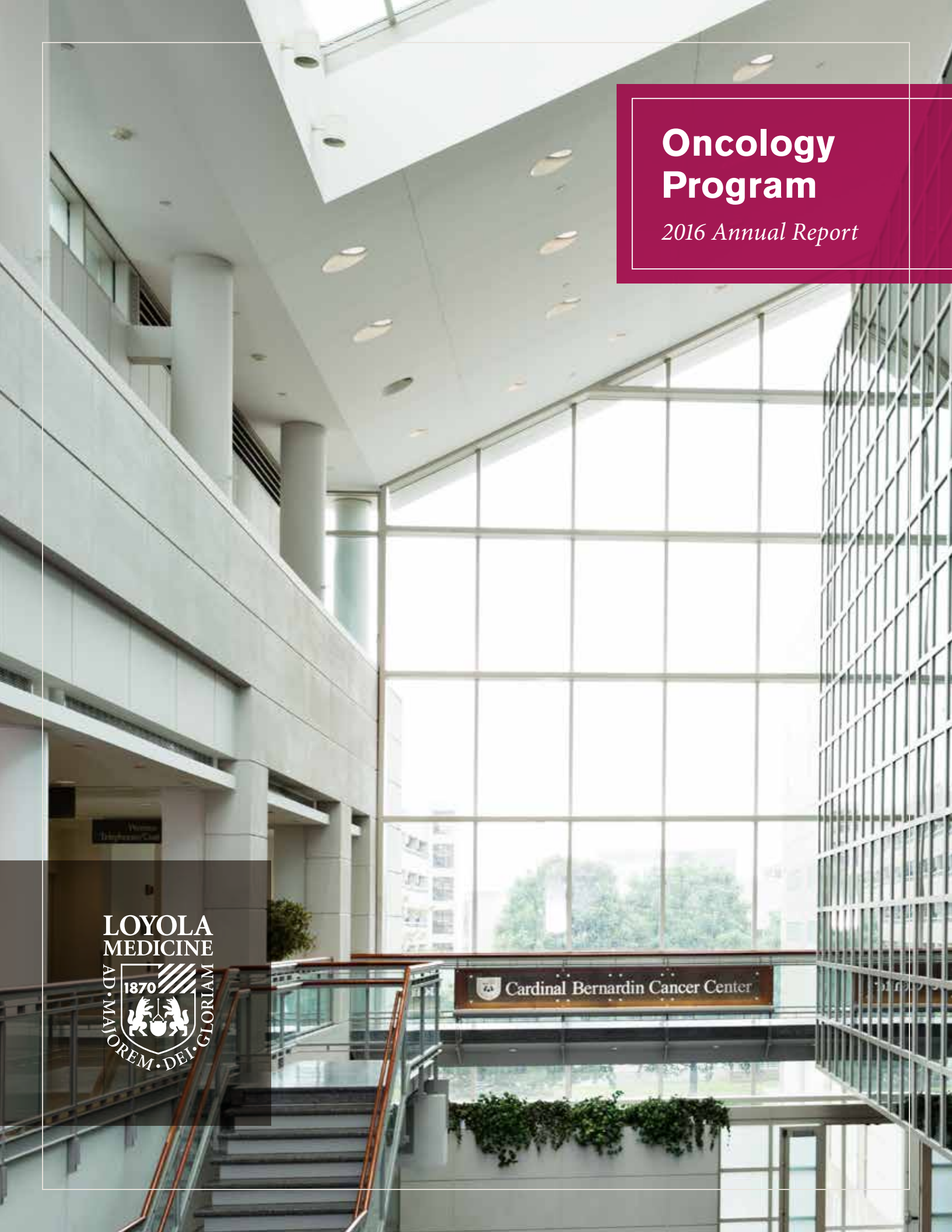

Oncology Program

2016 Annual Report

LOYOLA MEDICINE

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Mission Statement

Trinity Health Mission Statement

We serve in Trinity Health, in the spirit of the Gospel, to heal body, mind and spirit to improve the health of our communities, and to steward the resources entrusted to us.

Loyola University Health System is committed to excellence in patient care and the education of health professionals. We believe that our Catholic heritage and Jesuit traditions of ethical behavior, academic distinction and scientific research lead to new knowledge and advance our healing mission in the communities we serve. We believe that thoughtful stewardship, learning and constant reflection on experience improve all we do as we strive to provide the highest quality healthcare.

We believe in God's presence in all our work. Through our care, concern, respect and cooperation, we demonstrate this belief to our patients and families, our students and each other. To fulfill our mission, we foster an environment that encourages innovations, embraces diversity, respects life and values human dignity. We are committed to going beyond the treatment of disease. We also treat the human spirit.

Loyola University Health System (LUHS) is a member of Trinity Health. Based in the western suburbs of Chicago, LUHS is a quaternary care system that includes Loyola University Medical Center (LUMC), located on a 61-acre campus in Maywood, Gottlieb Memorial Hospital (GMH), on a 36-acre campus in Melrose Park, and convenient locations offering primary and specialty care services throughout Cook, Will and DuPage counties. At the heart of LUMC is a 547-licensed-bed hospital that houses the Center for Heart & Vascular Medicine, the Cardinal Bernardin Cancer Center, a Level 1 trauma center, a burn center, a children's hospital, Loyola Outpatient Center and Loyola Oral Health Center. The campus also is home to Loyola University Chicago Stritch School of Medicine, Loyola University Chicago Marcella Niehoff School of Nursing and the Loyola Center for Fitness. The GMH campus includes a 254-licensed-bed community hospital, a Professional Office Building with 150 private practice clinics, an adult day care program, the Gottlieb Center for Fitness, the Loyola Center for Metabolic Surgery and Bariatric Care and the Loyola Cancer Care & Research at the Marjorie G. Weinberg Cancer Center at Melrose Park.

Trinity Health is one of the largest multi-institutional Catholic health care delivery systems in the nation. It serves people and communities in 22 states from coast to coast with 93 hospitals and 120 continuing care locations — including home care, hospice, PACE and senior living facilities — that provide nearly 2.5 million visits annually.

Brand Promise

The people of Loyola promise patients that we go beyond the illness to treat the whole person.

The Cardinal Bernardin Cancer Center is located on the east side of the campus and faces First Avenue. Parking is available in a parking lot in front of the building and valet parking is available at the entrance. A coffee bar is located just inside the building on the first floor. Named in honor of the late Archbishop of Chicago Joseph Cardinal Bernardin, the Cancer Center was the first free-standing facility in Illinois dedicated to cancer research, diagnosis, treatment and prevention. Loyola's Cancer Center contains all outpatient cancer care along with extensive research laboratories, offices and educational space. Many of the multidisciplinary clinics within the Cancer Center provide a one-visit, one-team approach, providing patients with a diagnosis and treatment plan in the same day. Patients can see their physician, have lab work done, undergo chemotherapy and have cancer care-related prescriptions filled, among many other services in the building.

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Message from the Chairman

The year 2016 brought combined improvements to the wide array of cancer services available to patients of Loyola University Medical Center, American College of Surgeons Accredited Oncology Program. It is with great pleasure offer my congratulations to the entire cancer team from administration to all clinical and volunteer staff in this institution for providing high-quality cancer care to our patients, meeting and exceeding the standards set by our Cancer Program.

This report provides an overview of the Program's organization of services and highlights a statistical summary in a narrative, tabular and graphic form of all cancer cases diagnosed and treated at Loyola University Medical Center. Through our commitment and determination, the accomplishments of the Cancer Program is wholly dependent upon the tireless efforts of a team of caring professionals, without whom we could not strive to reach our goal in providing oncology service of highest caliber.

As an academic medical center, Loyola can offer the opportunity to enroll in clinical trials of experimental new drugs that are not available at most hospitals. These new treatments potentially can reduce side effects, prolong remissions, and in some cases cure cancers. As an academic medical center offering more than 400 cancer clinical trials, Loyola has access to many new drugs and therapies that are not available at most hospitals.

Loyola enrolls about 600 adult and pediatric patients in cancer clinical trials every year. Each month, on average, Loyola begins five new cancer trials and closes five trials upon completion. Loyola's Cancer Clinical Trials Office offers trials of groundbreaking new therapies and technologies, including immunotherapies; intraoperative radiation therapy and stereotactic body radiation therapy; precision medicine trials; and a trial of a cell expansion technology that could improve outcomes of umbilical cord blood stem cell transplants. Among the unique areas of cancer research at Loyola are first-of-its-kind clinical trials on several types of immunotherapies, which harness the patient's immune system to fight cancer. The immunotherapies, including engineered T cells and vaccines, are among the fastest growing areas of cancer research, wand Loyola's research predates recent reports of exciting trial outcomes. Loyola is conducting the first melanoma immunotherapy of its kind in the Midwest.

In 2016, Loyola researchers also have identified a tumor gene that may help to predict survival outcomes in patients with squamous cell carcinoma of the mouth and tongue. The finding eventually could help guide treatment. Depending on whether or not the gene is expressed, a patient may require more or less aggressive treatment than what is indicated by staging alone, said Carol Bier-Laning, MD, a Loyola head and neck cancer surgeon and co-author of the study. Among the advances in the surgical management of complex cancers at Loyola are robotic surgical techniques that more precisely resect tumors of various organs. Surgeons also are employing a complex procedure known as HIPEC to improve the quality of life of patients with advanced intra-abdominal cancers. HIPEC uses heated local chemotherapy that is administered after extensive surgical removal of cancers. Also, Loyola University Academic Center offers HDR Brachytherapy. Unlike low-dose rate brachytherapy, the radioactive "seed" in high-dose rate (HDR) brachytherapy is delivered in minutes and removed after treatment. HDR brachytherapy provides the ability to sculpt the radiation dose to reliably avoid healthy organs. And since the radiation source is removed immediately after treatment, patients do not have to take radiation precautions. The outpatient HDR brachytherapy treatment involves a one-hour procedure performed by the radiation oncologist in conjunction with the urologist. This is followed by a CT scan and sophisticated radiation treatment planning to maximize the chance the cancer is cured, while minimizing potential side effects. The individualized radiation dose is then delivered using a robotic

system, and the patient goes home later that day. Loyola is also the first center in Chicago to offer the Varian Edge radiosurgery system for stereotactic ablative radiotherapy. This system can treat variety of cancers, such as brain, lung and liver, including tumors that can be difficult to reach with traditional surgery.

