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*Andrzej Kawecki, Romuald Krajewski

Squamous cell carcinoma of head and neck organs: contemporary management and perspectives

Rak płaskonabłonkowy narządów głowy i szyi: aktualne zasady postępowania i perspektywy

Head and Neck Cancer Department, Centre of Oncology – M. Sklodowska-Curie Memorial Institute, Warsaw, Poland
Head of Department: prof. dr hab. med. Andrzej Kawecki, MD

S u m m a r y

Some 5600 head and neck malignancies are diagnosed each year in Poland. Among them squamous cell carcinoma constitutes over 90%, and 40% are carcinomas of larynx. Risk factors are well-defined and contribute to relatively high incidence (0.015-0.05/year) of second independent malignancies in these patients.

Pathological assessment should include malignancy grading (G1-G3) where G1 is well-differentiated and G3 non-differentiated tumor. It is one of strong prognostic factors along with regional lymph node status (N0-N3).

Management of a vast majority of patients who present with an advanced head and neck squamous cell carcinoma should be carried out by a multidisciplinary team. Principles of management are relatively complex due to multiplicity of organs and localizations in head and neck region. More than half of patients present with an advanced disease. Decision has to be made whether management with curative intent, palliative antineoplastic treatment or symptomatic/supportive management is indicated.

Recent advances in management of head and neck squamous cell carcinoma include improved reconstruction of post-resection defects with free microsurgical tissue transfer, improved precision of irradiation with intensity modulated radiation therapy, application of radiochemotherapy with cisplating and other chemotherapuetics, implementation of therapy acting through molecular targets. EGFR inhibitor cetuximab added to radiotherapy improved overall survival by 9%.

These improvements brought an incremental improvement but early diagnosis still remains the best and the safest way to improve outcomes in patients with squamous cell carcinomas of head and neck.

Key words: head and neck cancer, squamous cell carcinoma, radiotherapy, chemotherapy, molecular targeted therapy, reconstruction

S t r e s z c z e n i e

Rokrocznie w Polsce stwierdza się ok. 5600 nowych zachorowań na nowotwory narządów głowy i szyi. Ponad 90% spośród nich stanowią przypadki raka płaskonabłonkowego, w tym najczęściej raka krtani (ok. 40%). Czynniki kancerogenne są dobrze zdefiniowane i stanowią w tej grupie przyczynę wysokiego ryzyka (0,015-0,05/rok) zachorowania na drugi, niezależny nowotwór. Patomorfologicznie, wyróżnia trzy stopnie złośliwości raka (G1-G3), przy czym G1 oznacza nowotwór o wysokim stopniu zróżnicowania, a G3 niski stopień zróżnicowania. Podział patomorfologiczny ma istotne znaczenie prognostyczne, podobnie jak przerzuty w zakresie regionalnych węzłów chłonnych (N0-N3). Leczenie większości chorych, u których rozpoznawane są nowotwory o znacznym stopniu zaawansowania miejscowego i regionalnego, powinno być prowadzone przez zespół wielodyscyplinarny. Dobór postępowania zależny jest głównie od stopnia zaawansowania raka i jego lokalizacji w zakresie narządów głowy i szyi. Wyjściowo znaczne zaawansowanie stwierdzane jest u większości chorych. Leczenie może mieć charakter radykalny, paliatywny lub też wyłącznie objawowy. Postępy leczenia w ciągu ostatnich lat obejmują przede wszystkim wdrożenie nowoczesnych technik rekonstrukcyjnych w zakresie ubytków pooperacyjnych z uwzględnieniem płatów zespalanych mikrochirurgicznie, zwiększenie precyzji radioterapii przykładowo poprzez szerokie wdrożenie napromieniania o modulowanej intensywności wiązki, kliniczną aplikację jednoczesnej chemioradioterapii oraz wprowadzanie do praktyki leczenia ukierunkowanego molekularnie. Przykładowo, dodanie inhibitora szlaku sygnałowego naskórkowego czynnika wzrostu (EGFR) do radioterapii skutkuje poprawą odsetka wieloletnich przeżyć całkowitych o ok. 9%. Nowe strategie leczenia stanowią stopniowy postęp, tym niemniej w dalszym ciągu najbardziej prostą i bezpieczną strategią pozwalającą na poprawę rokowania jest rozpoznawanie raka we wczesnym stopniu zaawansowania.

