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Exposing a Tumor to Air

ABSTRACT & COMMENTARY

Synopsis: *Patients often express concern regarding tumor dissemination from surgical procedures. In this report, Yamaguchi and colleagues show that the detection of colorectal cancer cells in the mesenteric venous blood is associated with a worse survival. Detection of tumor cells in the peripheral blood after surgical manipulation is discussed.*

Source: Yamaguchi K, et al. *Ann Surg* 2000;232:58-65.

Yamaguchi and colleagues report on the use of reverse transcriptase polymerase chain reaction (RT-PCR) technology to detect circulating tumor cells in blood from colorectal cancer patients. The patients in this study were operated on in 1997 at Yamaguchi et al's institution in Japan. There were 38 operations for colon cancer and 14 for rectal cancer. RT-PCR was performed using cDNA primers specific for CEA and cytokeratin. Only the detection of mRNA for both CEA and cytokeratin was considered positive because of the potential for false-positive results with CEA alone. Samples collected included a pre- and postoperative specimen from the peripheral blood as well as a pre-resection intraoperative specimen obtained from the mesenteric venous blood.

Evidence for malignant cells in the mesenteric venous blood specimens was found in 16 (31%) of the patients as defined by a positive RT-PCR for both CEA and cytokeratin. There was a statistically significant relationship between PCR-positivity and stage. Importantly, the PCR-negative group survived significantly longer than the PCR-positive group. The PCR result was an independent prognostic factor based on a multivariate analysis. These data suggest that the demonstration of tumor cells being shed into the mesenteric venous blood provides important prognostic information.

Did surgical manipulation of the tumor cause any patients to become PCR positive? Considering the 49 peripheral blood samples that were PCR negative preoperatively, only five became PCR positive postoperatively. The relevance of this is unclear as two of the three peripheral blood samples that were PCR posi-

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tive preoperatively became negative postoperatively. Yamaguchi et al suggest that intermittent shedding and sampling errors can account for some false results.

COMMENT BY KENNETH W. KOTZ, MD

How many times has a patient expressed concern that exposing a tumor to air will cause it to spread? Does surgical manipulation allow dissemination of malignant cells? Unfortunately, this study titled "Significant Detection of Circulating Cancer Cells in the Blood by RT-PCR During Colorectal Cancer Resection" was not able to answer these questions. Of those 49 patients who were considered negative preoperatively, 44 remained negative and five became positive. Conversion of peripheral blood from a negative to a positive result was not clearly associated with an adverse outcome. In the same issue of the *Annals of Surgery*, another study did show significantly more tumor cell detection in the blood during resection of liver metastases from colorectal cancer compared with before or after surgery.[1] Other studies that have used PCR technology have also been able to show conversion from negative to positive PCR as a result of surgical manipulation of colorectal tumors.

Whether these findings will have any clinical benefit is unclear. Approaches to compensate for potential dissemination of tumor cells could include changing the surgical technique or starting the chemotherapy intraoperatively. A randomized clinical trial of the "no-touch technique" to address the role of surgery has been published.[2] The no-touch technique, involving the ligation of the lymphovascular pedicle before mobilization of the tumor, did not result in a statistically significant improved outcome.[2]

Early postoperative chemotherapy was shown to have a survival advantage for premenopausal women with estrogen receptor negative breast cancer,[3] a concept discussed by Dr. Ershler in the March 2000 issue of *Clinical Oncology Alert*.[4] Whether immediate postoperative initiation of standard chemotherapy administered peripherally would be more effective than the same chemotherapy started 3-4 weeks postoperatively has not been tested in colorectal cancer.

The use of a fluorouracil infusion into the portal vein, which is started on the day of surgery, has been tested.[5] Although only compared to no adjuvant therapy, the National Surgical Adjuvant Breast Project has shown that immediate postoperative portal vein infusions can be associated with a disease-free survival advantage and a trend toward overall survival.[5] Whether this technique is time-dependent or could have additive effects when combined with standard peripherally-infused chemotherapy is unproven.

