Postępy Nauk Medycznych, t. XXIV, nr 2, 2011

*Piotr Rutkowski, Zbigniew I. Nowecki

Sarcomas and melanomas

Mięsaki i czerniaki

Department of Soft Tissue/Bone Sarcomas and Melanoma, Cancer Center – M. Sklodowska-Curie Memorial Institute of Oncology
Head of Department: doc. dr hab. med. Piotr Rutkowski

S u m m a r y

The article summarizes the recommended management and new directions in diagnostics and therapy of sarcoma and melanoma patients. Primary malignant neoplasms of soft and bone tissues, e.g. sarcomas, are rare mesenchymal malignancies, comprising approximately 1% of all cancer incidence in adults. The recent advances in treatment of soft tissue sarcoma, both primary tumor and local recurrences/metastatic disease, indicate that combined therapy (standard combination of surgery with adjuvant radiotherapy, chemotherapy in selected cases and perioperative rehabilitation) in highly-experienced centers increased possibility of cure and limitations of extent of local surgery. Current combined therapy with using reconstructive techniques allows for limb-sparing surgery in majority of soft tissue sarcoma patients. The good results of local therapy may be expected only after planned (e.g. after preoperative biopsy – tru-cut or incisional) radical surgical excision of primary tumor with pathologically negative margins (R0 resection). The advances in sarcomas are related to introduction to clinical practice targeted therapy acting on molecular or genetic cellular disturbances detected during studies on etiopathogenetic mechanisms of sarcoma subtypes. Gastrointestinal stromal tumors (GIST) are the model example of successful molecularly targeted therapy (introduction of imatinib and sunitinib into clinical practice) [Polish Clinical GIST Registry; http://gist.coi.waw.pl]. Due to rarity of sarcomas and necessity of multidisciplinary therapy, the crucial issue is that management of these tumors should be hold in experienced oncological sarcoma centers. In cutaneous melanomas the crucial step is excisional biopsy of suspicious melanomatous skin lesions likely to be diagnosed as early melanomas. Early diagnosis and surgical removal of cutaneous melanoma not only improves patients' prognosis, but it is also associated with approximately 90% likelihood of cure. The main achievement in melanoma management was introduction sentinel node biopsy into routine practice. Current studies are focused on indications for limitations of necessity of completion lymph node dissection in positive sentinel node cases (Rotterdam criteria). The recent discoveries in immunotherapy (anti-CTLA4 antibodies) and molecular targets give a hope for improvement of outcomes of patients with metastatic melanomas.

Key words: melanoma, sarcoma, gastrointestinal stromal tumors, therapy, advances, molecular targets

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

Artykuł stanowi podsumowanie zasad postępowania i nowych kierunków w diagnostyce i leczeniu chorych na mięsaki i czerniaki. Pierwotne nowotwory złośliwe tkanek miękkich i kości, czyli mięsaki, są rzadkimi nowotworami pochodzenia mezenchymalnego, stanowiącymi około 1% wszystkich zachorowań na nowotwory u osób dorosłych. Największą poprawę wyników w leczeniu chorych na mięsaki upatruje się we wprowadzeniu zasad leczenia skojarzonego, czyli leczenia chirurgicznego z radioterapią (przed- lub pooperacyjną) i chemioterapią (zależną od typu mięsaka) w wyspecjalizowanych ośrodkach. Postępowanie takie zwiększyło szansę na całkowite wyleczenie chorego lub uzyskanie długoletniego przeżycia, oraz na ograniczenie zasięgu operacji (wykonanie operacji oszczędzającej kończynę zamiast amputacji). Korzystnych wyników miejscowych leczenia mięsaków można spodziewać się tylko w przypadku planowego (tzn. po wcześniejszej biopsji) całkowitego wycięcia guza w mikroskopowo wolnych od nowotworu granicach (tzw. resekcja R0). Postęp jest związany z wprowadzeniem do praktyki klinicznej leków o celowanym działaniu związanym z molekularnymi lub genetycznymi zaburzeniami w komórkach, które uczestniczą w etiopatogenezie tych nowotworów. Modelowym przykładem skutecznego leczenia ukierunkowanego molekularnie jest zastosowanie inhibitorów kinaz tyrozynowych (imatynibu i sunitynibu) w leczeniu nowotworów podścieliskowych przewodu pokarmowego (ang. *gastrointestinal stromal tumors* – GIST) [Rejestr Kliniczny GIST w Polsce: http://gist.coi.waw.pl]. Z uwagi na rzadkie występowanie mięsaków oraz konieczność skojarzonego postępowania najważniejsze jest prowadzenie diagnostyki i terapii już od początku w ramach wielodyscyplinarnego zespołu w ośrodku onkologicznym o odpowiednim doświadczeniu i zapleczu diagnostycznym. W odniesieniu do chorych na czerniaki zasadnicze znaczenie ma biopsja wycinająca podejrzanych zmian barwnikowych skóry, które mogą być wczesnymi czerniakami. Wczesne rozpoznanie i chirurgiczne usunięcie czerniaka nie tylko poprawia rokowanie, ale daje szansę wyleczenia u około 90% chorych. Znaczący postęp w diagnostyce chorych na czerniaki stanowiło wprowadzenie biopsji węzła wartowniczego. Obecne badania koncentrują się na ustaleniu wskazań do ograniczenia rozległości uzupełniającej limfadenektomii u chorych