Słowa kluczowe: rak narządów głowy i szyi, rak płaskonabłonkowy, radioterapia, chemioterapia, leczenie ukierunkowane molekularnie, techniki rekonstrukcyjne

INTRODUCTION

More than 90% of head and neck (H&N) organs malignancies are squamous cell carcinomas (SCC). **In Poland H&N tumors constitute 5.6% of all malignant tumors and 5600 new cases are diagnosed each year** (1). Squamous cell head and neck cancer (SCHNC) is much more frequent among men, with male/female ratio of 4.5-5/1. Larynx is the most common site, and in men SCC of larynx constitutes 4% of all newly diagnosed malignancies. The highest incidence of SCHNC is in people aged over 50. During last decade the incidence in Poland was rather stable, with slight increase seen among women.

Surgery and radiotherapy (RTH) are traditional, well-established methods of treatment for SCHNC. In early stages of disease (T1-2, N0) these methods used alone or in combinaton give satisfactory outcomes. In advanced stages, which are seen in about 70% of newly diagnosed cases in Poland and in other countries, combined surgery and RTH or radiochemotherapy (RCTH) are used, but results continue to be unsatisfactory with 5-year survival of only 30-40%. Additional problems arise from significantly increased rate of treatment toxicity in patients undergoing RCTH. New treatment protocols, in particular targeted therapies, are intensively investigated in order to improve outcomes in this poor-prognosis, advanced disease group, as well as in recurrent or metastatic SCHNC.

ETIOLOGY AND PATHOLOGY OF SCHNC

SCHNC arises in mucosa of head and neck organs. Localization in the larynx is the most frequent (40% of all SCHNC), then in decreasing order of incidence in oropharynx, oral cavity, lower lip, hypopharynx, paranasal sinuses and nasal cavity (2).

Carcinogens in SCHNC are well-defined and include tobacco smoke (SCC of larynx and oropharynx), alcohol (oral cavity, oropharynx, hypopharynx), chronic mechanical irrtation (oral cavity). These factors also cause high risk of second, independent malignancy, mainly in respiratory system. Such tumors arise in 0.015-0.05 patients per year (3). Recently, human papilloma virus (HPV) infection has been identified as an etiologic factor in selected SCHNC, particularly those of oropharynx and oral cavity. SCCs related to HPV infection are more sensitive to radiation and carry a better prognosis.

SCHNC cells show multiple molecular abnormalities. Suppressor gene mutations, amplification of oncogenes, chromosomal aberrations, overexpression of growth factors lead to progression of tumors and cause resistance to treatment. Expression of epidermal growth factor receptor (EGFR), and activation of its signaling pathway are found in almost all SCHNCs. Radiation is one of factors stimulating this expression, and it is at the same time the treatment modality used in vast majority of patients. Activation of EGFR-dependent tyrosine kinase pathway results in proliferation, migration and invasion of tumor cells, as well as in reduced apoptosis and in angiogenesis. Clinical equivalents of these processes are progression of the tumor and resistance to radiotherapy and chemotherapy (CTH), caused mainly by reduced apoptosis, which facilitates repair of damages caused by treatment (4).

Pathological assessment of SCHNC classifies these tumors into 3 grades of differentiation. G1 is a highly differentiated SCC, G2 is intermediate and G3 is non-differentiated (2). Majority of oral cavity, larynx, hypopharynx tumors are G1 or G2, while G3 tumors are frequent in oropharyngeal localization. This grading has significant clinical impact, as G1 and G2 tumors tend to grow slowly and give distant metastases in 15-20% (2). G3 tumors grow more rapidly, distant metastases appear earlier, with high frequency. However, high-grade, non-differentiated SCC is more sensitive to RTH and CTH.

MANAGEMENT PLAN

Management plan is a critical element in diagnosis and treatment of SCHNC. First line of treatment determines an outcome, because of very limited efficacy of second line treatment. Decision on the most appropriate treatment plan has to take into account both tumor-related and patient-related factors. Clinical staging according to TNM/AJCC classification, tumor localization and pathological grade are the most important. There is growing evidence that molecular characteristic of the tumor and HPV infection will soon be also used. Important factors that relate to patient are functional and nutritional status, and co-morbidities (3).