Yamaguchi et al have shown evidence that circulating colorectal cancer cells can be detected in mesenteric venous blood samples. In a multivariate analysis, only the detection of mRNA in mesenteric venous blood for both CEA and cytokeratin was significantly associated with survival. For example, at one year, those patients who were positive for both CEA and cytokeratin had a survival rate of nearly 60%, whereas if either the CEA or cytokeratin (or both) were negative, the one-year survival rate was more than 90%. The clinical usefulness of this information remains to be proven. ❖

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LES Relaxing Drugs and the Rise in Esophageal Cancer

ABSTRACT & COMMENTARY

Synopsis: *There has been an increase in esophageal cancer in the past three decades and this may, in part, relate to an increase in the use of drugs that reduce lower esophageal sphincter tone. In this case control study from Sweden, a positive association between the long-term use of such drugs and esophageal adenocarcinoma (but not squamous cell carcinoma or gastric adenocarcinoma) was revealed. Thus, drugs that relax the lower esophageal sphincter, such as aminophyllins, nitroglycerin (long- and short-acting), and benzodiazepines must be considered risks for the development of this malignancy. Patients requiring the long-term use of any of these drugs should be watched carefully for signs of reflux esophagitis and treated early if they develop.*

Source: Lagergren J, et al. *Ann Intern Med* 2000;133: 165-175.

The increase in esophageal cancer observed over the past several decades has not been satisfactorily explained.[1] Reflux esophagitis has been shown to be a clinical antecedent, particularly for adenocarcinomas, and it has been proposed that one factor may be the increased use of prescribed medications that reduce the lower esophageal sphincter (LES) tone and thereby permit a reflux of gastric acid. To address this question, Lagergren and colleagues performed a nationwide (Sweden) population-based case-control study with in-person interviews. They identified 189 patients with newly diagnosed esophageal adenocarcinoma, 262 with adenocarcinoma of the gastric cardia and 167 with esophageal squamous-cell carcinoma. Their prescription history was compared with 820 matched controls. Using multivariate logistic regression analysis, estimated incidence rate ratio was calculated.

For this analysis, five groups of LES-relaxing drugs were considered. These were selected because these drugs were in common use during the two decades prior to diagnosis, a time period considered relevant in light of the current understanding of the time required for the pathogenesis of esophageal and gastric cancers. Newer drugs, such as calcium channel blockers, which are known to relax LES, were not included in this analysis. The five groups of drugs that were included were: nitroglycerines, anticholinergics, β–adrenergic agonists, aminophyllines, and benzodiazepines.

There was a significant positive association between the use of LES-relaxing drugs and risk for esophageal adenocarcinoma. Ever users of any of the drugs had an estimated adjusted incidence rate ratio (IRR) of 1.8 (95% CI, 1.3-2.7) compared with never users. Treatment with LES relaxing drugs for less than five years was associated with a moderate but not statistically significant excess risk (IRR, 1.3 [CI, 0.6-2.9]), but treatment of five or more years carried an adjusted IRR of 2.4 (CI, 1.5-3.8). Among the patients with esophageal adenocarcinoma, 17.5% reported daily use of at least one of the studied drugs for five years or more, compared to 6.6% of controls (adjusted IRR, 3.8 [CI, 2.2 to 6.4] for daily users compared with never users).

In contrast to the striking data for adenocarcinoma of the esophagus, squamous cell carcinoma of the esophagus and adenocarcinoma of the stomach were not significantly linked to prior use of these drugs. Furthermore, by using the multivariate model, there was no evidence of confounding by socioeconomic status, body mass index, tobacco smoking, alcohol use, or dietary intake of fruit and vegetables. However, the association of adenocarcinoma of the esophagus and LES-relaxing drugs was found to be tightly linked to experiencing symptoms of reflux esophagitis.

COMMENT BY WILLIAM B. ERSHLER, MD

Among white men in the United States, the incidence of adenocarcinoma of the esophagus is increasing more rapidly than any other tumor type.[2] The reason for this has not been satisfactorily explained. However, reflux esophagitis is a known risk factor[3] and it stands to reason that drugs associated with decreased LES tone would be potential risks for esophageal adenocarcinoma. This report supports that hypothesis. Commonly prescribed drugs that are known to have the untoward effect of lowering LES and producing reflux were found to be associated with a significant and dose-related increase in esophageal adenocarcinoma. These drugs, such as aminophyllin, nitroglycerin (short- and long-acting), the anticholinergics and the β–agonists have been commonly prescribed for decades in Sweden. Other drugs, such as calcium channel blockers, tricyclic antidepressants, α–adrenergic antagonists, nicotine derivatives, and chlorpromazines are also known to reduce LES and are now more commonly used in Sweden and the United States. With the expanded use of these agents, it is likely that the incidence of adenocarcinoma of the esophagus will continue to climb.

