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Radiotherapy of squamous cell cancer metastases from unknown primary site to neck lymph nodes

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Aim. Metastases to neck lymph nodes are frequently the first symptoms of cancers arising in head and neck anatomical region (30-40%). In a some of those cases (c. 5%) the primary site remains unknown. The aim of this paper was to evaluate results of radiotherapy for neck lymph nodes metastases from an unknown primary site.
Material and methods. Thirty six patients with squamous cell carcinoma cervical nodes metastases from unknown primary site were treated between 1980-1995 in the Maria Skłodowska-Curie Memorial Institute of Oncology in Gliwice. Eighteen patients (50%) underwent combined therapy (surgery with postoperative radiotherapy), 16 (44.5%) underwent radiotherapy alone and only 2 patients were treated with surgery alone. Surgical treatment consisted of tumorectomy (90%), only 10% of patients underwent uni-or bilateral radical lymph node dissection. Total radiation doses for radiotherapy alone ranged from 30 Gy to 76 Gy, and postoperatively – from 20 Gy to 60 Gy.
Results. 3-years disease free survival (DFS) rates were 45% in combined treatment group and 20% in group receiving radiation therapy alone (p=0.028). After a median follow up of 39 months, 10 primary tumours were discovered – 8 in head and neck regio and 2 in lower respiratory tracts. 3-years DFS rate in group with discovered primary tumours was 46%, while other patients – 33% of 3 years DFS.
Conclusions. Our results suggest the need for complementary, elective irradiation of the neck lymph nodes, as well as the entire pharynx, postoperatively.

Ocena skuteczności leczenia promieniami przerzutów raka płaskonabłonkowego z nieznanego ogniska pierwotnego do węzłów chłonnych szyi

Wprowadzenie. Przerzuty do węzłów chłonnych szyi są często pierwszym objawem nowotworów rozwijających się w tym regionie anatomicznym (30-40%). Znajomość topografii spływu chłonki z narządów regionu głowy i szyi, jak i klinicznych objawów guzów, rozwijających się w tym regionie anatomicznym, jak i nowotworów o innych lokalizacjach, znacznie ułatwia wykrycie ogniska pierwotnego raka. Jednakże w niewielkim odsetku przypadków (około 5% wszystkich rozpoznań przerzutów do węzłów chłonnych), pomimo przeprowadzonej dokładnej diagnostyki, niemożliwe jest znalezienie ogniska pierwotnego. Celem niniejszej pracy była ocena wyników radioterapii w takich przypadkach.
Materiał i metody. Analizie poddano grupę 36 chorych, leczonych w Instytucie Onkologii w Gliwicach w latach 1980--1995, z powodu przerzutów raka płaskonabłonkowego do węzłów chłonnych szyi z nieznanego ogniska pierwotnego. Pierwszym objawem choroby w grupie 33 mężczyzn i 3 kobiet w wieku od 26 do 85 lat (mediana 56,5) były powiększone węzły chłonne szyi. U 18 (50%) chorych zastosowano skojarzoną metodę leczenia (chirurgia z poooperacyjną radioterapią), 16 (44,5%) leczonych było samodzielnym napromienianiem. Jedynie u dwóch chorych wykonano wyłącznie zabieg operacyjny. W większości przypadków leczenie chirurgiczne polegało na wyłuszczeniu guza (90%), jedynie u 10% chorych leczonych operacyjnie wykonano jedno- lub obustronne usunięcie układu chłonnego szyi. Całkowite dawki w przypadku samodzielnej radioterapii wyniosły od 30 Gy do 76 Gy, w przypadku pooperacyjnej – od 20 Gy do 60 Gy.
Wyniki. Odsetek 3 letniego przeżycia bezobjawowego w grupie leczonych metodą skojarzoną wyniósł 45%, a w grupie leczonych samodzielną radioterapią 20% (p=0,028). W 10 przypadkach, po średnim okresie obserwacji 39 miesięcy, nastąpiło ujawnienie się ogniska pierwotnego – w 8 przypadkach w regonie głowy i szyi, w 2 – w obrębie dolnych dróg oddechowych. Przeżycie bezobjawowe w grupie chorych z ujawnionym guzem pierwotnym wyniosło 46%, w porównaniu do pozostałych chorych – 33% trzyletnich przeżyć bezobjawowych.