The above factors determine whether treatment with curative intent will be possible. Such treatment is preferred for patients with local and loco-regional disease. The optimal decision process leading to formulation of management plan should be a discussion in an interdisciplinary oncology panel/team. Only in early stages, when therapeutic options are very well defined, single specialist management (surgery or RTH) is appropriate.

Treatment strategy that gives higher probability of cure should be preferred. If two strategies have similar probability of achieving cure, functional outcome and patient preference should decide. Individual patient factors that will determine treatment tolerance have to always be taken into account. Eventually, treatment plan, available options, risks and expected outcomes should be presented to the patient, who will make decision and give his informed consent.

TREATMENT WITH CURATIVE INTENT

Clinical stage of disease according to TNM/AJCC staging system determines treatment modality. In cT1-2N0 stages surgical therapy, RTH or combination of these methods are indicated and result in 60-90% 5-year survival (2, 3). Prognosis significantly depends on localization. The highest cure rate is typical for glottic cancer, whilst cancer of hypopharynx carries the worst prognosis. Functional and cosmetic results in these cases are satisfactory, along with good quality of life.

RTH should be planned and delivered on the basis of three-dimensional reconstructions of diagnostic images. Conventional fractionation regime is commonly used, but efficacy of accelerated RTH has also been demonstrated (3, 5). RTH as single method has strictly defined indications which include SCC of larynx, hypopharynx and oropharynx (3). In T1N0 and in selected T2N0 interstitial brachytherapy is an accepted alternative.

Surgical resection is indicated in early stage SCC of oral cavity, lower lip and paranasal sinuses. If resection with organ preservation is possible, T1-2N0 cancer of the larynx can also be treated surgically (3). Oncological results are similar to those of RTH, but quality of voice appears to be better after irradiation.

Combination of surgery and RTH in SCHNC is used exclusively as an initial resection followed by adjuvant irradiation (2, 3). Indications for combined treatment have to be based on detailed pathological examination of surgical specimen. In case of close surgical margins (less than 5 mm), dispersed infiltration by tumor cells, low grade tumor (G3), invasion of deep muscles, cartilage or bone (pT4) irradiation is indicated (3). When pathology shows non-radical resection R2 (macro- or microscopic), a reoperation should be the first option. If it is not possible, radical radiotherapy should be delivered.

It is accepted that metastasis to even a single regional lymph node makes an indication for adjuvant RTH. When more unfavorable prognostic factors, as extracapsular spread or metastases to multiple lymph nodes (> 2) are present, more aggressive adjuvant therapy is advised, including RCTH based on cisplatin (3, 6, 7). Principles of adjuvant therapy presented above are applicable also to more advanced SCHNC.

Patients with SCHNC in clinical grades III and IV (cT3-4 cN1-3) present very difficult challenges. In Poland, but also in other developed countries, some 2/3 of newly diagnosed cases are in these grades. Traditional surgery and RTH combination gives 5-year locoregional control in less than 40%. Results are slightly better in SCC of larynx and lower lip. Moreover, risk of distant metastases is significantly higher in this group, particularly if large metastases to neck lymph nodes are present. Intensive clinical research conducted in 90s resulted in new standard of conservative treatment for advanced SCHNCs. Concurrent radiotherapy and chemotherapy improved long-term survival by 7-25% in comparison to RTH alone (8-12). RCTH proved to be the best organ-preservation treatment, an useful alternative to disfiguring surgical procedures and more efficient alternative to RTH as adjuvant therapy in cases with poor prognostic factors (6, 7, 13).

Results from randomized trials have been confirmed by metaanalyses, which showed 8-11% improvement in survival after RCTH. It has been demonstrated that combination of irradiation with cisplatin is the most efficient, and that therapeutic gain does not depend on RTH fractionation regime (14-17).

The above-mentioned findings have established contemporary standard of care for grade III-IV SCHNC, which is either surgery with adjuvant RTH/RCTH, or RCTH in patients who cannot be operated upon or are candidates for organ-preservation treatment.

Surgery is preferred as an initial treatment for patients with SCC of oral cavity, larynx, paranasal sinuses and in cases of SCC of oropharynx or hypopharynx where non-surgical therapy is contraindicated (3). Surgical procedures have to include same-stage closure of resection cavity with local flaps, distant pediculate flaps or free flaps with microvascular anastomosis. Availability of a wide range of reconstruction methods is necessary to achieve acceptable functional and cosmetic result, particularly after an extensive resection.

