

SOUTHEAST CANCER CENTER



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MEDICAL CENTER**

Glioblastoma Multiforme

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BACKGROUND: Grade III (anaplastic astrocytoma, AA) and grade IV (glioblastoma multiforme, GBM) astrocytomas are the most common primary brain tumors in adults and account for about 2.3% of all cancer-related deaths. In North America, the



Medical Director Dr. Steve Stokes (center), Dr. Mark Dosmann (left) and Dr. Jarrod Adkison (right) lead SAMC's Southeast Cancer Center.

estimated age-adjusted incidence of GBM is 3.0 per 100,000. It occurs more commonly in males (male:female ratio of 3:2) and is typically diagnosed in patients in their sixth or seventh decade.

The high-grade astrocytomas diffusely infiltrate surrounding tissues and frequently cross the midline to involve the contralateral brain. Patients often present with symptoms of increased intracranial pressure, seizures, or focal neurologic findings related to the size and location of the tumor and to associated peritumoral edema.

The most important prognostic factors in patients with high-grade astrocytomas are histologic diagnosis (median survival of three years with AA versus 9-15 months with GBM), age (<age 50 better than >50), performance status (better survival with higher performance status), type and duration of symptoms, and extent of surgical resection.

More extensive surgical resections improve the quality of life and neurologic function of patients with high-grade gliomas by reducing mass effect, edema, and steroid dependence. Resection of > 98% of the tumor volume prolongs survival relative to subtotal resections, but extensive subtotal resections do not appear to confer any survival advantage. For

this reason, most neurosurgeons attempt to achieve maximal resection while minimizing the risk to critical areas of the brain.

Radiotherapy has been of key importance to the treatment of high-grade astrocytomas after excision or biopsy. A randomized trial conducted in the 1970s found survivals at 1 year of 3% with surgery alone, 12% with post-operative BCNU, and 24% with post-operative radiation.

The current radiotherapy standard for this disease is partial brain irradiation given over approximately 6 weeks. The ability to focus the beam and tailor it to the irregular contours of brain tumors and minimize the dose to nearby critical structures has improved greatly in the past few years with intensity-modulated and image-guided (IMRT and IGRT) techniques.

Alternate dose-fractionation schedules have been explored in clinical trials without significant improvement in outcome. The role of focal radiation techniques (e.g., stereotactic radiosurgery and I-125 radioactive seed implant) in this diffusely infiltrative disease remains undefined.

Temozolomide (Temodar, TMZ) received U.S. Food and Drug Administration approval for the treatment of patients newly diagnosed with GBM in March 2005. A prior phase III randomized study found a statistically superior median survival (14.6 versus 12.1 months) and 2-year survival (26.5% versus 10.4%) when temozolomide administered with post-operative radiation therapy followed by 6 cycles of adjuvant temozolomide was compared with radiation therapy alone.

Subsequent analyses suggest low tumor content of MGMT ((O-6-methylguanine-DNA methyltransferase) is associated with improved chemotherapy responsiveness to alkylating agents like temozolomide. Regardless of treatment assignment during an EORTC/NCIC trial, overall survival was improved by 55% in patients with methylation of MGMT (i.e., lower expression of MGMT) ($p < 0.001$). When the data were analyzed according to MGMT status and treatment assignment, the 2-year survival rate of patients with low levels of MGMT was 46% in the group receiving temozolomide plus radiotherapy and 22.7% in the group receiving only

radiotherapy ($p=0.007$); in patients with high levels of MGMT, the 2-year survival rate was 13.8% with combined treatment and less than 2% with radiotherapy alone. Since the survival was improved with the addition of temozolomide to radiation therapy regardless of MGMT status, its testing has not become routine in clinical practice.

CLINICAL OUTCOME STUDY AT SAMC: 23 patients with biopsy-proven glioblastoma multiforme were treated at the Southeast Alabama Medical Center from 2003 through 2008. Patient age ranged from 37 to 84 at diagnosis.

Eight patients underwent subtotal resections, 12 had gross total resections, and three had biopsy only. Thirteen of the patients were treated by all three treatment modalities (surgery, radiation therapy, and adjuvant Temodar), while the remainder were treated by either one or two of these modalities.