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Podsumowanie. Przedstawiona analiza wyników leczenia chorych na zespół CUP pośrednio wskazuje na konieczność elektywnego, pooperacyjnego napromieniania zarówno całego układu chłonnego szyi, jak i błon śluzowych trzech pięter gardła i krtani po radykalnym chirurgicznym usunięciu przerzutowo zmienionych węzłów chłonnych.

Key words: head and neck lymph nodes metastases, CUP-syndrome, unknown primary site, radiotherapy
Słowa kluczowe: przerzuty do węzłów chłonnych, zespół CUP, nieznane ognisko pierwotne, radioterapia

Head and neck node metastases are frequently the first symptoms of cancers arising in this anatomical region (30-40%) [1-3, 6]. Discovering in physical examination enlarged neck nodes, and then confirmation of malignant disease by biopsy or histopathological examination of dissected node suggests that occult primary site is located within mucosal membrane of upper respiratory, alimentary tracts or systematic disease (lymphoma). Knowledge of head and neck region lymphatic drainage and clinical presentation of tumours arising in this region as well as cancers of others localisation, makes finding of primary site easier. However there is often a need of more advanced diagnostical workup especially endoscopies and modern imaging procedures.

There is a high probability of occult infiltration of pharyngeal mucosal membrane if squamous cell cancer neck nodes metastases are diagnosed. There are some regions difficult to approach during routine laryngeal examination: Rosenmüller fossa and the roof of nasopharynx, base of the tongue and basal part of tonsil in the middle pharynx, pyriform sinuses and postcricoid area in hypopharynx, and laryngeal vestibules. Each of them is frequently the „silent" location of arising tumour. Thus in such clinical situations in many laryngological and oncological centres modern diagnostic methods are conducted (ie. rhinopharygoscopy with elective biopsy, spiral computer tomography and/or magnetic resonance of pharynx, parapharyngeal spaces and base of the skull, elective dissection of soft palate tonsil ipsilateral to the involved nodes), which frequently discover the occult primary site of tumour. However in a small proportion of all cases (about 5% of all head and neck diagnosed metastases), primary site can not be discovered, in spite of conducting all diagnostic procedures [1-4, 6]. In such clinical situations individual indication to oncological treatment should be considered and the optimal therapeutic strategies should be undertaken.

As far, there is no generally acceptable schedules of treatment of patients with squamous cell carcinoma dissemination to the lymphatic nodes of head and neck. Although the necessity of involved lymphatic nodes dissection is beyond the doubt [1-6], still several methods of elective or adjuvant treatment are discussed [1, 2, 5-8].

Since the end of eighties, in Maria Sklodowska-Curie Memorial Institute of Oncology in Gliwice elective radiotherapy after surgical dissection of metastatic nodes in cases of cancer of unknown primary site (CUP-syndrome) is used. This treatment is conducted as conventional irradiation of whole head, neck and supraclavicular lymphatic nodes, surgically removed nodal bed and mucosal membrane of whole pharynx, from the base of the skull to the end of upper part of oesophagus with a total dose of 50-54 Gy given in 25-30 fractions, with eventual dose escalation to the involved nodal bed and/or clinically „suspected" regions of pharynx.

The aim of this work was to evaluate the results of treatment of patients with squamous cell cancer head and neck lymphatic nodes metastases from unknown primary site treated in Institute of Oncology in Gliwice, as well as the trial to estimate the kinetics of primary tumour site occurring.

Material

Thirty six patients – 33 man and 3 woman with head and neck lymphatic nodes squamous cell cancer metastases treated between 1980-95 in Centre of Oncology-Institute in Gliwice were involved in this study. Median age in group of male was 56 years, in group of females 57 years (range 27-85 years). All patients were in good or very good general condition (according to ZUBROD scale: 0-1). Median haemoglobin level was in male and female group 13,8mg/dl and 13mg/dl respectively.

In all cases the first symptom of disease were enlarged lymphatic nodes of head and neck region. Time from occurring the first sign of cancer to the first examination by a specialist ranged from one week to 12 months (median 3 months).

Analysis of topography of involved lymphatic nodes was performed using the Lindberg nomenclature, which identifies groups of deep neck nodes: para- and retropharyngeal nodes, and superficial: submental and submandibular, upper, middle and lower level in anterior and posterior chain in relation to sternocleidomastoid muscle.