RCTH is recommended for patients with SCC of oropharynx and of hypopharynx, as an alternative to surgery (3). The therapy should follow these principles:

- RTH planning and delivery based on 3D reconstruction of diagnostic images (3D conformal RTH), and preferred irradiation method should be intensity modulated radiation therapy (IMRT);
- CTH based on cisplatin;
- intensive supportive treatment, with particular attention to adequate nutrition; temporary percutaneous endoscopic gastrostomy (PEG) should be considered;
- close monitoring of radiation toxicity, symptoms of bacterial and fungal infection, blood parameters.

Use of modern irradiation technologies, mainly IMRT, is preferred because of better protection of normal tissues that should minimize radiation toxicity and complications. Single RTH fractionation regime with optimal results could not be established, and each center can use its own preferred method. Conventional fractionation (fraction dose Df = 1.8-2.0 Gy, delivered 5 times per week, total dose (TD) = 70 Gy), accelerated fractionation (simultaneously integrated boost (SIB)-IMRT, continuous accelerated irradiation (CAIR), concomitant boost, delivering of 6 fractions per week) or hyperfractionation (Df = 1.1-1.2 Gy delivered twice daily with TD escalation) are all accepted.

Efficiency of CTH regimes has not been directly compared, and superiority of cisplatin is accepted on the basis of indirect evidence (results of metaanalyses and toxicity profiles). Some centers prefer RTH with administration of carboplatin, hydroxyurea or docetaxel, but evidence supporting this practice is not available. Cisplatin should not be given with 5-fluorouracil, as antimetabolites have mucosal toxicity similar to that of irradiation, and this could lead to escalation of adverse effects.

Results of clinical trials have shown that benefit from RCTH is limited to a strictly defined group of patients characterized by good functional status (WHO grade 0-1), good nutritional status and no major comorbidities. RCTH, like RTH alone, is contraindicated in patients with cartilage, bone and skin invasion by the tumor.

Implementation of RCTH in clinical practice is undoubtedly significant progress in management of SCHNC. Nevertheless, only one out of seven treated patients does obtain tangible benefit, while results in advanced SCHNC (T4 and/or N3) remain poor. Clinical studies have also shown that RCTH is associated with marked toxicity, due mainly to escalation of radiation-dependent adverse reactions and systemic complications (18). Evidence from recent studies suggests an elevated rate of late complications, which may require surgical interventions and markedly reduce quality of life (19). These considerations indicate that new treatment methods, characterized by higher efficacy or lower complications rate should be developed.

The most promising new methods are combination of simultaneous RCTH and sequential CTH, and targeted therapies. The purpose of the first approach is to increase antineoplastic activity, primarily by more efficient elimination of subclinical distant metastases, but also by increasing probability of loco-regional control. This method is already used in nasopharyngeal carcinoma that carries high risk of distant metastases. In SCHNC patients the local control is of utmost importance. Therefore, also induction CTH is included, with subsequent RCTH. Induction CTH has been abandoned in 90s, as a result of negative randomized trials that compared it to RTH only (20). However, during the last decade new evidence suggested that role of induction CTH should be re-evaluated (21). Metaanalyses have shown that induction CTH with cisplatin and 5-fluorouracil increases long-term survival in small, but significant percentage of patients (5% vs RTH only) (16, 17). Application of induction CTH with RCTH instead of RTH only seems most interesting.

New treatment regimes with docetaxel have been introduced. Two non-randomized phase II trials demonstrated that combination of induction CTH and RCTH is clinically feasible, and response rate, 3-year disease-free and overall survival (OS) are high (22-25). Low rate (< 16%) of distant metastases was seen. Randomized trials compared classical induction CTH with cisplatin and 5-fluorouracil (PF) to a new experimental combination of PF and docetaxel (TPF). Phase III trial conducted in American centers showed significant improvement in loco-regional control and in overall survival. Median OS was 40 months longer in experimental arm – a result rarely seen in this kind of trials (26). Treatment toxicity was acceptable. Phase III trials comparing TPF induction CTH with RCTH to the "golden standard" of RCTH are in progress. The results could change present standards of care for SCHNC patients. Induction CTH with TPF is already registered for use in SCHNC patients, and it is particularly useful in massive neck lymph nodes metastases (N2-3).