It is one thing to uncover an association and even propose a mechanism for increased cancer risk. It is another

to actually do something about it. If, indeed, this association is true, then clinicians must be more vigilant to detect early symptoms and signs of reflux esophagitis in patients placed at higher risk for esophageal cancer on the basis of a prescribed drug. ❖

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Improving Treatment Responses for Hepatic Malignancy

ABSTRACT & COMMENTARY

Synopsis: *Treatment of liver malignancy remains only marginally effective. One reason for this is the heretofore limited role of radiation therapy because of the radiosensitivity of normal liver. In this report, a series of patients with hepatic malignancy were treated with high-dose radiation delivered in a focused manner such that normal liver was spared. Responses were impressive when compared to published experience. Future research developing this approach is clearly warranted.*

Source: Dawson LA, et al. *J Clin Oncol* 2000;18: 2210-2218.

Treatment of liver malignancy, whether primary or metastatic, has proven problematic. Historically, radiation therapy has not been a primary modality because it was technically difficult to protect the surrounding radiosensitive normal liver.[1,2] However, new three dimensional, conformal techniques have permitted the delivery of higher doses of radiation to localized intrahepatic disease and these have led to significantly higher response rates than would be anticipated from whole liver radiation alone.[3,4]

In the current phase I/II trial, 43 patients with unresectable intrahepatic cancer (27 with primary hepatobiliary cancer and 16 with metastases from colorectal primaries) were treated with high-dose conformal radiation therapy (RT) and intrahepatic arterial infusion of fluorodeoxyuridine (0.2 mg/kg/d). The radiation was precisely delivered to a target contoured by axial computed tomography using techniques developed at this institution (University of Michigan). Dawson and associates adjusted the dose and schedule by a method they had developed to predict and then deliver an equivalent risk of radiation-induced liver disease (RILD) (5). The starting dose of radiation subjected every patient to an estimated 10% maximal risk of RILD and the doses were adjusted upward in 10% increments. The maximal allowable prescribed dose was 90 Gy to the isocenter. The median tumor size was 10 × 10 × 8 cm and the median dose of RT was 58.5 Gy (range, 28.5-90 Gy) administered as 1.5 Gy twice daily.

The response rate in the 25 assessable patients was 68% (16 partial and 1 complete response). With a median potential follow-up period of 26.5 months, the median times to progression for all tumors, metastatic (colorectal) lesions, and primary hepatobiliary cancers was six, eight, and three months and overall survival was 16, 18, and 11 months, respectively. Upon further (multivariate) analysis, those that were treated with higher doses had superior outcomes. For example, the survival of patients treated with 70 Gy or more had not been reached by 16.4 months of analysis, whereas the median survival for those that received less was 11.6 months.

Dawson et al suggested that higher-dose, focused radiation is now feasible for the treatment of liver malignancy, either primary or metastatic and that higher dose radiation may result in higher response rates and longer survival.

COMMENT BY WILLIAM B. ERSHLER, MD

Treatment of malignancy in the liver, either primary or secondary, has been very disappointing. In recent years, hepatic resection of metastatic lesions has become more commonplace, and this approach has been predicated on the failure of any other intervention to enhance survival. Whole liver radiation is of limited value because of the radiosensitivity of the normal hepatic tissue. In many cases, surgical excision is not possible due to the size or location of the tumor or to host factors that preclude such extensive surgery. Thus, the new developments in radiation therapy are a welcome advance. Survival in patients treated to higher doses, using a well described technique that allows focused dosing to the tumor without injuring normal liver appears improved. What's more, it does not appear that the method has been used to the maximum yet. That is, additional doses of RT would have been possible in at least some of these patients.

This was not a randomized or otherwise controlled study, but a series of patients treated by a specific technique; thus, it is hazardous to become too enthusiastic about the results. Nonetheless, it's hard to hide that enthusiasm because the approach makes sense, it is an

application of new imaging and radiation physics advances, and the successes of other approaches have been so marginal. Accordingly, it's time to subject this approach to a more critical evaluation. Dawson et al will need to define their treatment populations more finely (either primary or secondary lesions) and choose a standard target dose (e.g., 70 Gy). They will also need to justify the hepatic arterial infusion of chemotherapy, inasmuch as this adds significant complexity to the widespread application of this approach. Perhaps a future randomized study could compare intrahepatic arterial chemotherapy vs. focal, high-dose RT vs. a combination of the two. ❖

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Thalidomide Diminishes Irinotecan Toxicity

ABSTRACT & COMMENTARY

Synopsis: *Thalidomide is currently being actively investigated as cancer treatment because of its anti-angiogenic and immunomodulatory effects. However, an important observation was recently discovered in a series of patients with colorectal cancer receiving irinotecan. This commonly used chemotherapeutic has an associated incidence of diarrhea that at times has been prohibitive, but in this small series of patients receiving irinotecan and thalidomide, there was virtually no gastrointestinal toxicity, including diarrhea. Thus, thalidomide might be a useful adjunct to chemotherapy for reasons in addition to its anti-tumor effect.*

Source: Govindarajan R, et al. *Lancet* 2000;356: 566-567.

