Review

Biological characteristics of cancers in the gallbladder and biliary tract and targeted therapy

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Abstract

Adenocarcinomas of the gallbladder (GBC) and bile ducts (cholangiocarcinoma) (combined as biliary tract cancers, BTC) are uncommon tumors in the United States, but are endemic in parts of South America and Asia. BTC are aggressive tumors with poor survival. Published response rates to chemotherapy are less than 30% and no survival benefit has been demonstrated from palliative systemic therapy. Improved understanding of the biological characteristics and molecular carcinogenic mechanisms of these malignancies may lead to improved therapeutic regimens for patients. © 2006 Published by Elsevier Ireland Ltd.

Keywords: Gallbladder; Biliary tract cancer; Molecular carcinogenesis; Chemotherapy; Transgenic models

1. Introduction—cancers of the gallbladder and biliary tract

Cancer of the gallbladder and cholangiocarcinoma (BTC) are invasive adenocarcinomas that arise from the epithelial lining of the gallbladder, intrahepatic (peripheral) and extrahepatic (hilar and distal common bile duct) bile ducts, accounting for an estimated 7480 new cases and 3340 deaths in the United States, in 2005 [1,2]. Intrahepatic bile duct cancers are included with primary livers cancers in the national databases, thus, the total number of BTC is somewhat higher than this figure. Between 1975 and 1997, both the incidence and mortality rates from intrahepatic cholangiocarcinoma markedly increased in the United States, with an estimated annual percentage change of 9.11% and 9.4%, respectively [2,3]. However, GBC are considered endemic in Japan, Southeast Asia, and parts of South America.

While anatomically these three malignancies are related and have similar metastatic patterns, each has distinct clinical presentations, molecular pathology, and prognoses. This group of tumors is characterized by local invasion, extensive regional lymph node metastasis, vascular encasement and distant metastases, all of which preclude resection. Complete
surgical resection offers the only chance for cure; however, a small percentage of patients present with early stage disease and are considered surgical candidates [4,5]. Among those patients who do undergo “curative” resection, recurrence rates are high; thus, the majority of patients with BTC will seek adjuvant or palliative chemotherapy. In general, gallbladder cancer is the most aggressive of the biliary cancers with the shortest median survival. These tumors are similar in their overall aggressive course and resistance to chemotherapy. Although cancers of the gallbladder, intrahepatic and extrahepatic bile ducts are distinct pathologic and surgical entities, from the perspective of systemic treatment options, these tumors are commonly combined in both retrospective series and prospective clinical trials. Thus for purposes of this review, they will be considered as a single tumor type.

2. Etiology and pathogenesis

The development of BTC appear to be associated with chronic inflammatory conditions, autoimmune disease, biliary calculi, anatomic anomalies, several infectious agents, and certain carcinogens. Chronic cholelithiasis and cholecystitis are closely associated with GBC, and between 50% and 100% of patients diagnosed with GBC have concurrent stones [6,7]. Primary gallbladder malignancy is incidentally found in 0.4–2% of laparoscopic cholecystectomy specimens [8–10]. The latency time from initial development of cholelithiasis to overt malignancy is believed to be 20 years [11]. Chronic mucosal irritation and damage are considered to major promoting factors for malignant transformation [7]. In Japanese patients an uncommon anatomic abnormality, the anomalous pancreatic-biliary duct junction (APBDJ) which leads to efflux of pancreatic juice into the gallbladder, is a predisposing factor for GBC and BTC [12]. Cholangiocarcinoma are associated with chronic cholecystitis and gallstone formation, chronic ulcerative colitis, hepatitis C virus and other chronic infections [13,14]. Bile acids may promote carcinogenesis by stimulating a variety of kinase signaling pathways [15–17].