Combination of RTH or CTH with targeted therapies concentrates on the receptor for epithelial growth factor (EGFR) The role of EGFR in SCHNC is well known (see above). Suppression of the receptor and associated tyrosine kinase signaling pathway should result in an antiproliferative effect, promotion of apoptosis, reduced sublethal lesions repair and in antiangiogenic activity (4). Expected clinical result should be breakdown of mechanism of resistance to irradiation and to cytostatic drugs. EGFR can be blocked by monoclonal antibodies binding to its extracellular ligand or by small-molecule tyrosine kinase inhibitors (TKI). **Majority of available evidence concentrates on chimeric monoclonal antibody cetuximab** (C225). Early trials evaluated combination of cetuximab with RTH and demonstrated acceptable toxicity of 400 mg/m^2 dose given iv. 7 days before RTH, and then continued as 250 mg/m^2 given weekly during RTH (27). Adverse reactions to cetuximab were acne-like rash, reactions during infusion, reduced magnesium level and less frequently headache, fatigue, diarrhea, hypocalcemia, and hypokaliemia. Randomized phase III trial showed that addition of cetuximab to RTH improves OS (9% increase in 5-year survival and 20 months longer median survival) and loco-regional control in patients with advanced loco-regional SCHNC (28, 29). There was no benefit as far as distant metastases were concerned. This suggests that therapeutic gain from cetuximab is based mainly on reduction of resistance to irradiation and not on direct cytotoxic activity. In contrast to RCTH, no increase in radiation-related toxicity was observed, and thus therapeutic gain comparable that obtained with new CTH regimes was achieved without increased toxicity. Adverse reactions specific to cetuximab did neither result in worsened quality of life nor in higher risk of secondary complications. The results of this trial served as basis for cetuximab registration in management of SCHNC patients with contraindications for RCTH. The ongoing trials compare directly RCTH based on cetuximab with conventional RCTH and will define a role of this drug in management of SCHNC more precisely.

Another monoclonal anti-EGFR antibody, panitumumab, is undergoing clinical trials. So far, trials of combined RTH and small-molecule tyrosine kinase inhibitors yielded negative results. Preclinical and early clinical trials of substances with other than EGFR targets, such as angiogenesis and hypoxia, are undertaken.

MANAGEMENT OF RECURRENT AND METASTATIC SCHNC

Treatment of choice for patients with residual tumor or with loco-regional recurrence is salvage surgery, as it is the only method offering a possibility of cure, even though in minority of cases only (3). Progress in reconstructive surgery allows for closure of very large defects that are typical in this kind of surgery. As result, indications for salvage surgery have been significantly expanded recently.

RTH retreatment alone or in combination with CTH can be considered in selected cases. It is applicable when there is limited target volume that does not in-

volve critical organs. Time from the first RTH is also important. It is accepted that retreatment should not be considered earlier than 6-12 months after previous RTH. Clinical data indicate that the longer time span the better are results of retreatment. In a few selected cases brachytherapy can be useful. Total radiation dose delivered as retreatment should approximate that of primary radical treatment. Technological progress in RTH results in expanded indications for retreatment, but still only minority of recurrent SCHNC are candidates for RTH retreatment.

In majority of patients neither salvage surgery nor retreatment are possible, and the only treatment option is systemic CTH. During last 30 years the standards of care for patients with recurrent or metastatic SCHNC have not changed. CTH based on cisplatin has been the method of choice, with PF (cisplatin 100 mg/m^2 on day1, 5-fluorouracil 1000 mg/m^2 in continuous iv. infusion on days 1-3 or 1-4, cycle length 21 days) being "golden standard". Randomized clinical trials published during 90s demonstrated that PF protocol gives significantly higher rate of therapeutic response when compared to other treatment methods, but these results do not translate into better survival indicators (30). Moreover, PF protocol generates relatively high costs mainly due to obligatory hospitalization during continuous 5-fluorouracil infusions.

The risk of serious adverse reactions is also important. Clinical trials have shown that PF is beneficial only in patients with good functional status (WHO performance scale grades 0-1), and/or in high-grade SCC (G3) (31). In remaining patients, if functional status is not worse than WHO grade 2, less toxic treatment with methotrexate can be considered. Patients in WHO performance scale grade worse than 2 do not obtain benefit from CTH (31).