We also offer intraoperative radiotherapy (IORT) for multiple malignancies. This device is used following tumor excision in patients at risk for recurrences. It delivers low-energy, high-dose radiation (50kV x-rays) directly to the tumor bed, with a rapid dose fall off to surrounding normal structures.

Loyola is the first in Illinois, and one of only nine in the country to be accredited by the American Physical Therapy Association (APTA) as a post-professional residency program for physical therapies in women's health.

Loyola has a new Preferral app, an easy tool to refer patients to Loyola primary care providers and specialists. The app enables a referring physician to search for and find up-to-date information on Loyola providers; personalize a directory with referral favorites; send a convenient referral to patients to encourage their follow-through on care plans; and send physician details to a patient by text message. Physicians who refer patients to Loyola can access patients' electronic health records through LoyolaConnect. LoyolaConnect cuts down on time-consuming phone calls, faxes and paper transactions. Loyola plans to increase the number of cancer trials as it streamlines the approval process, with a faster time from concept to treatment.

A new service, Loyola Medicine Transport LLC, is providing basic and advanced life support, non-emergent van transportation, lab and courier services for Loyola University Medical Center and Gottlieb Memorial Hospital, along with the hospitals' ambulatory sites.

Loyola has partnered with Community Emergency Medical Service, Inc., the largest nonprofit ambulance provider in the United States. Loyola Medicine Transport's fleet includes 13 ambulances and 12 courier vehicles. Transport patients who don't meet the medical necessity for an ambulance or wheelchair will be transported more efficiently and cost-effectively with a new medi-van service called "Medi-ride."

Loyola Medicine Transport is part of our commitment to population health management and to ensure that patients receive the highest quality of care and service throughout the continuum of care.

The Operational Excellence Team at Loyola continues the Lean transformational journey with the addition of Six Sigma principles. With the implementation of Lean Six Sigma, Loyola University Health System (LUHS) has the benefit of combining Lean's focus on eliminating non-value-added activities with Six Sigma's philosophy of reducing process variability. This combination ultimately helps LUHS remain an efficient health system that is both financially sound and a satisfying place to work. All of this supports the primary goal of providing high quality and highly reliable patient care and patient experience.

Constantine Godellas, MD
Oncology Program Committee Chairman

Member List

The Cancer Committee membership is multidisciplinary, representing physicians from the diagnostic and treatment specialties and non-physicians from administrative and supportive services. The following list of Committee members in 2016 reflects the multidisciplinary nature of the Cancer Committee:

Member	Specialty
Constantine Godellas, MD Oncology Program Committee Chairman	Surgical Oncology
Gerard Abood, MD Oncology Program Cancer Liaison Physician	Surgical Oncology
Carol Bier-Laning, MD	Otolaryngology
Davide Bova, MD	Diagnostic Radiology
Violeta Dimovic, CTR	Manager, Oncology Data Management
Elisa Estrada	Oncology Data Management
Debbie Fager	ACS Representative
Linda Ippolito, RN, APN, AOCNS	Nursing
Kathleen Fujiu, RN, BA, BSN, MBA, OCN	Nurse Manager 6 West, Coordinator
Kathy Grego, RHIT, CTR	Oncology Data Management, Coordinator
Ewa Jaraczewska	Manager, Orthopedic Surgery & Rehabilitation
Elizabeth Henry, MD	Hematology/Oncology
Kate Heraty	Genetic Counselor
Tess McCoo	Radiation Therapy, Director
Edward Melian, MD	Radiation Therapy
Angelique Mercier	Genetic Counselor
Stephanie Mills, RHIT	Oncology Data Management
Laura Morrell	Social Work, Cancer Center, Coordinator
Patricia Mumby, PhD	Professor, Psycho-Oncology
Gayle, Payonk	Cancer Service Line, Oncology Support Ex Director
Ceil Petrowsky, RN, MSN, CCRC	Manager Cancer Clinical Trials Office
Maria Picken, MD, PhD	Professor of Pathology & Director of Renal Pathology
Mark Speyer, MD	Palliative Care
Sheryl Svoboda	Dietitian, Cancer Center
Peter Tortorice	Manager, Pharmacy Oncology

Prepared by: V. Dimovic, CTR

Medical Services

All patients at the Cardinal Bernardin Cancer Center begin with a visit to one of the center's specialty or multidisciplinary clinics. There, the patient and family meet with the cancer specialist responsible for establishing an individual treatment plan and coordinating care. Within our unique multidisciplinary setting, a patient will meet with a team of cancer experts that may include surgeons, medical oncologists, radiation oncologists, radiologists, pathologists and plastic surgeons. These specialists work together to evaluate a patient's condition. During the same visit, patients might also meet with a nutritionist, nurse, social worker or other supportive staff.

Programs and Services

Below is a list of our programs and services for cancer care:

Art Therapy

Bone Marrow Transplantation

Breast Cancer

Breast Care

Breast Oncology Center

CAN-HELP Cancer Information Service

Cancer Genetics Evaluation Program

Cancer Risk Assessment & Prevention

Cancer-Pediatric Hematology & Oncology: Through our membership in the Children's Oncology Group, we participate in clinical trials and studies for pediatric conditions such as: Leukemia, Lymphoma, Brain Tumors, Neuroblastoma, Wilm's Tumor, Rhabdomyosarcoma & Other Soft Tissue Sarcoma, Bone Malignancies

Cancer Survivorship Program

Caregivers Class for Bone Marrow Transplant Patients

Centers for Fitness

Chaplain Services

Chemotherapy Classes

Clinical Research

Coleman Foundation Image Renewal Center

Gastroenterology Services

Gastrointestinal Oncology Center

Gynecologic Oncology Services

Head and Neck Oncology Clinic

Hematology Clinic

Hematology/Oncology Services

Home Care & Hospice

Melanoma Clinic

Neuro-Oncology Clinic

Nutrition Services

Psychology Support Services

Radiation Oncology Services

Screening and Early Detection - Cancer

Skin Cancer and Mohs Micrographic Surgery Center

Speech Therapy

Surgical Oncology

Thoracic and Lung Oncology Program & Urologic Oncology Clinic

**click on bolded programs and services to view website page.*

Primary Site Table — 2016

The following table summarizes the primary sites by gender for 2016. The top five most frequent occurring cancers at Loyola University Medical Center in 2016 were: breast, lung, prostate, thyroid and colorectal.

TABLE: 1

Primary Site	Male	Female	Analytic	Non-analytic	Total
ALL SITES	**1223**	**1266**	**2489**	**309**	**2798**
Oral Cavity	**104**	**48**	**152**	**26**	**178**
Lip	3	0	3	1	4
Tongue	32	18	50	10	60
Oropharynx	2	1	3	1	4
Hypopharynx	6	1	7	1	8
Other	61	28	89	13	102
Digestive System	**217**	**179**	**396**	**49**	**445**
Esophagus	17	6	23	4	27
Stomach	26	10	36	3	39
Colon	42	44	86	16	102
Rectum	27	26	53	11	64
Anus/Anal Canal	5	5	10	0	10
Liver	47	25	72	6	78
Pancreas	32	36	68	2	70
Other	21	27	48	7	55
Respiratory System	**129**	**99**	**228**	**31**	**259**
Nasal/Sinus	8	6	14	2	16
Larynx	24	4	28	15	43
Lung/Bronch-Small Cell	13	26	39	3	42
Lung/Bronc-Non-Small Cell	71	58	129	11	140
Other Bronchu-Lung	4	3	7	0	7
Other	9	2	11	0	11
Blood and Bone	**25**	**8**	**33**	**11**	**44**
Marrow	80	55	135	35	170
Leukemia	39	34	73	16	89
Multiple Myeloma	27	10	37	6	43
Other	14	11	25	13	38
Bone	**1**	**3**	**4**	**2**	**6**
Connective/Soft Tissue	**20**	**14**	**34**	**3**	**37**
Skin	**89**	**62**	**151**	**11**	**162**
Melanoma	82	56	138	9	147
Other	7	6	13	2	15

Primary Site	Male	Female	Analytic	Non-analytic	Total
Breast	**3**	**305**	**308**	**25**	**330**
Female Genital	**0**	**229**	**229**	**19**	**248**
Cervix Uteri	0	25	25	3	28
Corpus Uteri	0	131	131	6	137
Ovary	0	46	46	6	52
Vulva	0	20	20	4	24
Other	0	7	7	0	7
Male Genital	**244**	**0**	**244**	**28**	**272**
Prostate	222	0	222	25	247
Testis	16	0	16	2	18
Other	6	0	6	1	7
Urinary System	**160**	**66**	**226**	**35**	**261**
Bladder	80	28	108	23	131
Kidney/Renal	73	33	106	12	118
Other	7	5	12	0	12
Brain & CNS	**47**	**55**	**102**	**12**	**114**
Brain (Benign)	3	0	3	0	3
Brain (Malignant)	12	14	26	2	28
Other	32	41	73	10	83
Endocrine	**54**	**97**	**151**	**19**	**170**
Thyroid	41	89	130	13	143
Other	13	8	21	6	27
Lymphatic System	**63**	**41**	**104**	**11**	**115**
Hodgkin's Disease	9	4	13	2	15
Non-Hodgkin's	54	37	91	9	100
Unknown Primary	**7**	**4**	**11**	**1**	**12**
Other/Ill-Defined	**5**	**9**	**14**	**2**	**16**