Irinotecan (cpt 11, camptosar) is the only approved second-line chemotherapy for colorectal cancer in the United States. However, overall response rates remain low (< 20%) and treatment is often limited by severe gastrointestinal toxicity, most prominent of which is diarrhea.[1,2] Thalidomide, a glutamic acid derivitive, was originally introduced as a sedative but was removed after it was shown to be associated with severe teratogenicity. Recently, thalidomide has been shown to have antiangiogenesis and immunomodulatory properties, and its role in the treatment of cancer is currently being explored.[3]

In a pilot trial from the University of Arkansas for Medical Sciences, Govindarajan and colleagues treated nine patients with advanced colorectal cancer with thalidomide (400 mg, orally at bedtime) and irinotecan (325-350 mg/m^2 q 21 days). They discovered that there was a striking absence of diarrhea and/or nausea in the treated patients. After 2-8 cycles of irinotecan, all patients but one were able to complete therapy at the prescribed dose (1 patient required a 50% dose reduction because of asthenia); and all but one patient tolerated the thalidomide (1 patient had the dose reduced by 75% because of somnolence). Of the seven assessable patients, one achieved a complete antitumor response and two had partial responses.

Compared to previously published data, there was significantly less than expected nausea, vomiting, and diarrhea in the treated patients. Whereas published series would predict greater than 85% incidence of diarrhea with 30% grade 3 or 4, only one patient in this series had mild diarrhea and none had grade 3 or 4. Similarly, the incidence of nausea and vomiting was dramatically reduced.

COMMENT BY WILLIAM B. ERSHLER, MD

This brief report is remarkable because it highlights a new and potentially very important observation from a clinical trial. Thalidomide was added to the established second-line drug for colorectal cancer with the hopeful expectation of observing enhanced clinical responses. The series is too small and of too small a duration to conclude any effect at this time. However, the striking disappearance of nausea, vomiting, and diarrhea from the treatment group is remarkable and, in itself, may be of sufficient importance to move thalidomide into the recommended treatment plan.

The finding needs to be confirmed and additional questions need to be addressed. What dose of thalidomide is required and will you get the same protective effect if administered just on the day of chemotherapy and perhaps a few days after? This question, of course, would be precluded if the larger investigation demonstrates an additive anti-cancer effect of thalidomide, in which case, continuous treatment might be required. ❖

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Protection from Cancer by Anti-inflammatory Drugs

ABSTRACT & COMMENTARY

Synopsis: *A history of nonsteroidal anti-inflammatory drug use was examined in a large series of cancer patients and controls from the United Kingdom. Long-term use was associated with a decreased risk of colorectal, esophageal, and gastric cancer, but possibly an increased risk of pancreatic and prostatic cancers. No effect was seen on the development of breast or bladder cancer. Perhaps these findings are related to the known increased expression of the COX-2 gene in many of these tumors.*

Source: Langman MJ, et al. *BMJ* 2000;320: 1642-1646.

Previously published data has suggested an association of aspirin, or other nonsteroidal anti-inflammatory drug (NSAID) use and a reduced risk of certain malignancies.[1-3] The purpose of this study was to use a large database to establish whether this is true for the common malignancies in the United Kingdom. Langman and associates from the University of Birmingham examined data that had been contributed to a large U.K. database managed by the Department of Health. This database includes medical information, contributed by physicians throughout the United Kingdom, on more than 4 million individuals. During a two-year period (1993-1995), there were 12,174 people who first developed either gastrointestinal (esophagus, stomach, colon, rectum, or pancreas) or nongastrointestinal (bladder, breast, lung, or prostate) cancers. Each case was matched for age, sex, and general practice site with three controls. Langman et al went on to determine the relative risk for determining each of the cancers in the context of anti-inflammatory drug use (by prescription). The threshold for anti-inflammatory drug use was considered seven filled prescriptions over the previous three years.

