction of electronic treatment machines, such as the linear accelerator. In this machine electrons are accelerated on a radiofrequent wave guide to a velocity corresponding to an energy of 4 or 6 MV. These energized electrons are then used to generate megavoltage roentgen rays. This type of treatment machine has considerable advantages over the cobalt unit. The photon energy is higher, there are no penumbra problems as the generation focus is very small, and the treatment time is very short.

A further development was achieved with the introduction of the betatron to give either high energetic electrons or high energy roentgen rays for treatment. The electron beam has the advantage of being monoenergetic, which means that the penetration depth is limited and after a certain depth there is no activity left. The depth of activity depends on the electron energy. The use of electron beams is indicated in the treatment of tumours close to vital structures that must not be irradiated or as a part in a dose planning to achieve a proper dose distribution around the tumour area. Roentgen rays from betatrons are available with energies up to 40 MV. Energies higher than 40 MV are seldom used because of the radiation effect in the exit field on the back of the patient.

Electronic treatment machines of today are more advanced then the betatrons from the 1960s. Now the most convenient generator is the microtron and the racetrac-microtrone. Very large fields with a homogenous dose throughout the field can be achieved with the microtrones. They also have a high dose-rate and a short treatment time. The photon energy is approximately 20–40 MV.

Dose planning technique

The rapid development of gynecological radiotherapy has brought new and difficult problems. The extremely penetrating roentgen rays which nowadays can be produced for tumour treatment create new problems for dose planning as vital organs and structures must not be irradiated beyond their dose tolerance. This has created a need for careful dose planning by simulating the treatment situation and to make dose distribution diagrams of the tumour area and its surroundings. This was earlier done manually and was very time-consuming.

Computer technique has revolutionized the dose planning technique. Today we use computed tomography to obtain a detailed anatomical picture of the treatment area. The tumour area is indicated on the CT-scan and a computer will then apply different dose-diagrams, depth dose curves, field arrangements, and so on to the computerized picture of the tumour and its surroundings and in a few seconds the optimal arrangement of the treatment fields, their size and the qualities of the irradiation can be calculated by the computer, and a dose distribution diagram of the tumour and its surroundings will be drawn. What previously took one or two days to accomplish by manual examination can today be done by the computer in a few seconds. This represents a fascinating development in an important area of radiotherapy.

Enhancement technique

Today another type of development of radiotherapy has opened up, namely enhancing the effect of radiation by chemotherapy or by changing the radiosensitivity of the tissue, especially the tumour, by means of different kinds of chemicals. We also have another line of developments using different kinds of rays, for instance heavy particles and neutrons. Irradiation with neutrons opens up a new field as the effect of neutron beams is not oxygen-dependent in the same way as are roentgen rays. The low oxygen tension in tumours is an important problem in radiation treatment. Many of the more advanced tumours have necrotic areas in the center and a low oxygen tension, which increases their resistance to radiation. Using new kinds of irradiation beams or enhancing the radiosensitivity to roentgen rays might lead to better results in treating necrotic and advanced tumours.

Isotope technique

Development in the field of diagnostic radiology have presented us with new possibilities for the study and surveillance of tumour patients using the isotope technique. Today we can study the function of the kidneys and the flow through the ureters using the renographic technique. With the scintigraphic technique we can detect metastases in the bones, liver, brain, and so on. We can also use the isotope technique to study the effect of irradiation. Using bone marrow scintigrams it is possible to illustrate what 40 Gy in the pelvis where treating some gynecological tumours will do to the bone marrow. The active bone marrow in the lumbar region and the pelvis disappears and new bone marrow will be activated in the long bones. This explains why a combination of intense radiation of large bone marrow areas and chemotherapy can easily give rise to bone marrow depression.

Surgery

Surgical treatment of gynecological cancer has a long history. When radiotherapy was fast developing, surgical procedures became less popular, but when modern anaesthesia, parenteral nutrition and antibiotics and so on became available, surgery was further developed in the field of gynecological cancer. A new stage in surgical treatment of cancer of the cervix was initiated by professor Joe Vincent Meigs at Harvard Medical School in Boston in the beginning of the 1950s. Many Scandinavian gynecologists - like myself - studied with Dr Meigs to learn the technique of an advanced surgical attack on cancer of the cervix.

Not all cervical cancer patients can be treated surgically. For a successful surgical result the tumour should be in an early stage and not necrotic or infected. With a tumour, growing in the lateral parts of the pelvis, surgical treatment is not optimal. The more radical an operation, the better the results, but the complication risk will also be greater, especially with fistulation and lymphodema.

The 5-year survival rate after surgical treatment of selected early cases of cancer of the cervix without lymph node metastases is in the same order as in unselected radiologically treated cases. When the lymph nodes in the pelvis are involved the results after surgery will be poor. These facts indicate a combination of radiotherapy and surgery in some cases. In young patients with early tumours and without demonstrable lymph node metastases the ovaries can be saved.