Early stage gallbladder and bile duct cancers may present pathologically as subtle mucosal abnormalities, such as plaque or ulcerations. Over 90% of gallbladder carcinomas are papillary or tubular adenocarcinomas with mucin-producing or signet-ring cells. The remaining 10% are adenosquamous carcinomas, anaplastic carcinomas, and rarely carcinoid tumors or embryonal rhabdomyosarcoma. These tumors can be subdivided at least two etiological categories including those that arise in the setting of cholelithiasis (squamous, adenosquamous and some adenocarcinomas) and those that arise from anatomic or functional abnormalities of the biliary system [18,19]. Only 10% of gallbladder cancer patients have a tumor confined to the gallbladder wall at the time of diagnosis. Subendothelial invasion and spread to neurovascular structures, regional lymph nodes, and contiguous liver are common and occur early in the natural history of BTC. The key prognostic factors for survival are completeness of resection, lymph node status, and tumor differentiation [20–23]. Median survival for unresectable or recurrent BTC is less than 6 months and less than 5% survive 5 years [24–26]. A clear role for therapy for advanced disease has not been established in either gallbladder or cholangiocarcinomas, although external beam radiotherapy, chemotherapy, and less commonly brachytherapy, are routinely offered to patients. The small numbers of prospective trials that have been conducted in general include heterogeneous patient populations in terms of disease site, surgical stage, and lymph node status thus these studies are difficult to interpret.

3. Current status of cytotoxic therapy in BTC

Systemic chemotherapy has produced some transient responses for unresectable or metastatic tumors. Due to the relatively small numbers of patients, controlled chemotherapy clinical trials are few in number. Several cytotoxic agents have been studied as single agents or in combinations with response rates in the 0–30% range; however, no chemotherapy regimen has been shown to prolong survival in patients with advanced BTC [27–36]. Table 1 summarizes results of several selected clinical trials in BTC. Complete responses are rare and the duration of responses is usually 3–6 months. Currently, there are no data from randomized, prospective clinical trials to support routine use of adjuvant, neoadjuvant

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>RR%</th>
<th>SD%</th>
<th>MS (months)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>23</td>
<td>30</td>
<td>34</td>
<td>9.3</td>
<td>[54–56]</td>
</tr>
<tr>
<td>5FU + carboplatin</td>
<td>14</td>
<td>21</td>
<td>28</td>
<td>NA</td>
<td>[57]</td>
</tr>
<tr>
<td>5FU/LV + cisplatin</td>
<td>29</td>
<td>34</td>
<td>38</td>
<td>9.5</td>
<td>[58]</td>
</tr>
<tr>
<td>Gemcitabine, capecitabine</td>
<td>45</td>
<td>31</td>
<td>42</td>
<td>14</td>
<td>[59]</td>
</tr>
<tr>
<td>5FU, leucovorin, MMC</td>
<td>20</td>
<td>25</td>
<td>21</td>
<td>6.5</td>
<td>[60]</td>
</tr>
<tr>
<td>5FU, LV ± etoposide vs. BSC</td>
<td>37</td>
<td>NA</td>
<td>NA</td>
<td>6.5 vs. 2.5</td>
<td>[61]</td>
</tr>
<tr>
<td>Gemcitabine, cisplatin</td>
<td>40</td>
<td>27.5</td>
<td>32.5</td>
<td>9</td>
<td>[62]</td>
</tr>
<tr>
<td>CEF vs. FAM vs. BSC</td>
<td>89</td>
<td>No survival difference</td>
<td></td>
<td></td>
<td>[63]</td>
</tr>
</tbody>
</table>

Abbreviations: 5FU, 5 fluorouracil; UFT, uracil + tegafur; LV, leucovorin; MMC, mitomycin C; BSC, best supportive care; CEF, cisplatin, etoposide, 5 fluorouracil; PR, partial response; SD, stable disease; MS, median survival; NA, not available.

Study was retrospective series.
or palliative chemotherapy in BTC. Clearly, new therapeutic regimens based on our evolving understanding of the molecular biology and carcinogenic mechanisms underlying development of BTC are needed for this disease.

4. Molecular carcinogenesis

Current hypotheses suggest that the gallbladder and bile duct cancers originate from pre-malignant epithelial dysplasia, which gradually progress to atypical hyperplasia and carcinoma in situ, and eventually invasive carcinoma. Recent work is beginning to elucidate the carcinogenic events that play a role in development of carcinoma of the gallbladder and biliary tract. The major events are summarized in Table 2, and those most clinically relevant to this review are discussed in more detail.