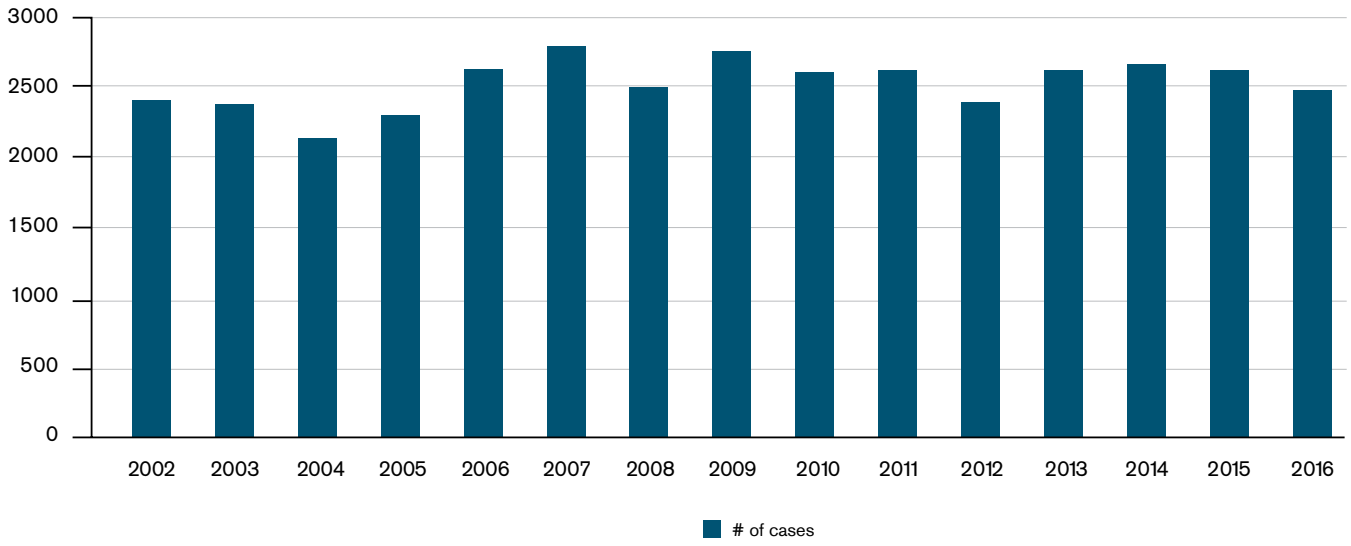
Analytic: A case first diagnosed and/or receiving first course treatment at the facility, or diagnosed at autopsy.

Non-Analytic: Any case diagnosed at another facility and receiving all first course treatment at that facility, then seen at Loyola University Medical Center for subsequent treatment.

Data Analysis

GRAPH 1: INCIDENCE PER YEAR

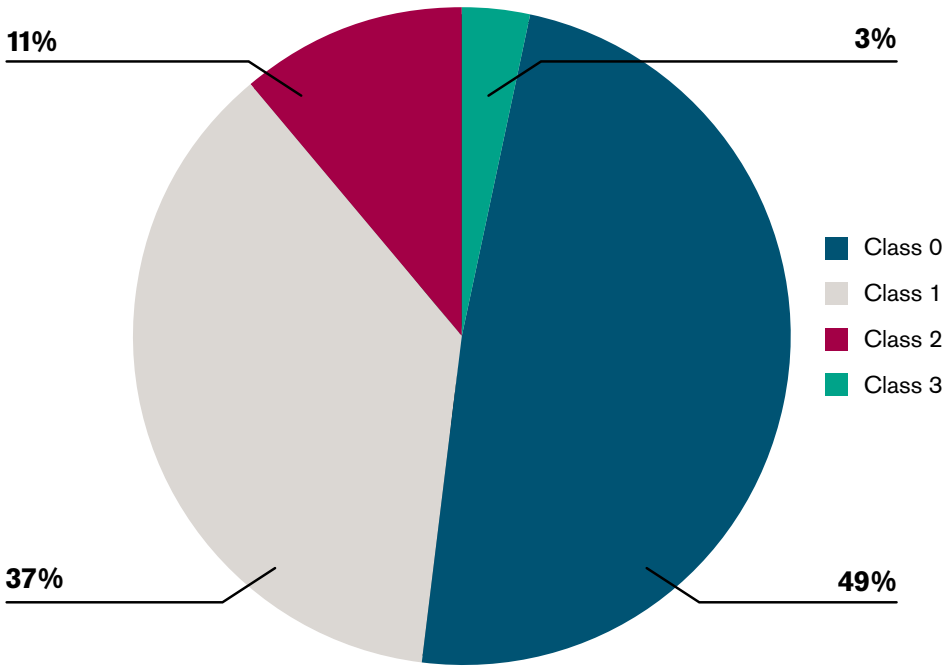
Data shows the number of analytic cases diagnosed and treated at Loyola University Medical Center in 2016.



In most of the 2016 cases, a total of 49 percent (1363), patients received their initial diagnosis at LUMC; 37 percent (1027) of patients were diagnosed elsewhere, but came in our facility to be treated; 3 percent (94) of patients were diagnosed at our facility and all their first course of therapy was done elsewhere; and 11 percent (309) of the patients came here for treatment of recurrent disease. (See Figure 1)

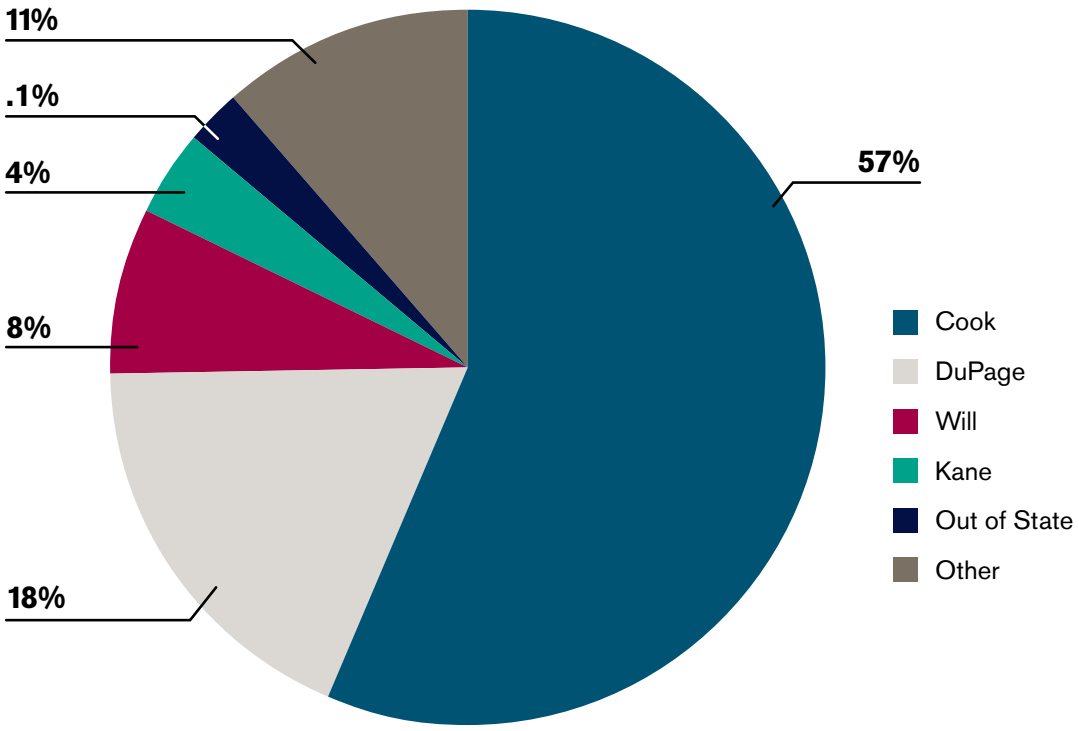
Total 2,498

FIGURE 1: CLASS OF CASE



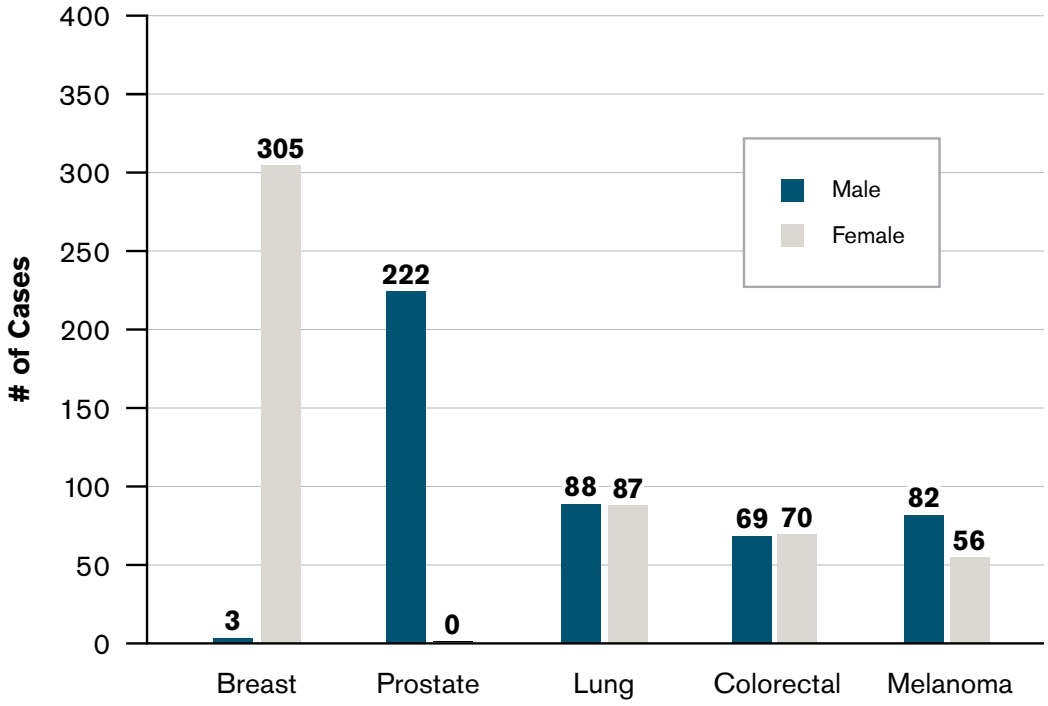
Most of the 2016 cases, 57 percent (1,587) of the patients were seen from Cook county, followed by 18 percent (507) from DuPage, 8 percent (213) from Will, and 4 percent (112) from Kane. Out-of-state cases accounted for .1 percent (64) and the remaining others accounted for 11 percent (318).