Clinical staging

The clinical staging of cervical cancer has changed over the last few decades, indicating the interest in early diagnosis. Swedish initiative have been dominant in this field.

In 1929, the League of Nations introduced a clinical staging in which stage I was defined as cancer confined to the cervix at clinical examination. This staging remained valid until 1950, when a new classification was made, introducing stage 0 as cancer in situ of the cervical epithelium. Stage I then indicated that the tumour was invasive and confined to the cervix.

In 1961, FIGO agreed on a new, more detailed staging. Stage I was divided into stage IA, defined as 'early stromal

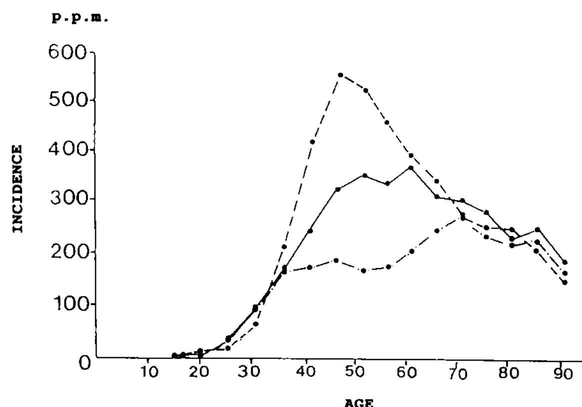

Fig. 2. Age-specific incidence of cancer of the uterine cervix in Sweden at various periods of time. --- 1958–1967 (n = 8744); —— 1968–1976 (n = 6607); ·–·– 1977–1984 (n = 5165).

invasion' and stage IB covering the rest of the cases allotted to stage I.

In 1970 FIGO introduced a one-step further development in staging early stages of cancer of the cervix. Stage 0 was as previously preinvasive cancer, stage I was split into subclinical cancer divided into IA either 'early stromal invasion' or 'occult cancer' and stage IB, covering the rest of cases allotted to stage I. In 1976 a new FIGO classification was introduced where 'occult cancer' was allotted to stage IB and marked 'occult'.

'Early stromal invasion' has never been well defined. The thickness of the epithelium is approximately 0.25 mm and 5 mm is half the cervical wall. In 1991 FIGO divided stage IA into IA1 = minimal microscopic stromal invasion and IA2 = obvious invasion but less then 5 mm.

The incidence of lymph node metastases in so-called microinvasive cancer is about 1.5% at an invasion of between 1 and 5 mm. Below 1 mm metastases are rarely seen, but when the invasion is more than 5 mm the rate of metastases increases rapidly. It might therefore be logical to use 'minor treatment' when the invasion is below 1 mm but when the invasion exceeds 1 mm the indication for 'major treatment' increases with the depth of the invasion. The death rate from cancer of the cervix with microinvasion less than 5 mm is below 1%.

Early diagnosis

Various examination methods have been used to arrive at an early diagnosis of cervical cancer. Colposcopy, which has been an essential method, was originally developed in Germany and introduced in Sweden in the 1950s. Exfoliated cytology was also introduced in the 1950s for early diagnosis of cervical cancer. The first laboratories in Sweden were founded in Gothenburg and Stockholm. The cytological technique was used in mass screening for early detection of cervical cancer. The screening program was started in the southern part of Sweden in the middle of the 1960s and is now nation-wide.

The age-specific incidence of cervical cancer at various periods is illustrated in Fig. 2, showing the incidence before and after one and two decades after the introduction of the screening program. The peak incidence in the age group 40–50 years has been considerably decreased. Among the female population below 50 years of age the mortality rate of cervical cancer in the population has fallen rapidly since the screening program was started.

Cancer in situ

The mass screening program has led to a large increase in the diagnosis of so-called cancer in situ of the cervix. This condition is poorly understood. From an epidemiological point of view eight out of nine cases cannot be of neoplastic origin.. The diagnostic tools available cannot, however, distinguish between real neoplastic carcinoma in situ and non-neoplastic lesions. This is a dilemma, meaning that we have to treat all cases, because we cannot distinguish the neoplastic lesions from the others. Today different methods for treatment of 'cervical intraepithelial neoplasia' are available. Extirpation methods are competing with destruction methods and laser evaporation is getting more and more popular.

Fine-needle aspiration cytology

Fine-needle aspiration cytology has been frequently used for interpreting tumours in the pelvis and in lymph nodes. This method was developed in Sweden (5) and today it is a very useful and reliable method for deciding whether tumours in the pelvis and swelling of the lymph nodes are neoplastic or not and for typing of malignant tumours.

Fig. 3. Gösta Forssell

The Swedish pioneers

Gösta Forssell (1876–1950) created the Radiumhemmet and was its director between 1910 and 1926 (6). He was professor of Medical Radiology from 1917 to 1936. In 1936 the professorship was divided into roentgen diagnosis and radiotherapy and, Forssell then turned to roentgen diagnosis. In 1912 and 1914 respectively Forsell published his first reports on radium treatment of cancer of the cervix. (Fig. 3).