The relation between inflammation, irritation and cancer was initially described in the 19th century by Virchow [27]. Many active substances including cytokines, tumor-necrosis factor (TNF) and pro-angiogenic molecules, are secreted by inflammatory cells, and these may affect the proliferation, differentiation, migration and survival of cells in the surrounding tissues, therefore, predisposing the biliary mucosa to tumorigenesis [28]. Epithelial growth factor is overexpressed and mutated ras oncogenes are found during the transition from pre-malignant lesions to overt cancers. Mutation and abnormal expression of tumor suppressor gene p53, cell cycle regulator cyclin E and apoptosis regulator Bcl-2 are all involved in development of invasive gallbladder cancer. Inactivation of the tumor suppressor gene p53 has an important and early role in gallbladder cancer that is associated with gallstones and chronic inflammation.

4.1. Cyclo-oxygenase

Cyclo-oxygenase is the rate-limiting enzymatic step in the conversion of arachidonic acid to prostaglandins [29–31]. Cyclo-oxygenase-1 (COX-1) and COX-2 are two different isoforms of cyclo-oxygenase. COX-1 is constitutively expressed in most tissues to generate prostaglandins for normal physiologic functions, whereas COX-2 is not normally expressed but can be induced by a variety of cytokines, mutagens, hormones, growth factors, and tumor promoters [32,33]. The genes encoding COX-1 and COX-2 are regulated at different transcriptional levels. COX-2 is overexpressed in a variety of gastrointestinal tumors including colorectal, gastric, esophageal, and pancreatic cancers [34].

As noted previously, clinical and pathological evidence has suggested that inflammatory conditions involving the bile ducts may predispose these ducts to development of carcinoma. A recent study showed COX-2 protein overexpressed both in BTC cancer cells, and adjacent non-cancerous ductal epithelial cells surrounded by inflammatory infiltrates. Noncancerous bile duct cells in inflammatory regions showed moderate expression but significantly higher levels of COX-2 protein when compared with noncancerous epithelial cells without inflammation. Although the signal mediating the stimulation of COX-2 expression has not been identified, the COX-2 protein, induced by inflammatory

<table>
<thead>
<tr>
<th>Molecular event</th>
<th>Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGF/EGFR</td>
<td>Overexpression measured by IHC common (&gt;50%) in BTC, and may be linked to tumor aggressiveness. EGFR may be induced by bile acids</td>
<td>[46,50,64–72]</td>
</tr>
<tr>
<td>HER2</td>
<td>High (60–80%) overexpression human BTC cancers and furan-rat model of BTC. Overexpression and gene amplification in human tumors</td>
<td>[70,73]</td>
</tr>
<tr>
<td>MET</td>
<td>Transmembrane receptor for HGF (hepatocyte growth factor); encoded by c-met proto-oncogene. Activation of c-Met by ligand increases invasiveness and metastases in cell lines; overexpressed in &gt;58% human cholangiocarcinoma specimens. Increased C-Met expression in early cholangiocarcinogenesis</td>
<td>[74–77]</td>
</tr>
<tr>
<td>COX</td>
<td>Strong evidence for role of COX-2 isoform in cholangiocarcinogenesis; may be stimulated by HGF and IL-6. Bile acids promote BTC cell growth via COX-2 pathway; COX-2 specific inhibitors decrease growth in cell lines. Induction of EGFR, MAPK</td>
<td>[78,79]</td>
</tr>
<tr>
<td>Angiogenesis</td>
<td>BTC are relatively hypovascular relative to other tumors; VEGF expression 30%. VEGF expression shown to be associated with LN metastases, poor survival</td>
<td>[80–85]</td>
</tr>
<tr>
<td>MUC-1</td>
<td>Biliary mucin core proteins (encoded by MUC3, MUC5B, MUC6 genes) play role in normal biliary epithelial cell cyto-protection; MUC4 strongly expressed in GB carcinoma</td>
<td>[86–88]</td>
</tr>
<tr>
<td>K-ras mutations</td>
<td>0–56% for intrahepatic; 0–100% for extrahepatic; 5–57% for GB cancers; data suggest BTC develops via K-ras-independent pathway (rates vary widely by method, author, ethnic and geographic distribution. Most mutations in codon 12)</td>
<td>[89,90]</td>
</tr>
<tr>
<td>Mcl-1</td>
<td>A potent anti-apoptotic Bcl-2 family member, Mcl-1 is overexpressed in BTC</td>
<td>[39,91–94]</td>
</tr>
<tr>
<td>Cyclin D1</td>
<td>Moderate (42%) overexpression BTC; associated with high proliferative activity poor prognosis</td>
<td>[95–97]</td>
</tr>
<tr>
<td>p53</td>
<td>Frequency of p53 overexpression ranges from 13% to 57% intrahepatic; 38%–79% extrahepatic, 44–94% for GB cancers; frequency of complete loss of chromosome 17p high</td>
<td>[46,90,98–106]</td>
</tr>
<tr>
<td>HGF</td>
<td>Mitogenic effect on cholangiocytes; enhances metastases</td>
<td>[74,76,107]</td>
</tr>
<tr>
<td>TGFβ</td>
<td>Close correlation between TGFβ signaling pathway disruption and BTC cell line growth. TGFβ may stimulate VEGF activity in BTC cells via autocrine and paracrine stimulation</td>
<td>[108,109]</td>
</tr>
</tbody>
</table>