Eleven patients received radiation therapy using intensity modulated radiation therapy (IMRT), 9 by three-dimensional conformal radiation therapy techniques, and one using brachytherapy techniques (Gliasite applicator). Most patients treated with radiation therapy had a course of 60 Gy in 30 fractions prescribed, but two patients elected not to receive any further therapy after resection, and four received less than the planned dose secondary to tumor progression and/or poor tolerance of treatment.

At the time of analysis 19 patients had expired, and four were alive at last contact (patient of age 37 alive at 48 months, age 55 alive at 38 months, age 53 at alive 27 months, and age 77 alive at 35 months).

The number of patients in the study was not sufficient for formal statistical analysis, but the overall survival is in line with that reported in the literature for the time period of treatment (2003-2008). As has been reported by others, there are trends for better survival for the younger patients and better survival with the use of combined adjuvant radiation therapy and Temodar compared to adjuvant radiation therapy alone (see Figure 1).

CURRENT CLINICAL ISSUES: It is difficult to assess the results of therapy using CT or MRI scans because the extent and distribution of contrast enhancement, edema, and mass effect are more a

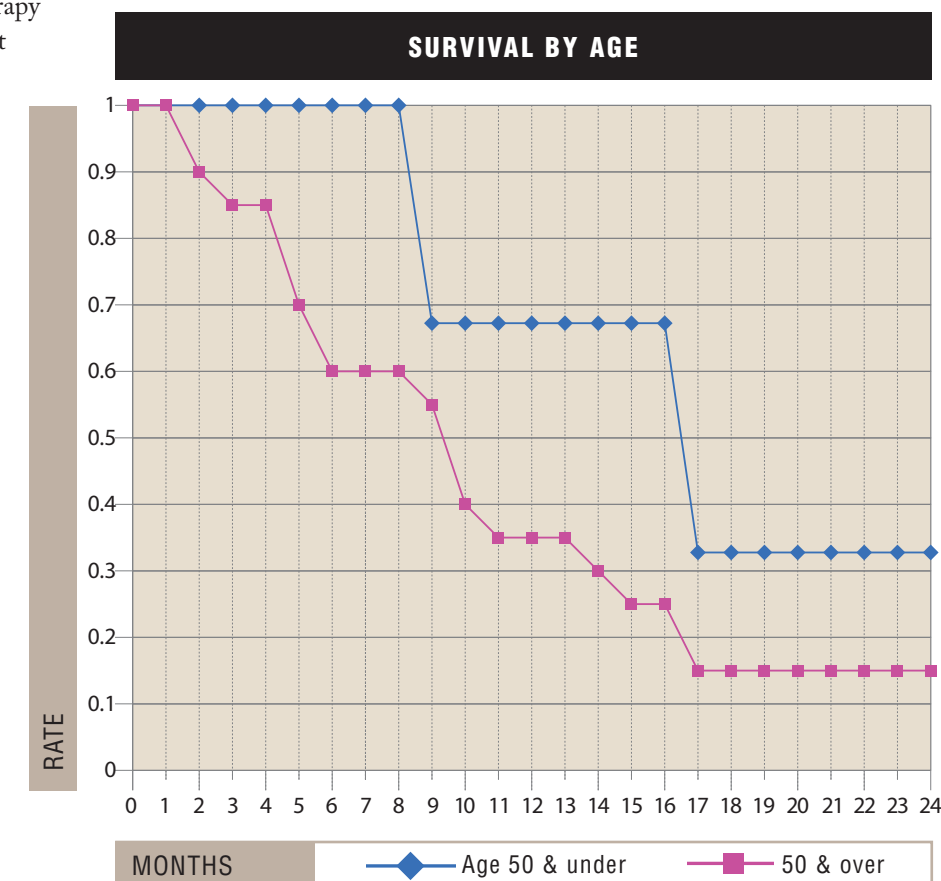


Figure 1

function of blood-brain barrier integrity than of changes in the size of the tumor. Anti-angiogenic agents such as bevacizumab (Avastin) produce high radiographic response rates, as defined by a rapid decrease in contrast enhancement on CT/MRI that occurs within days of initiation of treatment, which is partly a result of reduced vascular permeability to contrast agents rather than a true antitumor effect. Conversely, other factors that exacerbate blood-brain barrier dysfunction (such as surgery, radiation, and tapering of corticosteroids) can mimic tumor progression by increasing contrast enhancement, T2-weighted abnormalities, and mass effect.