Examining the data as a whole, it did not appear that the overall incidence of cancer was influenced by the use of anti-inflammatories. However, there did appear to be a protective effect against cancer of the esophagus (odds ratio 0.64, 95% confidence interval 0.41-0.98), stomach (0.51, 0.33-0.79), colon (0.76, 0.58-1.00), and rectum (0.75, 0.49-1.14), with dose-related trends. The risk of pancreatic cancer (1.49, 1.02-2.18) and prostatic cancer (1.33, 1.07-1.64) was increased among patients who had received anti-inflammatories but the trend was dose-related for only pancreatic cancer.

Langman et al concluded that anti-inflammatory drugs protected against esophageal, gastric, colon, and rectal cancers. They also have pointed out that these drugs may predispose to pancreatic and/or prostate cancer but they suggested that these observations might reflect undetected biases or chance error.

COMMENT BY WILLIAM B. ERSHLER, MD

In the United Kingdom, aspirin and other NSAIDs are available by prescription; thus, quantifying use may be estimated by filled prescriptions. This, and the large database maintained by the Department of Health, made this study feasible. What was found were trends toward reduced incidence of colorectal cancers among people taking these drugs, with the greatest reductions among those receiving more prescriptions. This is, more or less, a confirmation of other epidemiological studies, either cohort or case control.[1-3] However, the findings for esophageal and gastric cancer also showed protection and the results of prior surveys were not nearly as positive. This may be because of the size of the current database, which allowed confirmation of a trend that was observed, but not statistically significant in earlier, smaller studies.[3,4] In the current study, the protective effect of anti-inflammatory drugs was comparable for gastric and esophageal when compared to colorectal carcinomas. However, the study did not reveal any protection against nongastrointestinal tumors. This runs counter to other published reports in which aspirin, or other nonsteroidals, were shown to protect against breast cancer.[5]

The finding of an increased risk of pancreatic cancer is curious but must be interpreted with caution. This diagnosis is often difficult to make, and patients might be treated with NSAIDs for their analgesic properties in advance of the diagnosis thereby providing the appearance of an association. The same may also be true for the findings with prostate cancer, as undiagnosed back pain, ultimately proven to be metastatic disease, might initially be treated with NSAIDs.

Certainly, there has been no proven mechanism whereby NSAIDs protect against gastrointestinal malignancies. However, it should be noted that the cyclooxygenase-2 (COX-2) gene is overexpressed in many tumor types, including colon, esophagus, stomach, and breast,[6] and perhaps inhibition NSAID exposure inhibits tumorigenesis by inhibition of that enzyme. Future studies of specific COX-2 inhibitors in the context of cancer prevention will be of value. ❖

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Combined Hormonal Ablation for Premenopausal Breast Cancer

ABSTRACT & COMMENTARY

Synopsis: *Combined tamoxifen and buserelin treatment for metastatic, hormone receptor-positive breast cancer in premenopausal women was shown in a randomized, prospective, clinical trial to be superior to either agent administered singly. Patients who received buserelin, either alone or with tamoxifen, had reduced serum estradiol levels and this effect on estradiol may be the explanation for the improved clinical outcomes.*

Source: Klijn JGM. *J Natl Cancer Inst* 2000;92: 903-911.

Premenopausal women with metastatic, estrogen receptor (ER)-positive breast cancer have been treated successfully with hormonal ablation. Ovariectomy had been the treatment of choice but, in recent years, comparable success has been achieved with tamoxifen.[1] A summation of the published series in which tamoxifen was used in this situation reveals an objective response rate of 30%.[2] However, endogenous estradiol levels rise in premenopausal women treated with tamoxifen and this has led to the speculation that additional ablative therapy would be useful.[3] In this regard, buserelin, a lutenizing hormone-releasing hormone (LHRH) agonist offers theoretical advantage because its use might inhibit the production of estradiol that has been observed in tamoxifen-treated patients.

Researchers from the European Organization for Research and Treatment of Cancer-Breast Cancer Cooperative Group report the results from a randomized, three-armed, multi-institutional clinical trial in which tamoxifen alone, or buserelin alone, were compared to combined tamoxifen/buserelin treatment for premenopausal women (n = 161) with locally advanced or metastatic ER-positive breast cancer. The median follow-up was 7.3 years, during which 76% of the patients died, all of breast cancer.

Tamoxifen was administered at a dose of 40 mg/d and the buserelin was given by subcutaneous infection at a dose of 6.6 mg every eight weeks. The doses were the same for the patients receiving combined treatment as well as for those in the single treatment groups.