Abbreviations: EGFR, epidermal growth factor receptor; COX, cyclo-oxygenase; VEGF, vascular endothelial growth factor receptor; MUC-1, mucin core protein; HGF, hepatocyte growth factor; TGFβ, transforming growth factor.
reactions, probably affects carcinogenesis in bile duct epithelial cells [35]. Several authors have found COX-2 to be overexpressed in malignant biliary epithelium [36,37]. One study showed that constitutive expression of COX-2 was a normal feature of hepatocytes but not bile duct epithelium; in BTC, COX-2 was strongly overexpressed and at high frequency (92%), compared with 29% in normal bile duct of matched non-tumorous controls [37].

Bile acids may play a role in promoting carcinogenesis in the gallbladder and biliary tract by stimulating a variety of kinase signaling pathways [16,17,38], in part by activating the epidermal growth factor receptor (EGFR). A recent study of the effect of bile acids on EGFR stimulation and COX-2 expression in a human cholangiocarcinoma cell line, showed that EGFR is activated by bile acids and functions to induce COX-2 expression via a MAPK (mitogen-activated protein kinases) cascade. Bile acids enhanced COX-2 expression in the BTC cell lines and both EGFR kinase and Src (an indirect EGFR activation pathway) kinase-inhibitors blocked COX-2 induction by bile acids. The findings of this study may provide a link between the EGFR/MAPK activation and COX-2 induction by bile acids [16,17].

Recent work in BTC cell lines showed that proinflammatory cytokines induced COX-2 protein expression, that this COX-2 expression attenuates Fas-mediated apoptosis (possibly PGE2-mediated), and that this process was reversed by a COX-2-selective antagonist [39]. Recent data suggest a relationship between activated c-erbB2/c-erbB3 receptors and regulation of COX-2. In cultured human colorectal cancer cells, Vadlamudi et al. have shown that the inhibition of c-erbB2 signaling down-regulated COX-2 expression in these cells. In contrast, activation of the c-erbB2/c-erbB3 signaling pathway resulted in induced activation of the COX-2 promoters and expression of COX-2 mRNA and protein [40].

4.2. Growth factor receptors

The Type I family of growth factor receptors (EGFR, c-erbB-2, c-erbB-3, and c-erbB-4) is recognized as a proto-oncogene family, as it is associated with development of carcinoma in many tissues. Receptor tyrosine kinases are important in cell signal transduction and cell proliferation. The c-erbB-2 (HER-2/neu) proto-oncogene encodes a receptor tyrosine kinase, p185, which is closely related to the epidermal growth factor receptor (EGFR) [41]. Overexpression of c-erbB2 in carcinoma cell lines leads to enhanced cell invasion, migration and metastatic potential.

The expression of several proteins encoded by certain oncogenes in BTC specimens was first reported by Voravud et al. [42]. Of 63 BTC pathologic specimens examined 59 (95%) expressed c-myc, 47 (75%) expressed c-ras, and 46 (73%) expressed c-erbB-2 oncoprotein, compared with no detectable erbB-2 immunoreactivity found in intrahepatic biliary epithelia from normal adult and fetal human livers in the same study. Overexpression of ErbB2 (Her2-neu) has since been reported in a significant number of human gallbladder adenocarcinomas (55–70%) by several authors [52–66]. Two studies recently demonstrated a marked overexpression of HER2-neu receptor protein and mRNA transcripts in neoplastic biliary epithelium of chemically induced and transplanted rat BTC [36,43,44]. One study also observed positive COX-2 immunoreactivity in neoplastic epithelium in rat biliary cancer, but not in normal adult liver. Sirica and colleagues have demonstrated the co-expression and pathogenic relevance of COX-2 and erbB2 in an experimental animal model of BTC [45].