During the course of treatment there can be an increase in or the appearance of contrast-enhancing lesions, and worsening in cerebral edema, that can

Glioblastoma Multiforme Bibliography

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suggest tumor progression or recurrence. In patients who have such deterioration at two to three months following radiation therapy, 20-30% of these have spontaneous improvement without a change in therapy. This pattern (‘pseudoprogression’) is indistinguishable from that of tumor recurrence, and usually improves within a few weeks or months. In one study the median survival for those patients with pseudoprogression was significantly higher than for patients with true early progression (124.9 weeks versus 36.0 weeks, $p = 0.0286$) and the entire cohort (56.7 weeks).

Clearly, a more reliable approach is required for the identification of pseudoprogression in patients with GBM, as this would allow the identification of patients for whom there is no need to switch from effective adjuvant treatment to a potentially less effective and more toxic regimen. Magnetic resonance spectroscopy and PET imaging with amino acid tracers seems to be promising approaches in discriminating between treatment induced necrosis and true disease recurrence.

THE FUTURE: The survival for patients with glioblastoma has improved from an average of 10 months to 14 months after diagnosis in the last five years due to improvements in the standard of care therapy, including surgery, radiation therapy, and chemotherapy. Although the average survival with this disease remains suboptimal, the outcomes for individual patients are variable and a small fraction of patients do much better than expected (some patients surviving beyond five years).

New discoveries are being made in basic and translational research, which are likely to improve this situation further in the next ten years. These include agents that block one or more of the disordered tumor proliferation signaling pathways, and that overcome resistance to already existing treatments. Targeted therapies such as anti-angiogenic therapy with anti-vascular endothelial growth factor antibodies (bevacizumab) are finding their way into current clinical practice.

Cancer Committee Report

The Southeast Alabama Medical Center Cancer Program is accredited by the American College of

Surgeons (ACOS) Commission on Cancer, designated as a Community Hospital Comprehensive Program (COMP) and is under the leadership of the Cancer Committee.

The Cancer Committee at Southeast Alabama Medical Center is a standing committee meeting quarterly. The Committee is comprised of physicians of varied disciplines, as well as other ancillary departments involved in the treatment and care of cancer patients. Goals are set annually to monitor and improve cancer patient care. Some of the goals set by the Committee are:

Participate in Clinical Trials: As a COMP the goal of the Cancer Committee is to ensure that patients are provided information about the availability of cancer-related clinical trials and that two percent of the total analytic caseload is enrolled into clinical trials. To help meet this goal, three project leaders have been selected to work on:

- Clinical trial affiliation with UAB
- Patient navigation
- Health information sharing

Offer Rehab: Southeast Alabama Medical Center offers physical, occupational and speech therapy. This includes a lymphedema specialist.

Increase cancer awareness and community outreach: The Cancer Committee keeps abreast and assists in programs to educate the community about cancer with emphasis on cancer prevention, early detection and screening. Programs offered to the community in partnership with the ACS are I Can Cope, Look Good-Feel Better, Reach to Recovery, Smoking Cessation and cancer support groups. Various health fairs sponsored by SAMC are offered throughout the year at different locations. These functions offer free screening such as Prostatic Specific Antigen (PSA) test for prostate cancer.

Provide patient and family support: A multi-disciplinary team approach is available to cancer patients at the Medical Center. Patients have access to support services either in-house or by referral through discharge planning to include: counseling, hospice, rehabilitation services, support groups, nutritional care, pastoral services, patient education and pain management.

Quality Patient Care: Quality improvement issues regarding compliance with the American College of Surgeons Commission on Cancer standards are discussed regularly and treatment standards are kept current, maintaining high standard of care for cancer patients in this area. Cancer Registry data is utilized in reviewing quality of care and performance improvement studies. A study on Glioblastoma Multiforme is presented in this report.

Provide multi-disciplinary approach to the management of cancer care: Tumor Conferences provide patients with consultative, diagnostic, and treatment planning by a team of highly trained and experienced physicians of different specialties and by allied healthcare professionals. One hour of continuing education is granted for each conference. Physicians can contact the Cancer Conference Coordinator at extension 4446 or 3710 to schedule a case for presentation.

Prevention and Early Detection: To improve screening in this area the Southeast Regional Health Screening Program was established to provide underserved residents in the area an opportunity to receive screenings. Services include screening digital mammograms, fecal occult blood testing, PSA (prostate specific antigen) tests, as well as vascular testing which includes: cholesterol, glucose, BMI, blood pressure, height, weight, and a written assessment. The 40-foot mobile unit travels to senior citizen centers, industries, churches, health fairs and other community events.