FIGURE 2: CASES BY DIAGNOSIS COUNTY



For all analytical cases, the most frequent site is Breast 31 percent (308). Next in frequency is the Prostate with 23 percent (222), Lung 18 percent (192); Colorectal with 14 percent (139) and finally Melanoma with 14 percent (138). (See Graph 2)

GRAPH 2: FIVE MAJOR SITES



For new analytic cases 51 percent (1,266) were female and 49 percent (1,223) male. Graph 3 below shows that the diagnosis of cancer was most found in the 60-69 year range for males and females.

GRAPH 3: AGE BY SEX

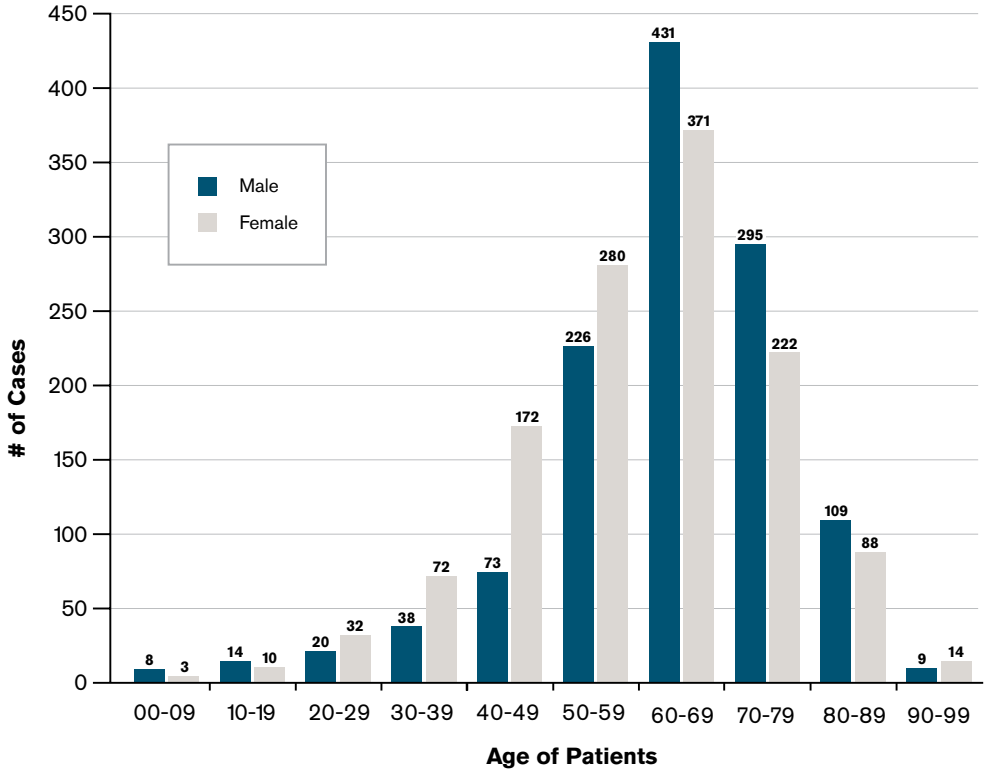
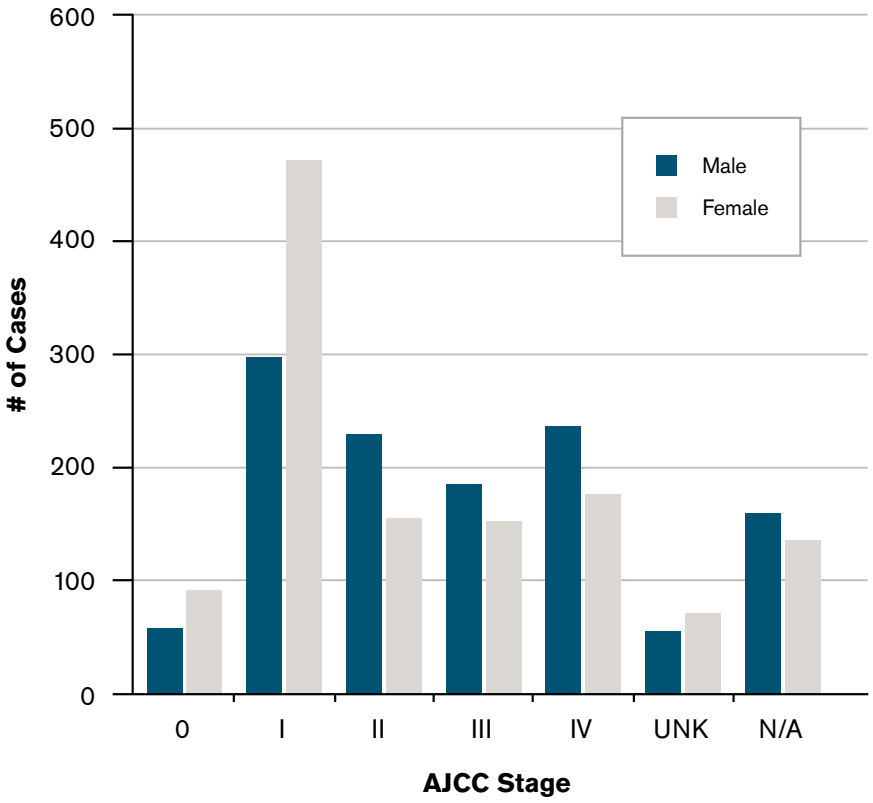


TABLE 2: AGE BY SEX

Age Range	Male	Female
0-9	8	3
10-19	14	10
20-29	20	32
30-39	38	72
40-49	73	172
50-59	226	280
60-69	431	371
70-79	295	222
80-89	109	88
90-99	9	14
Total (2,489)	**1,223**	**1,266**

For all analytic combined staged cases: (155) were Stage 0; (771) Stage I; (390) Stage II; (340) Stage III; (410); Stage IV, (130) Unknown Stage, and (293) Non-applicable.

GRAPH 4: AJCC STAGE BY SEX



Cancer Incidence by Sex and Site with the State and National

The American Cancer Society National estimates for site and sex distribution for all races were used to compare the estimates with Loyola University Medical Center data and the State of Illinois Cancer Statistics. The numbers reported are percentages of the total cases by sex. For the male population as compared to both the state and the nation, we observed quite a high incidence of Melanoma, Liver, Kidney, and Thyroid but a lower level of Prostate, Bladder, Colorectal, and Non-Hodgkin's.

For the female population as compared to the state and national, we observed quite a high incidence of Corpus Uteri, Thyroid, and Ovary, but a lower level of Breast, Lung, Colorectal and Non-Hodgkin's.

TABLE 3: MALES

SITE	LUMC % (n=1,223) Year-2016	ILLINOIS % (n=32,532) Year-2014	NATIONAL % (n=841,390)* Year-2016
Prostate	18.1	22.2	21.5
Lung	15.4	15.0	14.0
Melanoma	6.7	4.7	5.6
Bladder	6.5	7.0	7.0
Kidney	6.0	5.1	4.7
Colorectal	5.6	9.9	8.4
Non-Hodgkin's	4.4	4.6	4.8
Liver	3.8	2.2	3.4
Thyroid	3.4	1.7	1.8
Leukemia	3.2	3.2	4.1

**Estimated New Cancer Cases Year-2016*

TABLE 4: FEMALES

SITE	LUMC % (n=1,266)	ILLINOIS % (n=34,200)	NATIONAL% (n=843,820)
Breast	24.3	29.8	29.2
Corpus Uteri	10.3	6.7	7.1
Thyroid	7.0	4.5	5.8
Lung	6.9	13.6	12.6
Colorectal	5.6	8.5	7.5
Melanoma	4.4	4.2	3.5
Ovary	3.6	2.5	2.6
Non-Hodgkin's	2.9	3.9	3.8
Pancreas	2.8	2.7	3.0
Leukemia	2.7	2.2	3.1

Loyola University Medical Center

Patient Care Evaluation Study of Bladder Cancer 2012-2016

Constantine Godellas, MD
Chairman, Cancer Committee
Surgical Oncology

Violeta Dimovic, CTR
Manager, Oncology Data
Cancer Program

According to the National Cancer Institute, an estimated 76,960 (58,950 men and 18,010 women) new cases of bladder cancer will occur in the U.S. during 2016 year. Bladder cancer is the sixth most common cancer in the United States after lung, prostate, breast, colon and lymphoma cancer. It is the most common cancer in men but only the 11th most common in women.

Keeping track of the number of new cases, deaths and survival over time (trends) can assist scientists understand whether progress is being made and where additional research is needed to challenge, such as improving screening or finding better treatments.

The urinary tract consists of the kidneys, ureters, bladder and the urethra. The urinary tract is lined with transitional cell urothelium from the renal pelvis to the proximal urethra. Under normal conditions, the bladder, lower part of the kidneys, ureters and the proximal urethra are lined with the specialized mucous membrane referred to as transitional epithelium. Most cancers that form in the bladder, renal pelvises, ureters and proximal urethra are transitional cell carcinomas that derive from transitional epithelium.

Transitional cell carcinoma (urothelial carcinoma) of the bladder can be low-grade or high-grade.

- Low-grade bladder cancer often occurs in the bladder after treatment but rarely invades the muscularis wall of the bladder or spreads to other parts of the body.
- High-grade bladder cancer commonly recurs in the bladder and also has a strong tendency to invade the muscularis wall of the bladders and spread to other parts of the body. These cancers are treated more aggressively than the low-grade type and are much more likely to result in death.

Squamous cell carcinoma begins in squamous cells, which are thin, flat cells that may form in the bladder after long-term infection or irritation.

