allowed identifying new and specific treatment targets for malignant glioma. Trials using new agents blocking EGFR, PDGF and integrins are underway and some encouraging responses have been observed. The challenge remains to identify the patients who are most likely to benefit from new treatment approaches and integration of the novel agents into the existing multimodality treatments.

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Investigational therapies in glioma - from drugs to biological modifiers and back

S. Grossman. *The Sydney Kimmel Cancer Center at Johns Hopkins, Room G93, Baltimore, MD, USA*

Progress in the management of high grade gliomas has been modest during the past three decades. Although surgery and radiation provide clear benefits, additional improvement in survival from these modalities is unlikely. Chemotherapy currently adds little to outcome. Clinical research using novel agents and approaches are needed as these tumors remain rapidly progressive and universally fatal. A wide range of new compounds and delivery methods are now available for study. The efficacy of novel cytotoxic agents can be evaluated using small numbers of carefully selected patients with previously untreated glioblastoma multiforme. If responses are not seen in this patient population, an agent can be declared inactive and others can be studied. The efficacy of radioenhancers, antiangiogenesis and other non-cytotoxic agents can be assessed by administering them with radiation to 54 patients with newly diagnosed glioblastoma multiforme using survival as the endpoint. This will provide sufficient statistical information to make reasonable decisions regarding the development of these agents. Recent discoveries of interactions between enzyme inducing antiepileptic drugs and the pharmacology of biologic and chemotherapy agents have had a profound effect on clinical brain tumor research. Studies are now moving from measuring concentrations of novel agents in blood to measurements within the brain tumor using microdialysis catheters in patients with glioblastomas. Finally, a variety of novel locally administered therapies using convection or investigational devices to deliver interstitial radiation, chemotherapy, and biologics are entering trials. These will facilitate the development of combination therapies in patients with locally recurrent tumors. Each of these concepts and approaches will be presented using examples from the NABTT CNS Consortium to highlight the expanding potential for innovative clinical research in patients with high grade gliomas.

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Epidemiology (including HPV)

X. Bosch. *ICO-Institut Català d'Oncologia, Servicio de Epidemiologia y Registro Cancer, Barcelona, Spain*

Cervical cancer epidemiology and the causal association between Human Papillomavirus infections and cervical cancer. On several occasions, estimates of the burden of Human Papillomavirus (HPV) infections and of the closely associated cervical lesions have been produced. Data on invasive cervical cancer extrapolated to the existing population indicate for Europe some 65.000 new cases per year and an age-standard rate of 13 new cases per 100.000 per year. Data on genital HPV-DNA prevalence in representative samples of populations in different countries are limited. Typically the proportions of HPV-DNA carriers have been placed in the 15-40% range in the young, sexually active, age groups and between 3-10% range in the 35 and above age groups. Prevalence in the male external genitals is only available for a few countries and the evidence suggests that may be roughly similar to the prevalence in women.

The association of HPV and cervical cancer. State-of-the art amplification techniques have unequivocally shown that in adequate specimens of cervical cancer HPV-DNA can be detected in 90 to 100% of the cases as compared to a prevalence of some 5-20% from cervical specimens of women identified as suitable epidemiological controls. Detailed investigations of the few cervical cancer specimens that appear as HPV DNA negatives in most series has been occasionally conducted and the results strongly suggest that these are largely false negatives. As a consequence, the claim has been made that this is the first *necessary cause* of a human cancer ever identified, providing a strong rationale for the use of HPV tests in screening programs and for the development of HPV vaccines.