z dodatnim węzłem wartowniczym (kryteria rotterdamskie). Postępy w immunoterapii (przeciwciała anty-CTLA4) i określeniu celów molekularnych dają również nadzieję na poprawę przeżyć chorych na przerzutowe czerniaki.

Słowa kluczowe: czerniak, mięsak, nowotwór podścieliskowy przewodu pokarmowego, leczenie, postępy, cele molekularne

SARCOMAS

Primary malignant tumors of soft tissues and bone (sarcomas) constitute rare heterogenous group of mesenchymal neoplasms, with incidence accounting for approximately 1% of all new cases in adults (1). Significant progress in the treatment of soft tissue sarcoma, both primary tumor and local recurrences/ /metastatic disease, has been achieved in recent years. Multidisciplinary therapy in centers with high expertise is the crucial point in sarcomas' management. The first step in management of sarcomas is well-planned biopsy (tru-cut or incisional). Pathological diagnosis is based on assessment of morphological features and immunohistochemistry, but should also include molecular biology techniques (FISH – *fluorescence in situ hybridization* and RT-PCR – *reverse transcriptase-polymerase chain reaction*). Cytogenetic examinations confirmed that approximately one third of sarcomas harbour specific chromosomal aberrations, mainly translocations, e.g.: *myxoid liposarcoma* [t(12;16) (q13.3;p11.2); fusion gene FUS/DDIT3], *synovial sarcoma* [t(X;18) (p11.2;q11.2); fusion gene SS18/SSX1, 2 i 4], *alveolar rhabdomyosarcoma* [t(2;13) (q35-37;q14); fusion gene PAX3/FOX01A lub t(1;13) (p36;q14); fusion gene PAX7/FOXO1A], *clear cell sarcoma* [t(12;22) (q13;q12); fusion gene AFT1/EWS], *mięsaka Ewinga*/ /*PNET* [t(11;22) (q24;q12); fusion gene FLI1/EWS], *dermatofibrosarcoma protuberans* [t(17;22) (q22;q13); fusion gene COL1A1/PDGFβ], *desmoplastic small round cell tumor* [t(11;22) (q13;q12); fusion gene WT1/EWS] (2).

The main prognostic factors in sarcomas comprise primary tumor size and pathological grade as well as the presence of metastatic disease. However, the prognostication systems due to histological heterogeneity are still imperfect. There is a need for the search of new markers useful in predicting of clinical outcomes. One of the studied proposals are the investigations of correlations between serum levels of cytokines and soluble cytokine receptors with clinico-pathological features and prognosis of sarcoma patients. Studies performed by our group (3, 4) revealed that serum levels of some proinflammatory, hematopoietic and angiogenic cytokines and cytokine receptors are elevated, frequently in parallel, in a large percentage of sarcoma patients. Significant correlations with tumor size and grade suggest that some of these cytokines may be involved in the progression of these tumors.