Survival of patients with recurrent or metastatic SCHNC has not been longer than 9 months irrespective of CTH protocol, and quality of life has been poor. Very limited efficacy of the treatment justifies intensive research into innovative, more effective methods of treatment that would increase survival and improve quality of life.

New generation cytostatic drugs turned out to be ineffective. Even though proportion of therapeutic responses after monotherapy with taxanes (paclitaxel, docetaxel) has been higher when compared to that reported after cisplatin, phase III clinical trial has not shown better outcomes in patients treated with TP protocol vs those treated with classical PF protocol (32). Survival indicators were higher after standard PF.

Taking this into account, expectations to improve outcomes are based on targeted therapies. Similarly to primary radical treatment, the best-known recurrent or metastatic SCHNC target is EGFR, and majority of clinical data pertain to cetuximab. Downregulation of the receptor is supposed to exert antiproliferative and pro-apoptotic activity and to help overcome resistance to cytostatic drugs. The later effect is a rationale for combination of cetuximab with CTH. Cetuximab is administered as 400 mg/m^2 iv. initial dose at the start of CTH and then 250 mg/m^2 are given every week. This protocol has shown promising results in phase II trials (33). If therapeutic response was obtained, cetuximab was administered until progression or unacceptable toxicity occurred. The most important results published to date are from EXTREME phase III trial which compared efficiency of PF combined with cetuximab to PF only in first-line treatment of recurrent or metastatic SCHNC (34). Adverse reactions turned out to be similar in both arms, and toxicity specific to cetuximab (rash, reactions to infusion) had not been clinically significant. It has been shown that addition of cetuximab to standard PF protocol results in longer median survival (10.1 vs 7.4 months). Therapeutic gain was seen in all subgroups, except for patients in poor functional status and in elderly, who had short median survival irrespective of treatment. The later observation is interpreted as confirmation of earlier observations that such patients do not benefit from any antineoplastic treatment. Addition of cetuximab to PF has not caused deteriorated quality of life, in some aspects it has even improved (35). EXTREME was the first trial that demonstrated superiority of new therapeutic protocol over standard management in recurrent or metastatic SCHNC. However, it should be pointed out that combination of cetuximab with PF carries high cost, mainly due to prolonged administration in responders. Cost-effectiveness analysis is advisable. Trials evaluating effectiveness of another EGFR-targeted antibody, panitumumab, are in progress.

Prognosis in patients with progression after CTH based on cisplatin is particularly poor, and median survival does not exceed 4 months (2, 36). Standard of care that remains in such situation is treatment with methotrexate for patients in acceptably good functional status or best supportive care (3, 31). Clinical trials have shown that administration of cetuximab with or without cisplatin will produce therapeutic response in 10-20% of patients, with slightly longer survival indicators than in historic controls (33, 36, 37). Similar results, though with smaller proportion of tumor regression, have been observed after administration of small-molecule EGFR tyrosine kinase inhibitors – gefitinib and erlotinib. However, clinical trials that compared effectiveness of gefitinib and methotrexate, and docetaxel alone or with gefitinib, have not demonstrated therapeutic gain from addition of tyrosine kinase inhibitor (38).

Many potential drugs are investigated in preclinical or early clinical trials. These include inhibitors of angiogenesis (also multi-kinase inhibitors), of integrins pathway, insulin-like growth factor 1, cycline-dependent kinases and selective promotors of apoptosis (39, 40). Effectiveness of combined inhibition of molecular targets is also investigated, for example administration of EGFR and angiogenesis inhibitors (41).

SUMMARY

Recently, systematic progress has been made in management of SCHNC. Technological advances in surgical and RTH techniques are supported by expanding application of molecular targeted therapies that are combined with irradiation or CTH. This has led to improved outcomes (29, 34). Promising new drugs are investigated and may further improve prognosis. Early diagnosis, which is the most important favorable prognostic factor, still remains the best and the safest way to improve outcomes in SCHNC patients.

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Adres/address:
*Andrzej Kawecki
Professor of Radiotherapy and Clinical Oncology
Head and Neck Cancer Department
Cancer Center – M. Sklodowska-Curie Memorial Institute of Oncology
Roentgena Str. 5, 02-781 Warsaw, Poland
e-mail: a.kaweckidom@gazeta.pl