The most frequent metastases were in upper anterior neck nodes -16 cases (44.5%). Metastases to the middle and lower anterior nodes occurred in 7 (19.5%) and 5 (14%) cases respectively. Single metastases were observed in 28 patients (78%), multiple (to at least two nodes) in 8 cases (22%) (ipsilateral in 5 cases (14%), contralateral – in 3 8%). In all cases primary tumour was unknown and T-stage was indicated as Tx. There were10 cases(28%) in N1 stage, 9 (25%) in N2, 16(45%) in N3. In one patient N stage could have not been estimated. (Tab. I) Combined treatment was performed in 18 patients (50%), but only in 15 of them (41.5%) with radical intention. With radiotherapy alone 16 patients (44.5%) were treated, from whom 10 with radical intention (28%). Only in two cases (5.5%) surgery alone were performed. In general, surgical treatment consisted of tumorectomy (90%), only 10% of patients treated with surgery underwent uni-or bilateral lymphadenactomy (Tab. II)

Irradiation of whole pharynx and regional lymphatic nodes – 2 opposed fields extended from base of the skull to the upper margin of thyroid gland and fields encompassing the supraclavicular lymphatic nodes was used in 13 patients (36%) treated with irradiation. In remaining patients other radiotherapy techniques were used: portals limited to the involved nodes or nodal bed, or fields encompassing only one side of the neck. Radiotherapy was performed using γ Co60 irradiation. Posterior neck nodes after spinal cord exclusion (after median dose 46 Gy) were irradiated with 9 MeV electrons. Supraclavicular lymphatic nodes were irradiated with γ Co60 photons to the total dose 50 Gy. Total doses ranged from 30 Gy to 76 Gy, but in cases when radiotherapy was combined with surgery- from 20 Gy to 60 Gy.

Tab. I. Clinical stage of involved lymphatic nodes

Clinical stage	Lymph node's diameter (cm)	number of patients
N1	1-2	2
	>2	8
N2	<4	6
	4-5	1
	>5	2
N3	<8	4
	8-10	7
	>10	5
NX	-	1

Tab. II. Treatment modalities and early results

	Treatment		
	OP+RT	RT	OP
No. of patients	18 (50.0%)	16 (44.5%)	2 (5.5%)
Surgery type			
tumorectomia	16 (44.0%)	-	
limfadenectomia	2 (5.5%)	-	
Technique of RT:			
neck lymphatic system+pharnyx	7 (19.5%)	6 (16.5%)	-
tumor bed/tumor	11 (30.5%)	10 (28.0%)	-
Total dose of RT:			
20-40 Gy	3 (8.0%)	6 (16.5%)	-
41-50 Gy	7 (19.5%)	4 (11.0%)	-
>50 Gy	8 (22.0%)	6 (16.5%)	-
Early results of treatment:			
CR	12 (33.0%)	2 (5.5%)	-
PR	3 (8.0%)	10 (28.0%)	-
NC	3 (8.0%)	4 (11.0%)	2 (5.5%)

Statistical methods

Statistical analysis were performed using the Kaplan-Meier actuarial analysis. Results were evaluated using a Logrank test. As a criteria of efficiency of treatment 3-year disease free survival (DFS) was assumed.

Results

Complete regression of involved lymphatic nodes was observed in 14 cases (39%), partial in 13 cases (36%). No change in nodes diameter or progression during treatment were noticed in 9 patients (25%).

Generally, in a whole analysed group 3-year DFS rate was 36% (Fig.1). In a group treated with combined method (surgery with postoperative radiotherapy) DFS was 45%. However in group treated with radiotherapy alone DFS was only 20% (almost in half of those patients palliative form of treatment was used). The differences between these two groups were statistically significant (p=0.0028) (Fig. 2).

Considering the small number of patients treated with surgery alone (2 cases), this group was not involved in statistical analysis. One patient died of dissemination of the disease to the lungs 26 months after surgery, second was „lost" from observation after 28 months, both of them had symptoms of the active disease in head and neck region at that time.