Serum assays of IL-6 (interleukin 6), IL-8 and TNF RII (tumor necrosis factor receptor II) before and/or after the treatment may be useful in establishing prognosis of soft tissue patients. In bone sarcomas multivariate analysis showed that high serum levels of IL-1ra and TNF RI, the number of serum cytokine above normal cut-off values (0-1 vs. 2-5 vs. ≥ 6) and greater tumor local extent E (E2/4 vs. E5/6; p= 0.02) correlated significantly with shorter overall survival.

As mentioned previously the crucial point in sarcoma management is multidisciplinary approach and treatment of these tumors should be hold in experienced oncological sarcoma centers. **Good results of local therapy may be expected only after planned radical surgical excision of primary tumor with pathologically negative margins (R0 resection).** Surgery is essential modality, but the use of combined treatment (in soft tissue sarcomas: standard combination of surgery with adjuvant radiotherapy, chemotherapy in selected cases; in bone sarcomas: combination of perioperative neo- and adjuvant chemotherapy with local treatment in osteosarcoma and Ewing's family of tumors; and perioperative rehabilitation) in highly-experienced centers increased possibility of cure and limitations of extent of local surgery (2, 5, 6, 7). Current combined therapy together with the use of reconstructive methods allows for limb-sparing surgery in majority of soft tissue sarcoma patients (amputation in 10% of cases as compared to approximately 50% in the 1960-70s) and high percentage of bone sarcomas (with using oncological joint and bone replacement as well as expandable prostheses in children and adolescents). The slow, but constant, increase of rate of sarcoma patients with long-term survival has been observed. Contemporary 5-year overall survival rate in patients with extremity sarcomas is 55-78%. In case of diagnosis of metastatic disease the prognosis is still poor (survival of approximately 1 year).

The recent development in advanced sarcomas treatment is introducing molecular targeted therapy. It is well known that several sarcoma types are characterized by specific molecular abnormalities, and although transcriptional factors are weak therapeutic target we have fine example of dermatofibrosarcoma protuberans (DFSP), where dramatic clinical activity of imatinib targeting PDGF was confirmed. From the molecular point of view DFSP is characterized by the presence of distinctive, reciprocal rearrangement of chromosomes 17 and 22 in the form of translocation t(17;22) (q22;q13) or more commonly supernumerary ring chromosomes containing material from chromosomal regions 17q22 and 22q 13 (21-31). The rearrangement leads to the fusion of alpha chain type type a (*COL1A1*) localized on 17q22 to the platelet-derived growth factor beta (*PDGFB*) localized on 22q13. The formation of *COL1A1-PDGFB* fusion gene results

in the constitutional upregulation of *PDGFB* expression, leading to continuous autocrine activation of PDGF receptor B (PDGFRB) and as a consequence – to propagation of the mitotic signal by formation of an autocrine and paracrine loops. Advances in the understanding of the molecular mechanisms of DFSP have resulted in the implementation to the clinical practice the targeted therapy, inhibiting PDGFR. Imatinib mesylate is a tyrosine kinase inhibitor rationally developed and specifically directed against BCR/ABL, KIT, FMS (receptor for Colony Stimulating Factor 1), ARG (ABL-related gene) and PDGFR alpha and beta. Currently, imatinib therapy is the gold standard in the treatment of inoperable and/or metastatic and/or recurrent cases of DFSP, and this targeted therapy may potentially facilitate resection or decrease possible disfigurement. Significant percentage of patients may be rendered free of disease by surgery of residual disease following partial imatinib responses. Combined analysis of prematurely closed two phase II, single arm, open-label trials (European Organisation for Research and Treatment of Cancer no. 62027 and the Southwest Oncology Group no. S0345) regarding efficacy of imatinib in advanced DFSP, have demonstrated on 25 patients with advanced DFSP the clinical benefit with rate exceeding 70% and median time to progression of 1.7 years (9). Our research group (10) have proved dramatic activity of imatinib mesylate in advanced DFSP in the series of 15 patients treated with imatinib in routine clinical practice outside any trial, with clinical benefit rate approaching 80% as well as median PFS and OS being not reached.