Risk estimates from IARC's case control studies. The pool of IARC studies is large enough to provide, for the first time, type specific risk estimates for 18 types. The adjusted Odds Ratios (OR) for HPV DNA detection (the factor by which the reference risk of cervical cancer is multiplied if HPV DNA is detected) was OR any single type = 172.6 (95%CI: 122.2-243.7). Type specific risk estimates were as follows: HPV 16: OR= 435; HPV 18: OR= 248; HPV 45: OR= 198; HPV 31: OR= 124; HPV 33: OR=374; HPV 35: OR=74; HPV51: OR= 67; HPV 52: OR= 200; HPV 58: OR= 115; HPV 59: OR= 419. The risk for any given high-risk type was not statistically different from the risk reported for HPV 16. The risk related to the presence of multiple HPV types in the specimen is no different from the risk linked to a single HPV type. The standard estimates of the attributable fraction (AF%) -the proportion of disease that is related to HPV DNA- derived from these and most other studies range from 90 to 98%. The practical conclusions from these analyses strongly indicates that, under current evidence, group testing of clinical specimens for a cocktail of high risk types should be sufficient for screening and patient management. One of such tests, Hybrid Capture 2 (HC2), is commercially available and progressively introduced in clinical practice. Individual typing remains necessary in research settings and for studies evaluating therapeutic or preventive type-specific HPV vaccines.

Conclusion: The association between HPV exposures and cervical cancer has been recognized as causal in nature and furthermore as a necessary cause. This implies that in the absence of the persistent viral presence, cervical cancer is not expected to develop. This milestone recognition is reshaping the preventive scenario, in the screening and vaccination fields

Recommended reading:

[1] Bosch FX, Lorincz A, Muñoz N, Meijer CJLM, Shah KV. *The causal relation between human papillomavirus and cervical cancer.* J Clin Pathol 2002, 55(4): 244-265

[2] Muñoz N, Bosch FX, de Sanjosé S, Herrero R, Castellsagué X, Shah KV, Snijders PJF, Meijer CJLM, for the International Agency for Research on Cancer (IARC). *Epidemiological classification of HPV types causing squamous cell cervical cancer: Implications for prevention.* New Eng J Med 2003, 348(6): 518-527

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Surgery for primary and recurrent disease

M. Höckel. *Universitaet Leipzig Frauenklinik, Department of Ob./Gyn., Leipzig, Germany*

Standard surgical treatment of cervical carcinoma includes radical hysterectomy for FIGO stages IB and IIA and pelvic exenteration for advanced primary and locally recurrent central pelvic disease without pelvic side wall involvement. Current radical hysterectomy techniques are based on surgical anatomy which is in several aspects not compatible with human embryologic and fetal development. The operation is generally performed without visualization of the pelvic autonomic nerves. Adjuvant radiation is necessary to obtain acceptable local control rates for patients whose carcinomas exhibit histopathological risk factors. The rates of treatment-related severe complications and long-term sequelae appear to be higher than those for primary radiation although the oncological results are not better. The new total mesometrial resection (TMMR) is characterized by (i) the en bloc resection of the uterus, proximal vagina and mesometrium as a developmentally defined entity, (ii) transection of the rectouterine subperitoneal dense connective tissue above the level of the exposed hypogastric nerve and inferior hypogastric plexus and (iii) extended pelvic/periaortic lymph node dissection preserving the superior hypogastric plexus. From 1998 to 2002 71 patients with cervical cancer FIGO stages IB, IIA and selected IIB underwent TMMR without adjuvant radiation. 54% of the patients exhibited histopathological high risk factors. At a median observation period of 30 months 6 patients relapsed and 3 patients died. No patient had grade 3 or 4 complications. No severe long-term impairment of pelvic visceral functions related to autonomic nerve damage was detected. Based on these preliminary results TMMR achieves a promising therapeutic index by providing a high probability of locoregional control at minimal short and long term morbidity. Another new operation, the laterally extended endopelvic resection (LEER) extends the lateral resection plane of pelvic exenteration to the medial aspects of the lumbosacral plexus, sacrospinous ligament, acetabulum and obturator membrane. The inclusion of the muscles of the pelvic side wall and floor as well as the complete urogenital mesentery en bloc with pelvic organs in the LEER specimens allows the removal of a subset of locally advanced and recurrent cervical carcinomas fixed to the pelvic wall with free margins (R0). 36 patients with recurrent (n=29) or primary advanced (n=7) gynecologic malignancies involving the side wall of the lesser pelvis underwent LEER from 1996 until 2002. Severe postoperative complications occurred in 14 patients. Five-year survival probability was 49% for the whole group and 46% for those patients considered only for palliation with current treatment options. Patients without evidence of disease achieved good quality of life.