Much of the data described above has been derived from human surgical specimens, BTC cell lines, or carcinogen (furan)-induced animal models of BTC. GBC and cholangiocarcinoma are rare de novo in mice and rats. An elegant and unique genetically engineered mouse model of BTC cancer has been developed by investigators at the University of Texas M. D. Anderson Cancer Center (UTMDACC). Specifically, these investigators engineered a transgenic BK5.erbB2 (bovine keratin) model where expression of a wild type rat erbB2 cDNA was targeted to the basal epithelial layer of multiple epithelial tissues [46]. The original DNA construct was designed to examine the role of erbB2 in mouse skin tumors [47]. Subsequently, the investigators noted that tumors arise in the biliary tract as a consequence of elevated erbB2; specifically, papillary adenocarcinoma of the gallbladder develops in >90% of the homozygous BK5.erbB2 transgenic mice by 3–4 months of age, and adenocarcinomas in adjacent bile ducts occur in 30–100% of these mice. Further analysis demonstrated elevated EGFR and erbB2 protein levels, elevated levels of phosphorylated EGFR and erbB2, and elevated heterodimer formation between erbB and EGFR in biliary epithelia tissues in the transgenic mice. Upregulation of COX-2 mRNA and protein were also observed in the gallbladder carcinomas. Elevated MAP kinase activity and MAP kinase protein phosphorylation were increased in the transgenic mice, although protein levels of MAP kinase were not changed [46]. Separate but related work by Pai et al. [48] demonstrated in both colon cancer cell lines and an in vitro model, that prostaglandin E2 (PGE2), a product of COX-2 that has proliferative and mitogenic activity, rapidly phosphorylates EGFR and triggers the extracellular signal-related kinase 2 (ERK2)-mitogenic signaling pathway, via transmembrane G-protein-coupled receptor proteins (GCRP, EP receptors) [49]. More recent data from the mouse model has shown that tyrosines 534 and 424 of Src are phosphorylated, suggesting that Src is constitutively activated in BTC. STAT3 and Akt were phosphorylated (activated) as well. Additional proteins found elevated in the transgenic mice include E-cadherin (although invasive lesions lost E-cadherin expression), and mucin core protein, MUC4. There was also significant co-localization of MUC4 and erbB2 in the carcinoma tissue.

This mouse model is currently being studied at UTMDACC as a screening tool to further our understanding of the role of erbB2, COX-2, and other gene/protein overexpression
Table 3

<table>
<thead>
<tr>
<th>Molecular target</th>
<th>Agent/comboination</th>
</tr>
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<tbody>
<tr>
<td>EGFR ± HER2/neu</td>
<td>Anti-EGFR tyrosine kinase inhibitor(s) (erlotinib, gefitinib) ± Traztuzumab</td>
</tr>
<tr>
<td></td>
<td>GW527016 (lapatinib) (dual EGFR-HER2/neu blockade)</td>
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<tr>
<td></td>
<td>2C4 inhibits EGFR1-Her2 dimerization</td>
</tr>
<tr>
<td>HER2/neu + cytotoxic agent</td>
<td>Traztuzumab + gemcitabine ± 5FU</td>
</tr>
<tr>
<td>EGFR + cytotoxic agent</td>
<td>Anti-EGFR tyrosine kinase inhibitor + gemcitabine</td>
</tr>
<tr>
<td>COX-2</td>
<td>Celecoxib</td>
</tr>
<tr>
<td>MEK</td>
<td>CI 1040 (oral dual-specificity MEK 1–2 (MAP kinase/ERK kinase)) inhibitor</td>
</tr>
<tr>
<td>MTOR</td>
<td>Rapamycin, Everolimus, Bortezomib</td>
</tr>
</tbody>
</table>

in the development and growth of BTC, and to develop new therapeutic options for patients with this devastating disease. Such animal models provide very useful tools to understand human malignancies and to potentially link molecular carcinogenic pathways to therapeutic strategies. However, there are clear limitations to transgenic animal models, specifically that this model may overstate the importance of erbB2 amplification in human BTC.