James Heyman (1882–1956) came to the Radiumhemmet in 1914 (7). From 1916 he was responsible for the gynecological service. He was appointed director of the gynecological service in 1937. Heyman was trained in pathology, surgery and in obstetrics and gynecology. His interest was early focused on radiotherapy and he was appointed professor in 1938. (Fig. 4).

Heyman's first report on the treatment of cancer of the uterine cervix was published in 1915, and during the following years he developed this methods. His very important contribution 'The Stockholm method in radiotherapy of uterine cancer' was published in J Obst Gynecol Br Emp 1924, 31: 1–19. The Stockholm method was characterized as an 'intensive, intermittent and intracavitary radium treatment method'. From 1929 the radium treatment was completed with external radiation for better dose distribution throughout the pelvis.

At the Second International Congress of Radiology in 1928 Heyman described his methods of treatment for uterine cancer. This was a turning point. From this time on radiotherapy was the dominating therapeutic method used in the treatment of cancer of the cervix. However, in the 1950s surgery was reintroduced, as previously mentioned.

Heyman, together with Benner—radiophysisist—and Reuterwall—radiopathologist—, in 1941 developed the 'Heyman radium packing method' for treatment of cancer of the endometrium.

The League of Nations in 1928 set up a 'Sub-Commission' for the study of results of radiotherapy and for creating a staging system for cancer of the uterus to make comparisons of treatment results with different methods possible. Heyman was appointed chairman. This 'Sub-Commission' began publishing the 'Annual Report'. See below.

In 1938, Heyman together with Magnus Strandqvist, published the very important 'Atlas ', where the different stages of cancer of the cervix were described and depicted.

From the early 1940s Heyman was responsible for the education of students at the Karolinska Institute as far as gynecological cancer and its treatment was concerned. Under the guidance of Heyman the gynecological department at the Radiumhemmet was the leading institution of its field. Gynecologists and radiotherapists from all over the world came to him to listen and learn.

Hans-Ludvig Kottmeier (1903–1982) succeeded James Heyman as chief of the gynecological department at the Radiumhemmet in 1948, when Heyman retired (8). He was trained in surgery and in obstetrics and gynecology and had long experience in radiotherapy and oncology. He worked at the Radiumhemmet in 1933, and from 1938 to 1971, when he retired. (Fig. 5).

Kottmeier continued to develop the treatment methods that Heyman had introduced. He was masterly in his way to individualize the methods to fit the different patients and their tumours. He described the Stockholm method in detail in many scientific papers and textbooks as well as in many popular ones. In 1956 he was chief editor of the 'Annual Report on results of treatments of cancer of the uterus' started by Heyman in 1928. In 1956, 105 leading

Fig. 4. James Heyman

Fig. 5. Hans-Ludvig Kottmeier

institutions all over the world reported their results to the 'Annual Report'. In 1958 a 'Cancer Committee' of the international federation of gynecology (FIGO) took over the responsibility of this publication with Kottmeier as chairman until 1973. He was a devoted and very much appreciated editor of this publication , which enabled him to develop his international contacts and make the gynecological department of the Radiumhemmet to the worlds 'Mecca' of its field.

The cancer patient

Treatment of gynecological cancer is achieved not only by sophisticated machines and potent chemicals but there are also other dimensions, involving care of the sick person in which caring, love and understanding play an essential part. Gynecological cancer is not only a cancer disease, it is also a hazard to fertility in most patients. Knowledge about crises, their development and treatment has provided us with better understanding of the difficult situation of the cancer patient, especially those terminally ill. Being told that one has an incurable or severe disease gives rise to a series of reactions, starting with shock, followed by denial, aggression, depression, discussing and finally acceptance, where hope is a shrinking frame of reference during the events of the development of the disease. Knowledge there about is essential if we are to be able to handle cancer patients or severely sick or dying patients.

The cancer issue

Developments in the field of oncology have changed our understanding of cancer during the last century from an understanding at the level of organs, through the level of tissue down to the level of cells. Today we have started on the chromosomal understanding of cancer and are entering the molecular-biological aspects.

Microbiology and genetics have opened up new doors to an understanding of cancer. We now better understand how cancer agents initiate the cancer degeneration process. We are beginning to understand how ionizing radiation and chemicals interact with the DNA at a chromosomal level, for instance by transposing some part of one chromosome to another, where a fragment with oncogens is placed in a different milieu with another activity and may therefore be activated and play there parts in the cell. We are now understanding how viruses can initiate cancer in different ways. It has been shown that HPV 16 and 18 are closely connected with cancer evolution in the uterine cervix. This can explain the epidemiology of cancer of the cervix as a sexually transmitted disease (9).

Furthermore we have seen that metabolites from nicotine is concentrated 50-fold in the cervical mucus from the plasma. This can explain the enhancing factor of smoking in the epidemiology of cancer of the cervix (10).

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