The most striking example of targeted therapy of sarcomas is activity of imatinib mesylate (targeting BCR-ABL. KIT and PDGFR) **in inoperable and/or metastatic GIST** (gastrointestinal stromal tumor). GISTs have emerged during the recent years as a distinct sarcoma entity due to advances in the understanding molecular mechanism of their pathogenesis (11). Currently in all the epidemiologic studies GISTs are regarded as the most common mesenchymal neoplasms of abdominal cavity. They are believed to originate from precursors shared with interstitials cells of Cajal (ICC) – the gut pacemaker cells (the immunohistochemical marker of which is the CD117 antigen) and they may arise elsewhere in the gastrointestinal tract (most commonly in the stomach or the small bowel). A majority of GISTs are associated with activating, somatic, mutually exclusive mutations of two genes, *KIT* and *PDGFRA* (platelet-derived growth factor receptor-α), which are the early oncogenic events during GIST development. GISTs are morphologically and clinically heterogeneous, and their biological behavior is difficult to predict, ranging from clinically benign to malignant. The main criteria of aggressive behavior of GIST are based on the presence of invasion of surrounding structures and/or metastases (overtly malignant cases), as well as primary tumor size and mitotic index (fig. 1). Additional analyses of patients with primary tumor after complete macroscopic resection confirmed the significance of tumor anatomic location as independent prognostic factor (with better prognosis for gastric than small bowel GISTs) (12). Radical surgery is the treatment of choice in primary resectable gas-

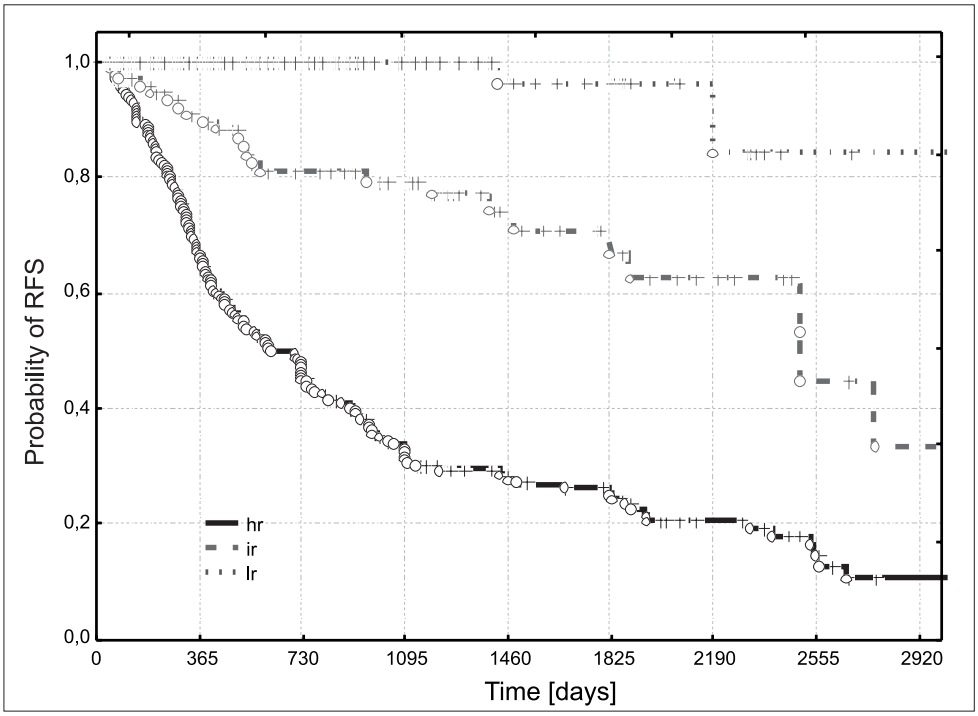

Fig. 1. Relapse-free survival (RFS) after resection of primary GIST according to NIH (National Institutes of Health) risk classification (data of Polish Clinical GIST Registry on 590 patients): hr – high-risk, ir – intermediate risk and lr – low-risk.