Adenocarcinoma begins in glandular (secretory) cells that are found in the lining of the bladder.

The bladder is also divided into muscle-invasive and non-muscle invasive disease, based on invasion of the muscularis propria (referred to as detrusor muscle), which is the thick muscle deep in the bladder wall.

Bladder cancer typically presents with gross or microscopic hematuria. Patients may also complain of urinary frequency, nocturia and dysuria, symptoms common in patients with carcinoma in situ.

The most useful diagnostic test is cystoscopy so that transurethral resection of the tumor(s) and/or biopsies can be performed.

Prognosis depends on the following:

- The stage of the cancer (whether it is superficial or invasive bladder cancer, and whether it has spread to other places in the body)
- The type of bladder cancer cells and how they look under a microscope
- Whether there is a carcinoma in situ in other parts of the bladder
- Patient's age and general health

If the cancer is superficial, prognosis also depends on the following:

- The number of tumors
- The size of the tumors
- Whether the tumor has recurred after treatment

The purpose of this study is to ensure that evaluation and treatment conforms to evidence-based national guidelines using the AJCC stage or appropriate staging, including appropriate prognostic indicators, and to provide an overview of classification of tumors at LUMC and compare the information of similar patients throughout the nation. For this reason, we have chosen patients treated in our institution from 2012 through 2016. This comparison will hopefully give us information as how our treatment can be modified to improve the quality and duration of life for our patients. This analysis addresses diagnostic evaluation, treatment modalities and prognostic factors.

We used the database of the cancer registry at Loyola University Medical Center (LUMC) to examine trends in patient care, determine patient outcomes and make crude comparisons to available national data. Between 2012-2016, there were 481 bladder cancer cases diagnosed and/or treated at LUMC. The purpose of the following analysis is to compare the population of cancer cases treated at LUMC with patients having the identical disease who are listed in the national database. We will attempt to explain any differences and propose specific interventions that may be helpful in the future. We will also review the histologic distribution, stage, treatment options and verify whether the appropriate grade and histology were assigned correctly in the electronic registry database.

The objective of this study is to determine the demographic breakdown of LUMC patient care, analyze the type of procedures done at initial diagnosis, and determine the role of surgery options, radiation therapy, systemic treatments, chemotherapy and immunotherapy. We will also review the pathologists reporting findings, as well as the pathologic report and make sure it contains all necessary information for correct decisions relating to further treatment steps. It should emphasize the clinical stage and grade for endoscopic specimens, depth of muscle invasion with clear statement of muscularis mucosa versus detrusor muscle invasion. This report will provide valuable information, which is essential in helping us to track progress and identify those areas where change is needed.

Table 1 highlights the bladder cancers diagnosed per year. Bladder cancer cases make up (~4.3 percent) of LUMC's overall cancer cases and is the 8th major site for 2016 year.

TABLE 1: CASELOAD/YEAR

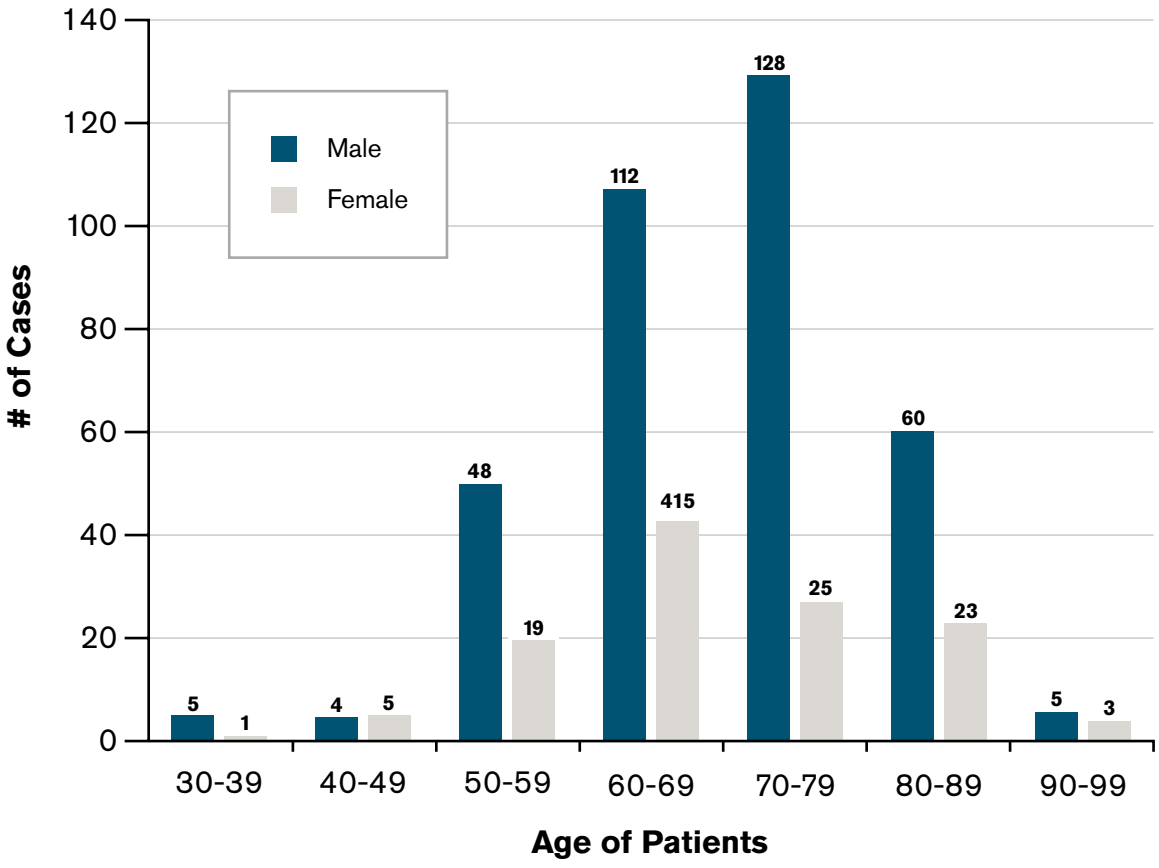
	Total	2012	2013	2014	2015	2016
LUMC	481 (100%)	83 (17%)	90 (19%)	93 (19%)	107 (22%)	108 (23%)

Age group ranged from 32 thru 94. Forty-four percent (32 percent) of the patients were diagnosed between ages 60-69. See Table 2 and Graph 1 below for details.

TABLE 2: AGE GROUP (2012-2016 YEAR)

Age Range	Male	Female	Transsexual	Total
30-39	5	1	0	6
40-49	4	5	0	9
50-59	48	19	1	68
60-69	112	42	0	154
70-79	128	25	0	153
80-89	60	23	0	83
90-99	5	3	0	8
Total	**362**	**118**	**1**	**481**

GRAPH 1: AGE GROUP (2012-2016 YEAR)



Accurate and uniform staging for a tumor is vital for prediction of its behavior, treatment selection, evaluation of response to establish and experimental treatments and exchange of information and data among institutions. The American Joint Committee on Cancer (AJCC)/International, tumor, node and metastasis (TNM) staging system is one of the most commonly used staging systems.

The following stages are used for bladder cancer:

In stage 0, abnormal cells are found in tissue lining the inside of the bladder.

These abnormal cells may become cancer and spread into normal tissue. Stage 0 is divided into stage 0a and stage 0is, depending on the type of tumor:

- Stage 0a is called papillary carcinoma
- Stage 0is is also called carcinoma in situ, which is a flat tumor on the tissue lining of the inside of the bladder.
- In Stage I, the tumor has grown deeper into the inner lining of the bladder, but has not invaded the muscle layer of the bladder.
- In Stage II, the tumor has invaded the muscle layer of the bladder
- In Stage III, the tumor has grown through the muscle layer to reach tissues near the bladder, such as prostate, uterus or vagina.
- In Stage IV, the tumor has invaded the wall of the pelvis or abdomen, but cancer is not found in any lymph nodes. Or, the cancer cells have spread to at least one lymph node or to parts of the body far away from the bladder, such as the liver, lungs or bones.

TABLE 3: ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage	T	N	M
Stage 0a	Ta	NO	MO
Stage 0is	Tis	NO	MO
Stage I	T1	NO	MO
Stage II	T2a	NO	MO
	T2b	NO	MO
Stage III	T3a	NO	MO
	T3b	NO	MO
	T4a	NO	MO
Stage IV	T4b	NO	MO
	Any T	N1-3	MO
	Any T	Any N	M1

Definitions:

Primary tumor (T)

TX: Primary tumor cannot be assessed

T0: No evidence of primary tumor

Ta: Noninvasive papillary carcinoma

Tis: Carcinoma in situ (i.e., flat tumor)

T1: Tumor invades subepithelial connective tissue

T2: Tumor invades muscle

pT2a: Tumor invades superficial muscle (inner half)

pT2b: Tumor invades deep muscle (outer half)

T3: Tumor invades perivesical tissue

pT3a: Microscopically

pT3b: Macroscopically (extravesical mass)

T4: Tumor invades any of the following: prostate, uterus, vagina, pelvic wall or abdominal wall

T4a: Tumor invades the prostate, uterus or vagina

T4b: Tumor invades the pelvic wall or abdominal wall

Regional lymph nodes (N)

NX: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastasis

N1: Metastasis in a single lymph node 2 cm or smaller in largest dimension

N2: Metastasis in a single lymph node larger than 2 cm but 5 cm or smaller in largest dimension; or multiple lymph nodes 5 cm or smaller in largest dimension

N3: Metastasis in a lymph node larger than 5 cm in largest dimension

Distant metastasis (M)

MX: Distant metastasis cannot be assessed

M0: No distant metastasis

M1: Distant metastasis

For comparative purposes, the National Cancer Database, Commission on Cancer, ACoS was used to perform or generate a comparison report on behavior (In situ/Malignant) of bladder cancer between our institution and all academic facilities nationwide. Comparison was based on information from 235 hospitals. See Table 4 below. The purpose of this aggregate report was also to evaluate the overall accuracy of differentiating superficial, non-invasive tumors from invasive tumors. Non-muscle-invasive bladder cancer embraces papillary tumors confined to the mucosa (Ta) or invading the lamina propria T1 but not the muscularis propria, as well as flat, high-grade tumors carcinoma in situ (CIS). These disease stages are associated with different malignant potential, so more specific characterization of each patient's disease is crucial to ensure that the most appropriate treatment and follow-up are offered. Accurate assessment of the patient's risk of progression will determine the extent to which cystectomy rather than bladder sparing treatment can benefit or harm long-term prognosis, thus guiding treatment options.