The orally active EGFR tyrosine kinase inhibitor (RTKI) gefitinib (Iressa, ZD1839) was administered to the mice 3 weeks prior to mating and throughout the study. Histologic analysis showed that the gefitinib-treated homozygous mice developed BTC at a significantly lower rate than controls. One of 20 (5%) gefitinib-exposed animals developed GB carcinoma and 70% (14/20) showed histologically normal gallbladders, whereas 88% (15/17) of controls developed carcinoma A compound designated GW2974, a potent dual specificity erbB2-EGFR RTKI, has also been screened. BTC developed in 8–10% of treated transgenic mice versus 65% of controls [50]. The oral COX-2 specific inhibitor Celecoxib has been screened and showed that 40% of treated mice develop BTC versus 65% of untreated controls. The agent rapamycin (sacrolimus), an inhibitor of MTOR (mammalian target of rapamycin), is currently under study in several other solid tumors, and reduced tumor incidence from 55.6% to 27.7%, \( p < 0.01 \) in the transgenic mice (personal communication, K. Kiguchi, J. Digiovanni, UTMDACC Carcinogenesis Lab; ES07784, CA76520, CA16672). Thus, this mouse model provides an excellent translational tool for the development of new therapeutic regimens in BTC patients.

5. Conclusions—linking molecular biology to targeted therapeutics

The recent approval of numerous “targeted” agents including gefitinib, erlotinib, cetuximab, trastuzumab, bevacizumab, imatinib, sorafenib and bortezomib, in a variety of solid tumors and hematologic malignancies, has clearly demonstrated the clinical efficacy of such agents. However, the overall modest activity of these as single agents underscores the importance of clearly establishing the relationship between molecular “target” expression by specific tumor types and individual patients’ tissue, and the activity of specific agents. Establishing kinase dependence and proper patient selection are central to the rational development of targeted therapeutics in cancer, particularly in the “orphan” tumors such as BTC and GBC, where patients for clinical trials and tissue specimens to establish molecular profiles are precious resources.

Clearly, further studies are needed to clarify any relevant functional relationship in GBC and BTC between EGFR, erb-B2 and COX-2 which at present are the principal clinically-relevant molecular abnormalities identified in these tumors. These represent exciting opportunities to design clinical trials of targeted therapies in BTC. The over-expression of these receptors in BTC, as demonstrated in both human pathologic specimens and pre-clinical models, justifies efforts to develop novel therapeutic approaches to these deadly malignancies. In support of this approach, there is emerging pre-clinical and clinical evidence in breast and lung cancers that co-expression of EGFR and HER2, as well as overexpression of these individual components, is important for oncogenic cell signaling and response to inhibitory agents [51–53]. Table 3 summarizes several possible clinical trial designs for available targeted agents in GBC and BTC, malignancies for which novel, effective new therapies are clearly warranted.

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Biography

Dr. Melanie B. Thomas received her medical degree from Boston University School of Medicine in 1996 and was the recipient of the Kahn Memorial Scholarship Award. After completing internship and residency in internal medicine at the Beth Israel Deaconess Medical Center in Boston, Dr. Thomas completed a fellowship and was Chief Fellow in Medical Oncology at the University of Texas M.D. Anderson Cancer Center. She is currently an Assistant Professor in the Gastrointestinal Medical Oncology Department at M.D. Anderson. Dr. Thomas is focusing her clinical practice and research in the areas of medical treatment of hepatobiliary tumors, specifically developing novel therapies for liver and biliary cancers. She is the Principal Investigator on several clinical trials in hepatocellular cancer, and a co-investigator on numerous clinical trials in other gastrointestinal malignancies. Dr. Thomas is an active member of many societies including The American Association for Cancer Research, The American Society of Clinical Oncology, The American Medical Association, and the Massachusetts Medical Society. She is the recipient of Merit Awards for clinical abstracts in 2000 and 2001 from The American Society of Clinical Oncology.