trointestinal stromal tumors, but virtually all GISTs are associated with a risk of recurrence, and approximately 40-50% of patients with potentially curative resections develop recurrent or metastatic disease. Currently, based on the data from ACOSOG Z9001 study, imatinib was registered for adjuvant therapy in patients after resection of primary GIST at significant risk of recurrence (13). Imatinib is also the standard of care in the treatment of patients with advanced (inoperable and/or metastatic) GIST. Several clinical trials have been conducted that confirmed high efficacy of imatinib in the treatment of GIST for the majority of patients with inoperable/metastatic disease. As compared to historical clinical data, with the median survival of patients being 10 to 12 months, current survival is strikingly superior – the reported median overall survival (OS) reached in imatinib trials is 57 months and median progression-free survivals (PFS) range from 2 to 3 years. The similar results were published by multicenter study of Polish Clinical GIST Registry (http://gist.coi.waw.pl) (16, 17). The correlation between the mutational status and the response to imatinib is well documented – tumors containing the most common exon 11 *KIT* mutation have the highest response rate (> 80%). Moreover, the response of patients with GIST with exon 9 *KIT* is dependend on the dose of the drug and these patients been identified as needing higher dosages of imatinib (800 mg/d) (11). The activity of imatinib have been also observed in treatment of *fibromatosis agressiva*, *pigmented villonodular synovitis/tenosynovial giant cell tumo*r (PVNS/TGCT, with presence of fusion gene *COL6A3-CSF1*) and *chordoma*. In case of GIST resistant to imatinib the second line therapy with sunitinib malate is registered. Sunitinib maleate, an oral multitargeted tyrosine kinase inhibitor of KIT and PDGFRs, as well as vascular endothelial growth factor receptors (VEGFRs), FMS-like tyrosine kinase-3 (FLT3), colony-stimulating factor 1 receptor (CSF-1R), and glial cell-line-derived neurotrophic factor receptor (REarranged during Transfection; RET). Sunitinib has demonstrated clinical activity with durable responses/stabilizations in approximately 40% of imatinib-resistant GIST cases (especially in exon 9 *KIT* mutants or wild-type GISTs). If sunitinib therapy fails clinical trials with novel agents (e.g. AMN107 – nilotinib, sorafenib, dasatinib) are ongoing.

There are also investigations on molecular targeted therapy in other sarcoma subtypes, e.g.: antiangiogenic therapy (bevacizumab, sunitinib, sorafenib in Kaposi sarcoma, *hemagioendothelioma/angiosarcoma* and *alveolar soft-part sarcoma*), trabectedine in myxoid/rond-cell liposarcoma, agents targeting PI3K/AKT, MET (e.g. in alveolar soft part sarcoma or clear cell sarcoma), Mek, mdm2/CDK, RAF kinase pathways, mTOR inhibitors (especially in rhabdomyosarcoma or PEComa), insuline-like growth factor receptor 1 inhibitors (IGFR1R; especially in Ewing's sarcoma and rhabdomyosarcoma), anti-RANKL antibodies (denosumab in giant-cell tumor of bone), multi-kinases inhibitors, metalloproteinase inhibitors (MMP), proapoptotic drugs, heat shock protein inhibitors or histone deacetylase inhibitors (tab. 1).

Table 1. Targeted therapy of sarcomas – registered and under development new drugs.

Sarcoma type	Agent	Molecular target
Registered indication		
GIST	Imatinib	KIT, PDGFRA
GIST	Sunitinib	KIT, PDGFR, VEGFR
DFSP	Imatinib	PDGFRB
Studied indications		
Vascular-origin sarcomas (angiosarcoma, hemangioendothelioma), alveolar soft-part sarcoma	Sunitinib, sorafenib, bewacizumab, pazopanib, cediranib	VEGFR
Myxoid/round-cell liposarcoma	Trabectedine	? NER/DNA helix
Pigmented villo-nodular synovitis	Imatinib	CSF1
PEC-oma (perivascular epithelioid cell), lymphangioleiomyomatosis, rhabdomyosarcoma	mTOR inhibitors	MTOR
Ewing's sarcoma, rhabdomyosarcoma	anti-IGFR	IGFR1
GIST	sorafenib, dasatinib, nilotinib	KIT, PDGFR, VEGFR
GIST	HSP-90 inhibitors	HSP-90
Alveolar soft part sarcoma, clear cell sarcoma	ARQ197	Met
Giant-cell tumor of bone	Denosumab	RANKL
Inflammatory myofibroblastic tumor	P02341066	ALK/MET
Dedifferentiated liposarcoma		MDM2/CDK4
Aggressive fibromatosis	Imatinib	?
Chordoma	Imatinib, imatinib + cisplatin, imatinib + mTOR inhibitor, Sunitinib, EGFR inhibitors	PDGFR, EGFR, mTOR
Solitary fibrous tumor	Antiangiogenic therapy (bewacizumab + temozolomide, sunitinib, sorafenib); IGF1R inhibitors	Angiogenesis, IGFR1