Cancer Registry Activity and 2009 Data Analysis

The goal of the Cancer Registry is to ensure accurate and timely collection of cancer data on patients diagnosed and /or treated at Southeast Alabama Medical Center. The Registry began collecting data in 1988. A total of 1,199 cases were added to the database in 2009, which included 604 males and 481 females with 1,085 of these newly diagnosed or analytic cases. The top primary site treated in 2009 was breast cancer which consisted of 19.7% of total cases. This was higher than state and national estimates (2009 Cancer Facts and Figures) published by the American Cancer Society).

Prostate and lung cases were second and third respectively, Colorectal remains fourth site in incidence for Southeast Alabama Medical Center (see Figure 4). The geographic distribution of patients treated during 2009 showed that nearly 26% were from Georgia and Florida (see Figure 3). Over half of patients treated in 2009 were between the ages of 60 and 79 (see Figure 2) shows that patients under the age of 50 totaled 131.

The focus of the Registry is to provide quality information to the National Cancer Database, Alabama Statewide Cancer Registry and to healthcare professionals, physicians, and hospital administration. Registry data is also utilized on a local level in patient care and performance improvement studies such as the recent study on Glioblastoma Multiforme documented in this report.

Lifetime follow-up is provided on all analytic cases since the re-established reference date of 2002. The Registry currently maintains a 97% follow-up rate, exceeding the American College of Surgeons standard of 90%.