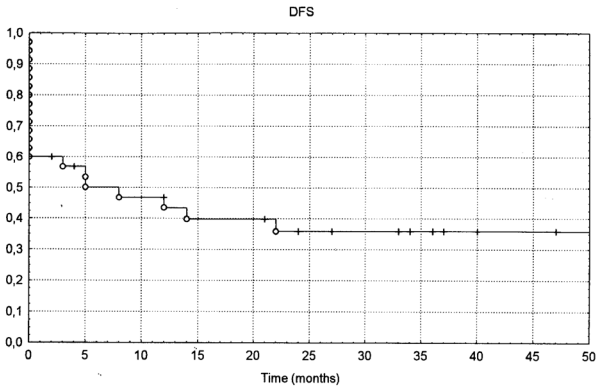

Fig. 1. Disease free survival in whole group

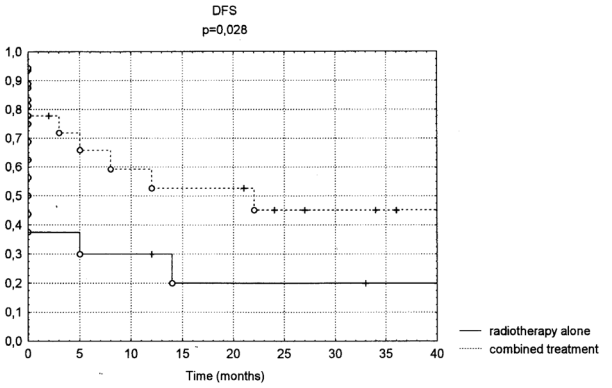

Fig. 2. Survival curves of groups treated with combined method and radiotherapy alone

Median disease free survival in group of patients treated with „large field" technique, encompassing all regional, head and neck lymphatic nodes (all patients treated with radical intention) was 39 months, and was almost six times higher then in group treated with others methods (7 months). Generally in group treated with radical intention 3 years disease free survival was significantly higher then in other cases (48% vs 9%, p=0.0002) (Fig. 3).

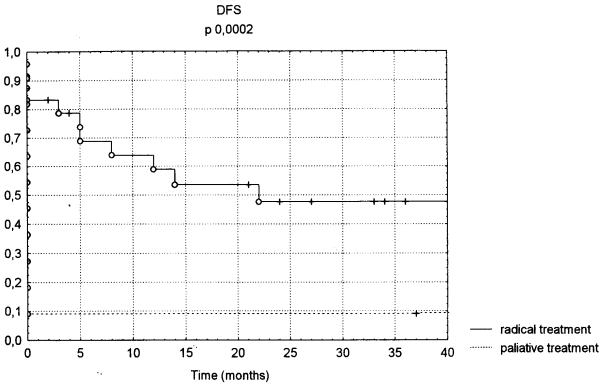

Fig. 3. Survival curves of groups of patients treated with radical and palliative intention

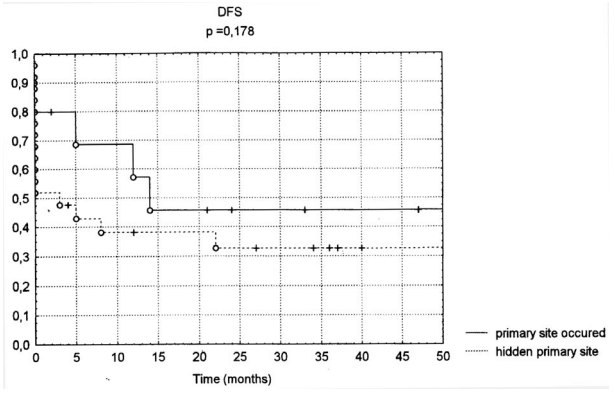

Fig. 4. Survival in groups with occurred and hidden primary sit

Revealing of the primary tumour site was observed in 10 cases. Median time from the first symptoms, metastatically changed head and neck nodes, to the primary site manifestation was 39 months. In 8 cases the primary site was in head and neck region (in 7 patients within previously irradiated area), in 2 cases primary tumour was located in lungs.

The most frequent primary tumour site in head and neck region was the tonsil, indicated in 3 of 8 cases. Median time from lymphatic nodes metastases to the manifestation of the tumour in this group was 19 months. Treatment of the lymphatic nodes in this patients was performed using surgery and postoperative radiation therapy-in 2 cases using „large", in 1 patient using „small", unilateral field.