TABLE 4: BEHAVIOR OF URINARY BLADDER CANCER

Behavior of Urinary Bladder Cancer Diagnosed in 2011, 2012, 2013, 2014, 2015
Loyola University Medical Center, Maywood IL vs. Academic Cancer Program Hospitals in All States
All Diagnosis Types - Data from 235 Hospitals

#	Behavior	My (N)	Oth. (N)	My (%)	Oth. (%)
1.	In situ	123	32,991	25.63%	42.73%
2.	Invasive	357	44,223	74.38%	57.27%
	Col. TOTAL	**480**	**77,214**	**100%**	**100%**

All of the cases were histologically classified as distinct types of bladder cancer. The different histologies represented among the cases showed a favorable prognostic subtype of papillary transitional cell carcinoma, which accounted for about 39 percent (189) of all the cases. Transitional cell, urothelial carcinoma accounted for 25 percent (120), 20 percent (98) accounted for papillary transitional cell carcinoma, non-invasive and the remaining showed other variety of rare cancers.

We reviewed 115 cases that had transurethral resection (TURB) to see if the pathological report indicated whether the lamina propria and muscularis propria are present as well as the degree of involvement is reported. Twelve in situ cases from the total 17 were interpreted and reported by the analysts as papillary non-invasive. The pathology reports did not contain a definite statement of non-invasion and in situ. All 12 cases were re-evaluated by the pathologist and corrected in the registry database to reflect the correct histology.

The quality of care for bladder cancer depends in part on accurate descriptions of tumor characteristics. An open communication pathway between the urologists and pathologists is essential for accurate diagnosis and appropriate treatment. A preferred set of terms are used and non-preferred terminology should be avoided. Diagnosis depends on cystoscopy and the histologic evaluation of the tissue obtained by the transurethral resection of the bladder (TURB) in papillary tumors or by multiple bladder biopsies in (CIS). In papillary lesions, a complete TURB is essential for the patient's prognosis. If the initial resection is incomplete, there is no muscle in the specimen, or a high-grade or T1 tumor is detected, a second TURB should be performed within two to six weeks.

Effective diagnosis and treatment of non-invasive bladder cancer requires active collaboration between urologists and pathologists due to the complex nature of the disease. It is incumbent upon urologists to make their best efforts to provide good-quality, well-documented specimens for pathologists. Pathologists in turn should strive for timely release of informative, unambiguous results. Consistent adherence by both groups to a common terminology for pathologic findings is critical for a clear understanding of the clinical situation. To this end, the trend toward greater use of standardized electronic data transfer may improve efficiency, reduce errors and minimize costs.

The more commonly used descriptions for non-invasion are listed below:

Definite Statements of Non-invasion

- Non-infiltrating; non-invasive
- No evidence of invasion
- No extension into lamina propria
- No stromal invasion
- No extension into underlying supporting tissue
- Negative lamina propria and superficial muscle
- Negative muscle and (subepithelial) connective tissue
- No infiltrative behavior/component
- Inferred Description of Non-invasion
- No involvement of muscularis propria and no mention of subepithelium/submucosa
- No statement of invasion (microscopic description present)
- (Underlying) tissue insufficient to judge depth of invasion
- No invasion of bladder wall; no involvement of muscularis propria
- Benign deeper tissue
- Microscopic description problematic for pathologist (non-invasion versus superficial invasion)
- Frond surfaced by transitional cells
- No mural infiltration
- No evidence of invasion (no sampled stroma)

Ninety-eight (20 percent) of the patients were staged as 0a and twenty (4 percent) were found be in situ, 0IS. The remaining 76 percent were invasive. Of all the cases, 68 percent (329) had a (undifferentiated) differentiation and reported as a Grade 4, 17 percent (84) Grade 2, 7 percent (36) were identified as Grade 3, and 4 percent (12) cases were reported as Grade 1. Histological grade was not known or not stated in 4 percent (20) cases. See Table 5 below for the histology distribution and stage.

TABLE 5: HISTOLOGY BY AJCC STAGE

	0a	0IS	I	II	III	IV	UNKNOWN	Total
Pap Trans Cell Ca	2	0	103	38	16	28	2	189
Trans Cell Ca; Urothelial Ca	0	1	36	26	26	31	0	120
Pap Trans Cell Ca Non-Invasive; Papillary Urothelial Ca	97	0	1	0	0	0	0	98
Transitional Cell Ca In Situ; Urothelial Ca In Situ	0	17	0	0	0	0	0	17
Small Cell Ca Nos; Reserve Cell Ca; Round Cell Ca; Small Cell Neuroendocrine Ca	0	0	3	1	1	6	0	11
Transitional Cell Ca Spindle Cell; Transitional Cell Ca Sarcomatoid	0	0	2	2	1	4	0	9
Squamous Cell Ca Nos Epidermoid Ca; Sq Cell Epithelioma	0	0	1	1	1	4	0	7
Trans Cell Ca, Micropapillary	0	0	1	3	2	1	0	7
Adenocarcinoma	0	0	1	0	1	2	0	4
Neuroendocrine Ca;	0	0	0	2	0	1	0	3
Squamous Cell Ca Keratinizing; Lge Cell Keratinizing; Epidermoid Ca Keratinizing	0	0	0	0	2	1	0	3
Pseudosacromatous Ca; Sarcomatoid Ca	1	0	0	1	0	0	0	2
Small Cell-Large Cell Ca; Combined Small Cell Ca; Mixed Small Cell Ca; Combined Small Cell Large Cell Ca	0	0	1	0	0	1		2
Adenocarcinoma w/Mixed Subtypes	0	0	0	0	1	0	0	1
Clear Cell Adeno	0	0	0	0	1	0	0	1
Mucinous Ca	0	0	0	0	1	0	0	1
Ca w/Neuroendocrine Diff	0	0	0	0	1	0	0	1
Adenocarcinoma Intestinal Type	0	0	0	0	1	0	0	1
Spindle Type Tumor	0	0	0	0	0	1	0	1
Ca In Situ Intrepithelial Ca Type	0	1	0	0	0	0	0	1
Ca Nos, Epithelial Tumor Malignant	0	0	1	0	0	0	0	1
Lymphoepithelial Ca	0	0	0	1	0	0	0	1
Total	**98**	**20**	**150**	**75**	**55**	**81**	**2**	**481**

Most all patients initially presented with gross or microscopic hematuria. Hematuria was documented as painless and intermittent. Some complained of irritating symptoms, including urinary frequency and urgency. The standard method of diagnosis was through urine cytology, CT, pylogram, cystoscopy and biopsy. A treatment option by stage was observed to be managed successfully by transurethral resection with fulguration, followed by intravesical biologic therapy or chemotherapy and/or segmental or radical cystectomy. This descriptive analysis of LUMC cancer registry data was reassuring in terms of the quality of patient care delivered for years 2012 to 2016. See Table 6 below for the distribution of treatment combination.

TABLE 6: DISTRIBUTION OF TREATMENT COMBINATION (LUMC 2012-2016)

	0a	0IS	I	II	III	IV	Unknown	Total
s	47	7	51	26	33	20	1	185
SC	27	0	26	37	17	44	0	151
SI	12	4	51	3	2	1	0	73
SCI	13	3	16	2	0	1	0	35
SCR	0	0	1	5	0	7	0	13
None	1	0	1	1	1	2	0	6
R	0	0	2	1	0	2	0	5
SR	0	0	0	0	2	3	0	5
I	0	3	1	0	0	0	0	4
C	0	0	1	0	0	0	0	1
CI	0	1	0	0	0	0	0	1
CR	0	0	0	0	0	1	0	1
SH	0	0	1	0	0	0	0	1
Total	**100**	**18**	**151**	**75**	**55**	**81**	**1**	**481**

S=Surgery C=Chemotherapy I=Immunotherapy R=Radiation H=Hormone

Five-year relative survival (percent), based on the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute by general stage at diagnosis, showed survival rates of; In situ to be 95.7 percent, Local 70.1 percent, Regional 35.2 percent and Distant to be at 5.0 percent. from 2007-2013 year. Our institution's data from the same years showed; In-situ 82 percent, Local 71 percent, Regional 39 percent and Distant at 11 percent. Statistically significant survival advantage is noted for all stages except the in situ. A 6 percent higher finding for the distant stage suggests that our treatment option for distant stage resulted to a higher cure rate.

This data is from a series of hospital registries and one population-based registry. The relative survival estimate is the ratio of observed survival to expected survival for a given patient cohort. Expected survival is based on mortality rates for the entire population, taking into account, as appropriate, the age, sex, race and year of diagnosis of the patients. Assuming that the presence of cancer is the only factor that distinguishes the cancer patient cohort from the general population, relative survival estimates the probability that a patient will not die of the diagnosed cancer within the given time interval. This is the same as the probability that the patient will either survive the interval or die of a different cause.