CUTANEOUS MELANOMA

Cutaneous melanoma incidence in Caucasians has been increasing rapidly for last years. Surgery remains the mainstay of melanoma therapy of all

sites and only early diagnosis combined with proper surgical therapy give currently the chance for cure the patients affected by this malignant tumor (18, 19). Excisional biopsy of suspicious melanomatous skin lesions (after careful skin examination using dermatoscopy) likely to be diagnosed as early melanomas is crucial in establishing diagnosis and prognostic factors. Early diagnosis and surgical removal of cutaneous melanoma not only improves patients' prognosis, but it is also associated with approximately 90% likelihood of cure.

The limited efficacy of systemic and adjuvant treatment (interferon) for metastatic melanoma emphasize the importance of effective initial surgical therapy. The next steps following excisional biopsy are: radical scar excision with adequate margins and sentinel lymph node biopsy (SNB). Modern recommendations regarding extent of final margins based on a few controlled, prospective trials limited definitive resection margins around primary melanoma site to 1-2 cm instead of previously used 3-5 cm margins (20, 21).

Sentinel node biopsy is perhaps the greatest contribution in surgical oncology of last two decades for assessment of the stage of regional nodes. In 1999 the World Health Organization declared SNB as a standard of care in melanoma patients without evidence of metastases, and American Joint Committee on Cancer (AJCC) incorporated SNB as a microstaging procedure in the TNM staging system (22). Several studies (including our series on more than 1000 cutaneous melanoma patients) have already proven that SNB offers several benefits in the course of melanoma patient management: better staging, avoiding unnecessary elective lymph node dissection, excellent prognostic information, facilitation of therapeutic lymphadenectomy, homogeneity of patient populations in clinical trials on adjuvant therapy, and – from the patient's point of view – increased sense of safety and accuracy of care (19, 23). The crucial trial regarding SNB – the first Melanoma Sentinel Lymph Node Trial I (MSLT-I) confirmed that this technique has an important diagnostic and prognostic role, but failed to demonstrate a survival benefit in the entire group of melanoma patients with sentinel node biopsy (24). Nevertheless, the status of regional lymph nodes is the most important prognostic factor influencing both disease-free and overall survival in melanoma patients (19, 24). In case of positive sentinel node biopsy the radical removal of lymph nodes of involved basin is indicated. Patients after completion lymph node dissection due to positive sentinel node have statistically significantly lower number of metastatic nodes than in group of patients after lymphadenectomy due to palpable metastases (25). The most important further question is possibility of limitation of necessity of completion lymph node dissection in selected cases with submicrometastases to sentinel node as well as ultimate defining of evaluation of sentinel node (immunohistochemistry, molecular techniques, carbon dye in mapping). Recent discoveries have stressed the prognostic role of SN tumor burden and microanatomic tumor deposit location. Van Akkooi et al. (26, 27) showed that sub-micrometastases < 0.1 mm according to the Rotterdam criteria have extremely favorable prognosis identical to patients with negative SNs, what has been recently confirmed on our group of patients (28).

There is need for new prognostic and predictive factors in melanoma patients. The studies on the analysis of presence of melanoma markers or circulating tumor cells in body fluids are one of the interesting directions. The results of RT-PCR analyses of melanoma circulating cells in blood specimens (especially from single, not serial determination studies) and of detection of melanoma molecular markers in SNs are controversial. We have introduced the technique of multi-marker (MM) RT-PCR assay for assessment of the presence of melanoma molecular markers in lymph fluid collected routinely after lymph node dissection and we have demonstrated that a positive result of the MM RT-PCR assay of lymph fluid is a valuable tool for the prediction of subclinical residual disease, early disease relapse, and shorter survival (29, 30).