The results indicated that the combined treatment of buserelin and tamoxifen did better than either treatment alone with regard to objective response rate (48% for combined, 34% buserelin, and 28% for tamoxifen), median progression-free survival (9.7 months vs 6.3 months and 5.7 months) and overall survival (3.7 years vs 2.5 years and 2.9 years). There was no significant difference between tamoxifen and buserelin when administered as a single agent, but the combined treatment was statistically significantly better in each of these outcome parameters.

Estradiol levels increased several-fold in those patients treated with tamoxifen alone, but fell by several-fold in those that received buserelin, either alone or in combination with tamoxifen.

COMMENT BY WILLIAM B. ERSHLER, MD

The treatment of metastatic breast cancer remains a challenge, particularly in premenopausal patients. Once the standard of care, ovariectomy has been replaced by tamoxifen because clinical trials have indicated comparable responses.[1] However, responses have been of relatively short duration and the majority of patients succumb to progressive disease. Patients treated with tamoxifen have been shown to have increased estradiol levels in their blood and this may reduce the effectiveness of the drug with regard to inhibition of breast cancer cell proliferation. As a single agent, buserelin has been shown previously to be comparable to tamoxifen and to ovariectomy in the treatment of metastatic breast cancer. As an LHRH agonist, it is known to inhibit estradiol synthesis. Thus, the combined hormonal approach makes sense.

Oftentimes, things that make such sense theoretically don't translate in the clinical sphere. Gratifyingly, however, this is not the case with the combined hormonal approach. Not only did the addition of buserelin impede the estradiol surge in tamoxifen-treated patients, but the combination also was shown to enhance the response rate, progression-free, and overall survival in patients with advanced disease. This

may well immediately translate into clinical practice.

However, several questions remain. Does it make sense to use combined hormonal ablation in adjuvant setting, particularly for premenopausal patients with ER-positive tumors? To what extent will combined hormonal therapy influence subsequent or concurrent chemotherapy responses? Will the addition of an aromatase inhibitor further lower estradiol levels and result in even greater clinical outcomes? These questions can only be answered by future clinical investigation. ❖

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CME Questions

8. Thalidomide has been shown to:

a. enhance the antitumor efficacy of irinotecan for patients with colorectal cancer.
b. reduce the incidence of diarrhea in irinotecan patients treated for advanced colorectal cancer.
c. enhance the antitumor efficacy of irinotecan for patients with non-small cell cancer of the lung.
d. reduce the incidence of diarrhea in irinotecan patients treated for advanced non-small cell cancer of the lung.

9. Which of the following is true regarding colorectal cancer and the study by Yamaguchi et al?

a. Detection of tumor cells in the mesenteric venous blood offers prognostic information.
b. Adjuvant chemotherapy started intraoperatively is more effective than when started 3-4 weeks postoperatively.
c. The "no-touch technique" results in a lower recurrence rate.
d. Adjuvant therapy is most effective when the RT-PCR converts from negative to positive in peripheral blood.

10. Drugs that reduce the tone of the lower esophageal sphincter have been shown to be used more commonly in patients with which of the following tumors?

a. Esophageal adenocarcinoma
b. Esophageal squamous cell carcinoma
c. Gastric adenocarcinoma
d. All of the above
e. None of the above

11. The long-term use of aspirin or other NSAIDs has been shown to reduce the incidence of all of the following tumor types *except*:

a. colonic.
b. esophageal.
c. pancreatic.
d. rectal.
e. gastric.

12. Which of the following statements about combined tamoxifen buserelin hormonal therapy for metastatic, premenopausal breast cancer is *not* true?

a. Overall survival is enhanced when compared to treatment with tamoxifen or buserelin alone.
b. Progression-free survival is enhanced when compared to treatment with tamoxifen or buserelin alone.
c. Estradiol levels are reduced when compared to treatment with tamoxifen alone.
d. Objective response rates are comparable to treatment with tamoxifen alone.

13. Which of the following statements about focal, high-dose radiation to liver cancer is true?

a. Any dose above 30 Gy is likely to cause radiation-induced liver disease in surrounding tissue.
b. A dose of 70 Gy can be safely administered and has been associated with favorable clinical outcomes.
c. A dose of 70 Gy is the limit above which toxicity overshadows favorable clinical outcomes.
d. A dose of 30 Gy can be safely administered and has been associated with favorable clinical outcomes.

In Future Issues:

More About Lung Cancer Treatment in the Elderly