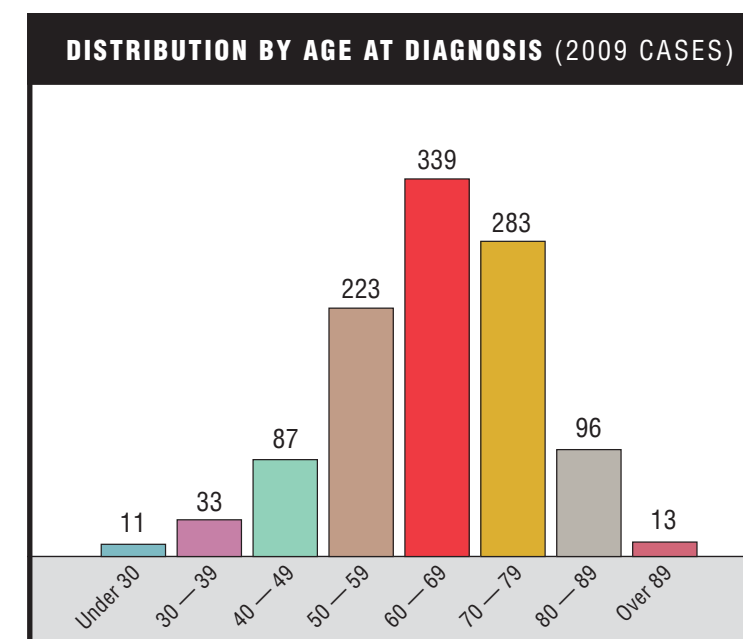


Figure 2

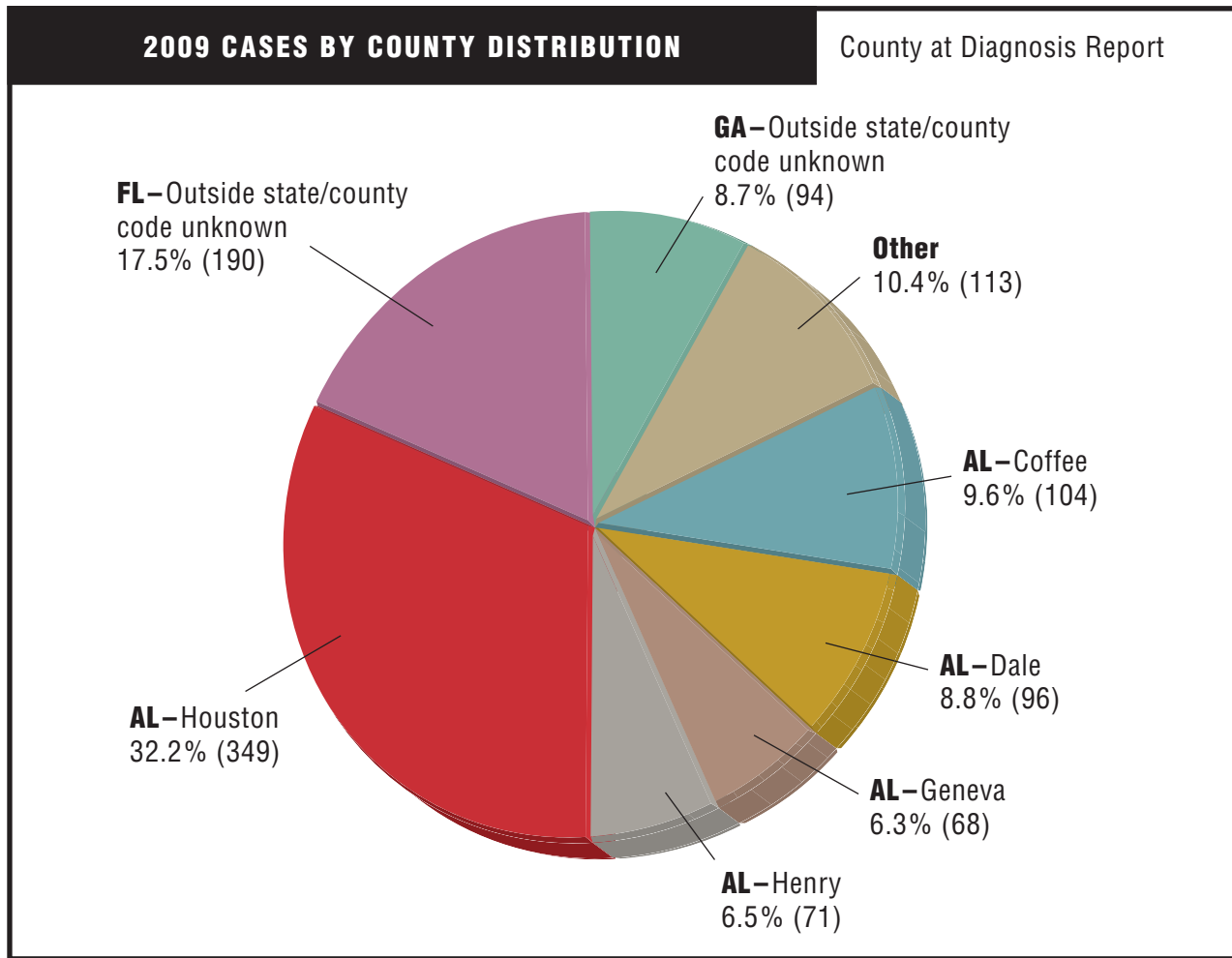


Figure 3

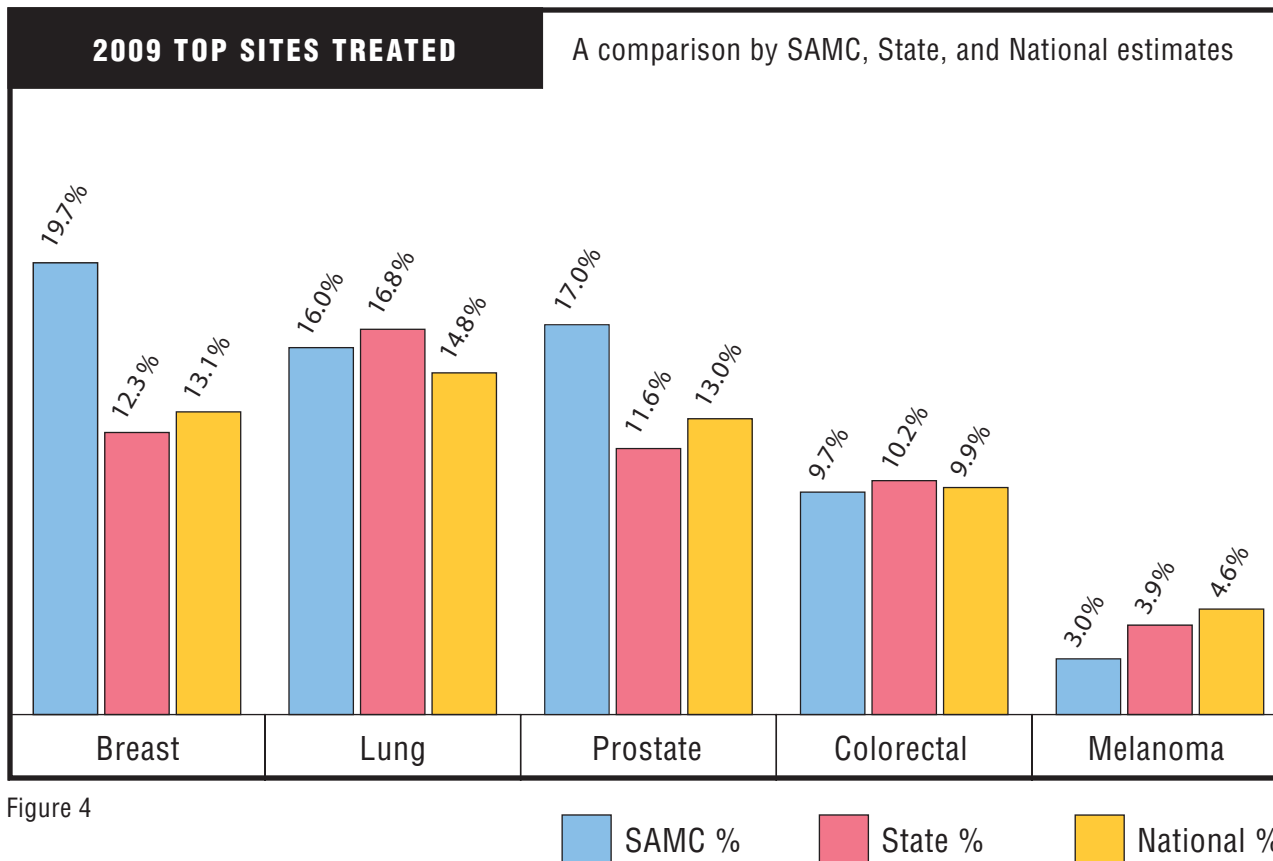


Figure 4

PRIMARY SITE TABLE	MALE	FEMALE	TOTAL 2009
ALL SITES COMBINED	604	481	1,085
ORAL CAVITY/PHARYNX	37	6	43
Tongue	6	2	8
Floor of Mouth	4	1	5
Gum and other Mouth	5	1	6
Nasopharynx	1	0	1
Tonsil	11	0	11
Salivary Glands	6	2	8
Oropharynx	2	0	2
Hypopharynx	2	0	2
DIGESTIVE SYSTEM	112	63	175
Esophagus	13	1	14
Stomach	12	3	15
Small intestine	7	2	9
Colon	51	29	80
Rectosigmoid	3	0	3
Rectum	12	10	22
Anus/Anal canal	2	0	2
Liver/Intrahepatic Bile Duct	5	3	8
Gallbladder	1	0	1
Other biliary	2	3	5
Pancreas	7	7	14
Other digestive system	1	0	1
RESPIRATORY SYSTEM	121	72	193
Larynx	17	1	18
Nasal cavity	1	0	1
Bronchus/Lung	103	71	174
SOFT TISSUE	2	0	2
SKIN*	21	13	34
BREAST	3	214	217
GENITOURINARY	224	50	274
Cervix Uteri**	0	8	8
Corpus Uteri	0	13	13
Ovary	0	9	9
Vagina	0	1	1
Vulva	0	4	4
Prostate	185	0	185
Testis	2	0	2
Bladder	24	7	31
Kidney/Renal Pelvis	10	7	17
Other Urinary organs	1	1	2
ENDOCRINE SYSTEM	12	19	31
LYMPHOMA	20	15	35
MYELOMA	4	2	6
LEUKEMIA	6	1	7
MESOTHELIOMA	3	0	3
KAPOSI SARCOMA	1	0	1
MISCELLANEOUS	17	6	23

* Excludes local basal and squamous cell carcinoma

** Excludes carcinoma in-situ of the cervix



Southeast Alabama Medical Center is a 420 bed regional referral center for the Southeast. With a medical staff of 300, 2,600 employees, and 200 volunteers, virtually every facet of medical care is available. The Southeast Cancer Center is an integral part of total patient care at SAMC. The Cancer Center provides a full spectrum of cancer care to a total service population of over 785,000, including all or part of 13 counties in southeast Alabama, six counties in the Florida panhandle and seven counties in southwest Georgia.

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