Until now the treatment of melanoma patients with distant metastases had a very limited efficacy (with standard systemic therapy with dacarbazine). The recent discoveries in targeted therapy (as BRAF inhibitors) and immunotherapy (anti – cytotoxic T-lymphocyte antigen-4 (CTLA4] therapy) give the opportunity for changing this landscape. The randomized, phase III study with using ipilimumab (a fully human monoclonal antibody against CTLA-4) in advanced, previously treated melanoma patients demonstrated activity of this drug with improvement of long-term overall survival (2-year overall survival rate 24% in stage IV) (31).

BIBLIOGRAPHY

1. Rutkowski P, Nowecki P (red.): Mięsaki tkanek miękkich u dorosłych. Monografia. editor. Medical Tribune, 1st ed. Warszawa 2009.
2. Ruka W, Rutkowski P, Krzakowski M et al.: Mięsaki tkanek miękkich u dorosłych – zasady postępowania diagnostyczno-terapeutycznego. Onkologia w Praktyce Klinicznej 2009; 5: 198l-210.
3. Rutkowski P, Kaminska J, Kowalska M et al.: Cytokine serum levels in soft tissue sarcoma patients: correlations with clinicopathological features and prognosis. Int J Cancer 2002; 100: 463-471.
4. Rutkowski P, Kaminska J, Kowalska M et al.: Cytokine and cytokine receptor serum levels in adult bone sarcoma patients: correlations with local tumor extent and prognosis. J Surg Oncol 2003; 84: 151-9.
5. McCarter MD, Jaques DP, Brennan MF: Randomized clinical trials in soft tissue sarcoma. Surg Oncol Clin N Am 2002; 11: 11-22.
6. O'Sullivan B, Davis AM, Turcotte R et al.: Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomized trial. Lancet 2002; 9325: 2235-41.