TABLE 7: TREATMENT OF UROTHELIAL (TRANSITIONAL CELL) BLADDER CARCINOMA
(According to NCCN Guidelines)

Tumor	Treatment
Low-grade Ta	Transurethral resection; NCCN guidelines recommends observation and strongly recommends administering a single dose of immediate intravesical chemotherapy within 24 hours of resection
High-grade Ta	Repeat transurethral resection (if lymphovascular invasion, incomplete resection, or muscle in the specimen), consider intra vesical bacilli Calmette-Guerin (BCG) or mitomycin
Carcinoma in situ Tis	Transurethral resection followed by intravesical BCG or mytomicin
Low-grade T1	Repeat transurethral resection followed by intra vesical BCG or mytomicin
High-grade T1	Repeat transurethral resection followed by intra vesical BCG or mytomicin or cystectomy
T2a or T2b (organ confined)	Radical cystectomy followed by chemotherapy in high-risk patients
T3a o T3b	Radical cystectomy followed by adjuvant chemotherapy, consider neoadjuvant chemotherapy
T4a, T4b or metastatic disease	Chemotherapy alone or in combination with radiation therapy, except in high-risk patients.

Pathology functions not in a vacuum but as a dynamic specialty that requires knowledge of patient history, clinical findings, and dialogue with clinical colleagues. Cooperative efforts to provide better patient care are important and, perhaps more than most other disease sites, are especially relevant in bladder cancer, where cystoscopic findings and patient history are critically relevant in the diagnosis of any bladder lesion. As such, it is important for pathologists to receive relevant patient information from the treating clinician and to be comfortable enough to open a dialogue in any patient case that presents a challenge. Likewise, the ever-evolving pathology literature related to bladder cancer diagnosis requires frequent communication to keep the clinician aware of changes in this arena, and it is important for the pathologist to recognize his or her role in this important aspect of communication. Finally, the ability to share areas of needed improvement in bladder cancer diagnosis as well as ideas on new research concepts and treatment modalities is vital to advancing a field that urgently requires new knowledge. As such, a team-based approach to bladder cancer that involves not only the pathologist and urologist but also the urologic oncologist, radiation oncologist, primary care physician, and researchers is vital.

In conclusion, urothelial tract tumors represent a spectrum of diseases with a range of prognosis. Continued monitoring for recurrence is all essential part of management. After a tumor is diagnosed anywhere within the urothelial tract, the patient remains at risk for developing a new lesion at the same or different location and with a similar or more advanced stage. Recurrence and progression are dependent on multiple clinical and pathological features as well as successful macro- and micro-ablation using traditional endoscopic surgical techniques and intravesical therapies, respectfully. Encouraging progress has been made in defining the standards of TURB and cystectomy specimen handling and diagnosis during the past several decades, although we are far from optimal care for these patients. Ongoing re-evaluation of how we handle pathologic specimens is critical not only for patient diagnosis and guiding treatment but for providing accurate material for ongoing research and biological understanding of the disease. Importantly, the role of ongoing communication among the various specialties that manage patients with this disease is a crucial component and should be optimized whenever possible. The cancer control research has an enormous potential to decrease morbidity and mortality from bladder cancer by enhancing strategies for screening and prevention and identifying approaches that can maximize patient's quality of life and overcome barriers to healthcare delivery.

Adjuvant Radiotherapy Use by U.S. Radiation Oncologists after Radical Cystectomy for Muscle-invasive Bladder Cancer

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Aims
Historic trials suggested significant toxicity with adjuvant radiotherapy (ART) after radical cystectomy for muscle-invasive bladder cancer (MIBC). However, recent trials have found improved locoregional control and the 2016 National Comprehensive Cancer Network (NCCN) guidelines recommend ART consideration for select patients at high risk of local recurrence. ART practice patterns among U.S. radiation oncologists are unknown and we carried out a survey to explore current trends.

Materials and methods
We conducted a survey of U.S. radiation oncologists regarding the management of patients with cT2-3N0M0 transitional cell MIBC. Responses were reported using descriptive statistics. Chi-square and univariate logistic regression of clinical and demographic covariates were conducted, followed by multivariable logistic regression analysis to identify factors predicting for ART use.

Results
In total, 277 radiation oncologists completed our survey. Nearly half (46 percent) have used ART for MIBC at least once in the past. In ART users, indications for ART include gross residual disease (93 percent), positive margins (92 percent), pathological nodal involvement (64 percent), pT3 or T4 disease (46 percent), lymphovascular invasion (16 percent) and high-grade disease (13 percent). On univariate logistic regression, ART use was associated with the number of years in practice (P ¼ 0.04), pre-cystectomy radiation oncology consultation (P ¼ 0.004), primarily treating MIBC patients fit for cystectomy (P ¼ 0.01) and intensity-modulated radiotherapy use (P ¼ 0.01). On multivariable logistic regression analysis, routine pre-cystectomy radiation oncology consultation (odds ratio 1.91, 95 percent confidence interval 1.04e3.51; P ¼ 0.04) and intensity-modulated radiotherapy use (odds ratio 2.77, 95 percent confidence interval 1.48e5.22; P ¼ 0.002) remained associated with ART use.

Conclusions
ART use is controversial in bladder cancer, yet unexpectedly has commonly been used among U.S. radiation oncologists treating patients with MIBC after radical cystectomy. NRG-GU001 was a randomised trial in the U.S. randomizing patients with high-risk pathological findings for observation or ART after cystectomy. However, due to poor accrual it recently closed and thus it will be up to other international trials to clarify the role of ART and identify patients benefiting from this adjuvant therapy.

Introduction

Radical cystectomy is the most commonly used curative treatment in patients with muscle-invasive bladder cancer (MIBC). Modern series suggest encouraging outcomes with this approach in most patients, but in patients with pT3/4 disease, locoregional recurrence with or without distant metastases can occur in up to nearly 50 percent of patients, particularly those with high-risk features, such as positive margins or limited nodal dissection. Adjuvant radiotherapy (ART) is routinely used in other pelvic malignancies to reduce the risk of locoregional recurrence and improve survival in some patients, and is supported by randomized data in these disease entities. ART for bladder cancer was explored in an Egyptian randomized trial of observation versus two ART regimens using two-dimensional radiotherapy techniques; an improvement in 5 year local control from 50 percent to 90 percent and improved disease-free survival were found. However, oncologists have not historically embraced ART, primarily due to concern for gastrointestinal toxicity, with rates as high 37 percent in one study

Yet, with the development of advanced radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT), as well as recognition of the high incidence of locoregional recurrence and consequent morbidity of pelvic recurrence, there has been a renewed interest in ART use for patients with MIBC. A second Egyptian randomized trial, this time using modern three-dimensional radiotherapy techniques, was recently presented and showed an improved locoregional control with the addition of ART, with grade 3 gastrointestinal toxicity of 78 percent. There are multiple international randomized trials testing the benefit of ART versus observation after radical cystectomy in patients with high-risk pathologic features after cystectomy. There are no data exploring radiation oncologists' practice patterns regarding the use of ART in MIBC in routine practice. We carried out a survey to describe U.S. radiation oncologists' actual radiotherapy and chemotherapy practices in the management of MIBC, and here we report the findings regarding ART utilization.

Materials and Methods

Survey Design

In October 2015, we designed an electronic survey regarding the radiotherapy and chemotherapy practices of U.S. radiation oncologists for cT2-T3 N0 transitional cell carcinoma bladder cancer patients using Google Forms (Google, Mountain View, CA, USA). We included 24 questions regarding respondent demographics, volume and type of MIBC patients seen in consultation, whether pre-cystectomy radiation oncology consultation is routinely carried out, preferred radiotherapy target volume and dose/fractionation, chemotherapy practices, IMRT utilization and ART utilization. The results of our bladder-preservation therapy analysis will be reported in a separate manuscript. The survey was emailed to 4,057 U.S. radiation oncologists on October 26, 2015, with one reminder emailed a week later.

Statistical Analysis

A statistical analysis was conducted using SAS release 9.4 (SAS Institute, Cary, NC, USA). Descriptive statistics for each item were carried out. Univariate analyses (UVA) were conducted using chi-square and logistic regression analyses to compare respondent and practice characteristics with treatment details. During the analysis, the state of practice was grouped into U.S. Census regions. Based on the UVA results, a multivariable logistic regression analysis (MVA) was then carried out to identify respondent and practice characteristics associated with ART use, and included covariates that had a P value <0.1 on UVA. During MVA, the most commonly treated bladder cancer patients were dichotomized into either patients who were unfit for cystectomy or patients who were fit for cystectomy (patients who were fit for surgery but were unwilling to undergo cystectomy and patients who were candidates for cystectomy and bladder-preserving therapy and were considering both options). IMRT use was dichotomized into almost never (< 10 percent) versus in select cases, frequently or almost always (10 percent to >90 percent). An alpha < 0.05 was considered statistically significant.

Results

Respondents

One hundred and eighty-one emails were undeliverable. There were seven responses stating that they would not take the survey because the respondent was either retired or did not treat MIBC. Seven respondents were not practicing radiation oncologists, and one respondent practiced outside of the USA. In total, there were 277 evaluable responses.

Table 1 describes the respondent demographic and clinical practice characteristics. Nearly half (46 percent) of the respondents reported that they have used ART in MIBC patients at least once in the past. Over half (56 percent) of the respondents have been in practice >10 years. Only 28 percent routinely see MIBC patients before cystectomy to discuss radiotherapy options. Most respondents most commonly see patients who are unfit for cystectomy (74 percent). Most (75 percent) use IMRT in select cases or more often (10 to >90 percent of patients).