Tonsilectomy was performed in the treatment of the primary site in all cases, in 1 patient postoperative radiotherapy was undertaken, using „large" field technique, to the total dose 60 Gy (re-irradiation). In the following two patients cancer of the tongue occurred with the median time of 55 months after the first symptoms. In this two cases radiotherapy alone was used in the treatment of the lymphatic nodes to the doses 66 Gy („large fields"), and 50 Gy („small fields"). Surgery was administrated in treatment of the primary tumour in one patient, in the second – chemotherapy was undertaken. In one case, 4 months after neck nodes metastases carcinoma of the nasopharynx has been occurring. Because of the poor general condition of this patient and advanced stage of disease symptomatic therapy was administered. In the next patient the primary tumour was located in the floor of the mouth, which revealed in 14 months after the end of radiotherapy of involved neck nodes in clinical N3 stage. Also in this case, considering progression of the disease in lymphatic nodes, symptomatic therapy was used. In the last patient during 64th month of observation after irradiation of the metastatically changed neck nodes in N3 stage, cancer of the larynx has been occurring together with the lung metastases. In the two cases of the remote lung cancer palliative form of radiotherapy was used.

Generally in group of patients with manifested primary tumour 46% of disease free survival was indicated, in comparison to the other patients – 33% of 3 years DFS.

Discussion

Notwithstanding that the cases of squamous cell cancer metastases from occult primary site to the head and neck lymph node are very rare, this problem is a point of interest of relative large number of publications. In majority of them importance of combined treatment of CUP-syndrome is emphasised [1-7]. However the majority of studies deal with cases treated during many years with relative inhomogenity of clinical material, as well as a small number of analysed groups. These factors do not let to draw the univocal conclusions. Also present study concern inhomogeneous group of patients. The reason of a wide, fifteen years, period of enrolment of the clinical material was based more on the irradiation of patients using megavoltage rays, than on uniform method of treatment, which was introduced into clinical practice during only just last 5 years (1990-95).

Since the beginning of 90's in Institute of Oncology in Gliwice in most patients with squamous cell cancer metastases from occult primary site, surgical dissection of involved neck node or nodes and postoperative radiotherapy of neck and supraclavicular lymphatic system as well as all levels of pharynx is recommended.

Surgery gives opportunity to microscopy examination of involved nodes, to define histopatological type of cancer and the presence of extracapsular invasion of the tumour. This last factor, prognostically especially important, as Strojan et all has shown, is certainly an indication to postoperative radiotherapy [4].

Postoperative irradiation of whole head and neck lymphatic system, as Jesse et al. has proved, could significantly decrease the risk of recurrence in the regional nodes at operated and opposite side of neck [1].

Almost all last published studies emphasizes significance of elective irradiation of whole pharyngeal mucosal membrane in CUP-syndrome treatment [2, 4, 7, 8]. For example Carlson et al. has observed, that 5 year disease free survival in group of patients with whole head and neck lymphatic system and mucosal membrane of all levels of pharynx irradiated approached 47% and was significantly, almost 2 times higher than in a group of patients irradiated using others, less radical techniques [7]. Such form of combined treatment of CUP-syndrome was administrated in our analysed material only in 8, treated during last five years, patients and almost 5 times longer disease free survival in this group was observed.

Harper et al [8] has shown that elective radiotherapy significantly reduces risk of primary tumour occurring in irradiated volume. The risk is about 10-15% for 5 year of observation and it does not differ from the risk of the new cancer occurring in the previously irradiated volume of mucosal membrane during radiotherapy of tonsil or a pharyngeal tumours.

The occurring of a primary tumour after treatment seems to be the separate problem. It is deal with 11% to 54% of patients with CUP- syndrome [1, 2, 4-8]and considerably more often primary tumour occur after surgery alone (about 30% of cases) than after combined treat-

ment or radiotherapy alone (6% and 15% of cases respectively).

An interesting problem seems to be a relative worst prognosis connected with primary site occurring (only 46% of 3 years DFS). Probably, in analysed material it is connected with an advanced clinical stages of primary tumours at the moment of the diagnose. In Kruk-Zagajewska et al. analysis, 3 year disease free survival was even lower, and ranged 30%. However the most important seems to be the thesis proposed in this study. They proposed an aggressive metastatic behaviour of occulted primaries, which makes radical treatment impossible.

Conclusions

The results of our study indirectly suggest the need for complementary, elective irradiation of the whole lymphatic drainage of the head and neck region, as well as the entire pharynx, postoperatively.

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