7. Bacci G, Picci P, Ruggieri P: Primary chemotherapy and delayed surgery (neoadjuvant chemotherapy) for osteosarcoma of the extremities. Cancer 1990; 65: 2539-2553.
8. Magenau JM, Schuetze SM: New targets for therapy of sarcoma. Curr Opin Oncol 2008; 20: 400-406.
9. Rutkowski P, Van Glabbeke M, Rankin CJ et al.: European Organisation for Research and Treatment of Cancer Soft Tissue/Bone Sarcoma Group; Southwest Oncology Group: Imatinib mesylate in advanced dermatofibrosarcoma protuberans: pooled analysis of two phase II clinical trials. J Clin Oncol 2010; 28: 1772-9.
10. Rutkowski P, Dębiec-Rychter M, Nowecki ZI et al.: Treatment of advanced dermatofibrosarcoma protuberans with imatinib mesylate with or without surgical resection. J Eur Acad Dermatol Venereol 2010 Jun 21. (Epub ahead of print).
11. Rutkowski P, Symonides M, Zdzienicki M, Siedlecki JA: Developments in Targeted Therapy of Advanced Gastrointestinal Stromal Tumors. [In:] Atta-ur-Rahman, M. Iqbal Choudhary (Eds.) Frontiers in Anti-Cancer Drug Discovery. 1st ed. Bentham Science Publishers 2010; 1: 428-448.
12. Rutkowski P, Nowecki ZI, Michej W et al.: Risk criteria and prognostic factors for predicting recurrences after resection of primary gastrointestinal stromal tumors (GISTs). Ann Surg Oncol 2007; 14: 2018-27.
13. DeMatteo R, Ballman KV, Antonescu CR et al.: Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet 2009; 373: 1079-104.
14. Casali PG, Jost L, Reichardt P, Schlemmer M, Blay JY: Gastrointestinal stromal tumours: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2009; 20 (suppl. 4): iv64-iv67.
15. Demetri GD, von Mehren M, Blanke CD et al.: Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. NEJM 2002; 347: 472-80.
16. Rutkowski P, Nowecki ZI, Dębiec-Rychter M et al.: Predictive factors for long term effects of imatinib therapy in patients with inoperable/metastatic CD117(+) gastrointestinal stromal tumors (GISTs). J Ca Res Clin Oncol 2007; 133: 589-97.
17. Ruka W, Rutkowski P, Kulig J et al.: Zasady postępowania diagnostyczno-terapeutycznego u chorych na nowotwory podścieliskowe przewodu pokarmowego (GIST) w 2008 roku. Nowotwory – Journal of Oncology 2008; 58: 493-602.
18. Ruka W, Krzakowski M, Placek W Et al.: Czerniaki skóry – zasady postępowania diagnostyczno-terapeutycznego. Onkologia w praktyce klinicznej 2009; 5: 20-32.
19. Testori A, Rutkowski P, Marsden J Et al.: Surgery and radiotherapy in the treatment of cutaneous melanoma. Ann Oncol 2009; 20 (Suppl. 6): vi22-vi29.
20. Eggermont AMM, Gore M: Randomized adjuvant therapy trials in melanoma: surgical and systemic. Sem Oncol 2007; 34: 509-515.
21. Thomas JM, Newton-Bishop J, A'Hern R et al.: Excision margins in high-risk malignant melanoma. N Engl J Med 2004; 350: 757-766.
22. Balch CM, Gershenwald JE, Soong S-J Et al.: Final Version of 2009 AJCC Melanoma Staging and Classification. J Clin Oncol 2009; 27: 6199-206.
23. Nowecki ZI, Rutkowski P, Nasierowska-Guttmejer A, Ruka W: Sentinel lymph node biopsy in melanoma patients with clinically negative regional lymph nodes – one institution's experience. Melanoma Res 2003; 13: 35-43.
24. Morton DL, Thompson JF, Ochran AJ Et al.: Sentinel-node biopsy or nodal observation in melanoma. NEJM 2006; 355: 1307-1317.
25. Nowecki ZI, Rutkowski P, Michej W: The Survival Benefit to Patients with Positive Sentinel Node Melanoma After Completion Lymph Node Dissection May Be Limited to the Subgroup with a Primary Lesion Breslow Thickness Greater Than 1.0 and Less Than or Equal to 4 mm (pT2-pT3). Ann Surg Oncol 2008; 15: 2223-2234.
26. van Akkooi ACJ, de Wilt JHW, Verhoef C et al.: Clinical relevance of melanoma micrometastases (< 0.1 mm) in sentinel nodes: are these nodes to be considered negative? Ann Oncol 2006; 17: 1578-1585.
27. van Akkooi AC, Nowecki ZI, Voit C Et al.: Sentinel node tumor burden according to the Rotterdam criteria is the most important prognostic factor for survival in melanoma patients: a multicenter study in 388 patients with positive sentinel nodes. Ann Surg 2008; 248 (6): 949-55.
28. Rutkowski P, Nowecki ZI, van Akkooi AC et al.: Multimarker Reverse Transcriptase-Polymerase Chain Reaction Assay in Lymphatic Drainage and Sentinel Node Tumor Burden. Ann Surg Oncol. 2010 Jul 7. (Epub ahead of print).
29. Ruka W, Rutkowski P, Nowecki ZI et al.: Detection of melanoma cells in the lymphatic drainage after lymph node dissection in melanoma patients by using two-marker reverse transcriptasepolymerase chain reaction assay. Ann Surg Oncol 2004; 11: 988-97.
30. Nowecki ZI, Rutkowski P, Kulik J et al.: Molecular and biochemical testing in stage III melanoma: multimarker reverse transcriptasepolymerase chain reaction assay of lymph fluid after lymph node dissection and preoperative serum lactate dehydrogenase level. Br J Dermatol 2008; 159 (3): 597-605.
31. Hodi FS, O'Day SJ, McDermott DF Et al.: Improved Survival with Ipilimumab in Patients with Metastatic Melanoma NEJM 2010; 10.1056/nejmoa1003466.

otrzymano/received: 21.12.2010
zaakceptowano/accepted: 10.01.2011

Adres/address:
*Piotr Rutkowski
Klinika Nowotworów Tkanek Miękkich, Kości i Czerniaków
Centrum Onkologii – Instytut im. M. Skłodowskiej-Curie
ul. Roentgena 5, 02-781 Warszawa
e-mail: rutkowskip@coi.waw.pl