TABLE 1: RESPONDENT DEMOGRAPHIC AND CLINICAL CHARACTERISTICS (N=277)

Respondent characteristic	n (%)
Number of years in practice	
0-2	18 (6%)
3-5	30 (11%)
6-10	45 (16%)
>10	156 (56%)
In residency	28 (28%)
Primary practice setting	
VA Hospital	6 (2%)
Academic Hospital	101(36%)
Community Hospital or Private Practice	176 (61%)
U.S. Census Region	
Midwest	90 (32%)
Northwest	54 (19%)
South	80 (29%)
West	53 (53%)
Consultation clinic setting	
Single specialty clinic as a referral from physician from another specialty	225 (81%)
Multidisciplinary clinic with physicians representing multiple specialties	52 (19%)
Number of patients with non-metastatic bladder cancer treated over the past year	
0	19 (7%)
1-3	160 (58%)
4-6	64 (23%)
>6	34 (12%)
Routinely see patients before cystectomy to discuss radiotherapy options	
No	200 (72%)
Yes	77 (28%)
Non-metastatic bladder cancer patients most commonly treated	
Patient who are unfit for cystectomy	206 (72%)
Patients who are fit for surgery but are unwilling to undergo cystectomy	31 (11%)
Patients who are candidates for cystectomy and bladder-preserving therapy and are considering both	40 (14%)
Intensity-modulated radiotherapy use	
Almost never (<10%)	64 (23%)
In select cases (10-50%)	73 (26%)
Frequently (51-90%)	67 (24%)
Almost always (<90% of patients)	73 (26%)
Adjuvant radiotherapy use	
Yes	127 (46%)
No	150 (54%)

Univariate Analysis for Adjuvant Radiotherapy Use

Table 2 depicts the UVA results for ART utilization. The number of years in practice was associated with ART use, with those who were 0e2 years in practice or >10 years in practice more likely to use ART (P=0.04). Routine pre-cystectomy radiation oncology consultation (P= 0.004) and most commonly treating patients fit for cystectomy (P= 0.01) were also associated with ART use, whereas 'Almost never (<10 percent of patients)' IMRT use was inversely related to ART use (P=0.01).

TABLE 2: UNIVARIATE ANALYSIS FOR ADJUVANT RADIOTHERAPY USE

Practice characteristics	Adjuvant radiotherapy		P Value*
	No	Yes	
Number of years in practice			**0.04**
0-2	8 (44%)	10 (56%)	
3-5	21 (70%)	9 (30%)	
6-10	28 (62%)	17 (38%)	
>10	74 (47%)	82 (53%)	
In Residency	19 (68%)	9 (32%)	
Primary practice setting			**0.94 ˜**
VA Hospital	3 (50%)	3 (50%)	
Academic Hospital	56 (55%)	45 (45%)	
Community Hospital or private practice	91 (54%)	79 (46%)	
US Census Region			**0.42**
Midwest	54 (60%)	36 (40%)	
Northwest	25 (46%)	29 (54%)	
South	44 (55%)	36 (45%)	
West	27 (51%)	26 (49%)	
Consultation clinic setting			**0.20**
Single specialty clinic as a referral from physician from another specialty	126 (56%)	99 (44%)	
Multidisciplinary clinic with physicians representing multiple specialties	24 (46%)	28 (54%)	
Number of patients with non-metastatic bladder cancer treated over the past year			**0.36**
0	12 (63%)	7 (37%)	
1-3	90 (56%)	70 (44%)	
4-6	34 (53%)	30 (47%)	
>6	14 (41%)	20 (59%)	
Routinely see patients before cystectomy to discuss radiotherapy options			**0.004**
No	119 (60%)	81 (40%)	
Yes	31 (40%)	46 (60%)	
Non-metastatic bladder cancer patients most commonly treated			**0.01**
Patient who are unfit for cystectomy	121 (59%)	85 (41%)	
Patients who are fit for cystectomy	31 (40%)	42 (59%)	
Intensity-modulated radiotherapy use			**0.01**
Almost never (<10%)	46 (72%)	18 (28%)	
In select cases (10-50%)	33 (45%)	40 (55%)	
Frequently (51-90%)	36 (54%)	31 (46%)	
Almost always (<90%)	35 (48%)	38 (52%)	

** Chi-square test. † Fisher's exact test.*

Multivariable Analysis for Adjuvant Radiotherapy Use

Table 3 depicts the MVA results for ART utilization. Routine pre-cystectomy radiation oncology consultation (odds ratio 1.91, 95 percent confidence interval 1.04e3.51; P=0.04) and IMRT use (odds ratio 2.78, 95 percent confidence interval 1.48-5.22; P=0.002) were associated with increased odds of ART use. The number of years in practice (P= 0.05) and most commonly treating patients fit for cystectomy (P= 0.07) were no longer significantly associated with ART use, but did continue to exhibit a trend towards increased ART use.

TABLE 3: MULTIVARIABLE ANALYSIS PREDICTING FOR ADJUVANT RADIOTHERAPY USE

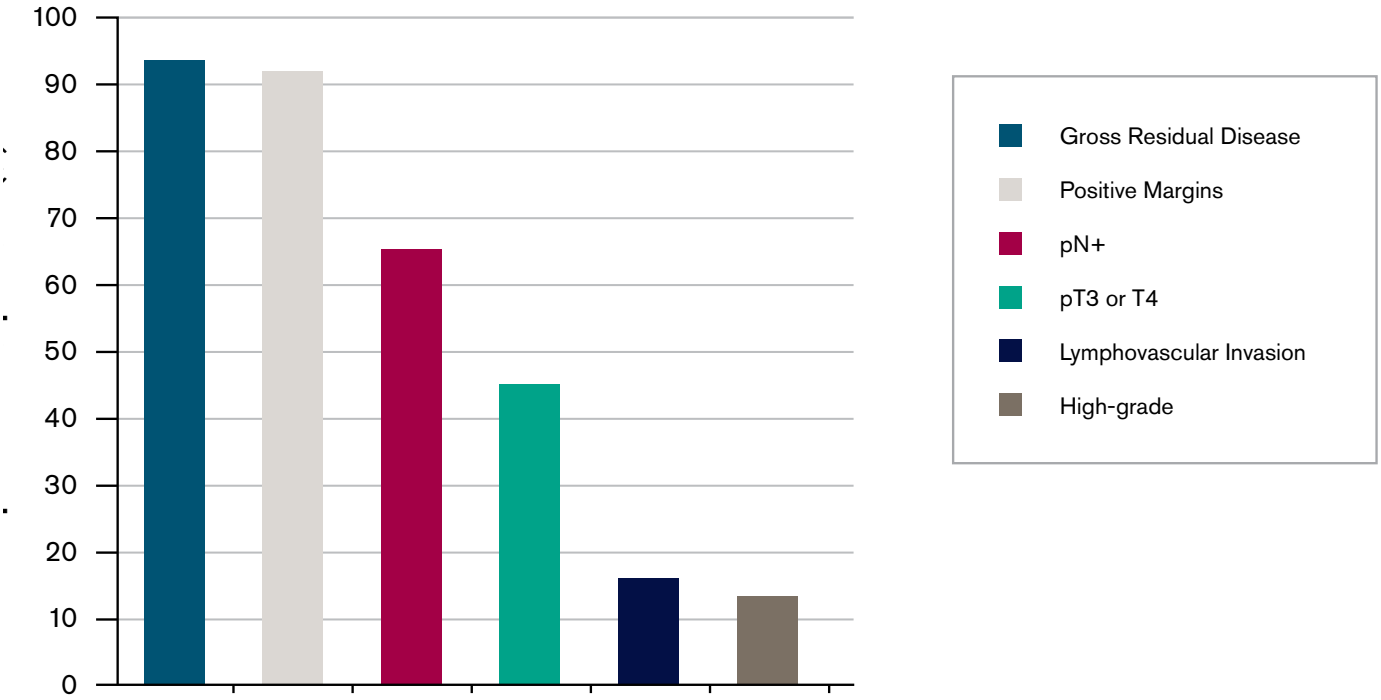
Covariate	Odds ratio (95%) confidence interval)	P value*
Number of years in practice		**0.05**
0-2	Reference	
3-5	0.38 (0.11-1.37)	0.14
6-10	0.53 (0.16-1.70)	0.28
>10	0.88 (0.31-2.49)	0.82
In Residency	0.30 (0.08-1.08)	0.07
Routinely see patients before cystectomy to discuss radiotherapy options		
No	Reference	
Yes	1.91 (1.04-3.51)	0.04
Non metastatic bladder cancer patients most commonly treated		
Unfit for cystectomy	Reference	
Fit for cystectomy	1.77 (0.95-3.29)	0.07
Intensity-modulated radiotherapy use		
Almost never (>10% pf patients)	Reference	
In select cases, frequently, or almost always (10% to >90%)	2.78 (1.48-5.22)	0.002

**Logistic regression.*

Indications for Adjuvant Radiotherapy Use

Within the subgroup of ART users, the most common indications for ART (Figure 1) were gross residual disease (93 percent) or positive margins (92 percent), followed by pathological nodal involvement (64 percent), pT3/4 disease (46 percent) and lymphovascular space invasion (16 percent), and high-grade disease (13 percent).

FIGURE 1: INDICATIONS FOR ADJUVANT RADIOTHERAPY IN THOSE WHO USED IT (N=127)



	Clinicopathologic Indication					
	Gross Residual Disease	Positive Margins	pN+	pT3 or T4	Lymphovascular invasion	High-grade
N	118	117	81	58	20	17
Proportion (%)	93%	92%	64%	46%	16%	13%

Discussion

Radical cystectomy is the most common definitive therapy delivered to patients with MIBC. For patients with aggressive features at the time of surgery, such as pT3/4 disease or positive surgical margins, the risk of loco-regional recurrence may be as high as nearly 50 percent. Furthermore, these patients have an extremely poor prognosis after recurrence, with a median survival of about 6 months. Combining concerns for morbidity/mortality related to pelvic recurrences with the principles of other pelvic malignancies, ART to the pelvis is an attractive approach to try to prevent disease recurrence. Yet, studies conducted in the two-dimensional radiotherapy era, with relatively rudimentary radiotherapy techniques, raised concern for toxicity with this approach, despite also showing disease control benefits, and have tempered enthusiasm for this approach. More recent studies, the evolution of sophisticated radiotherapy techniques that limit the dose to normal tissues and better quantification and stratification of the risk of pelvic recurrence have brought renewed interest in ART and NRG Oncology leadership deemed it important to investigate the clinical importance of ART in a randomized phase II trial, NRG-GU001, which was developed for patients in North America, including trials at Tata Memorial Hospital in India, the University of Ghent in Belgium, GETUG-AFU in France, and the Cairo NCI. Given the usually conservative nature of radiation oncology practice patterns in the USA, with solid clinical evidence required for incorporation of treatment modality in any disease site and where toxicity concerns must be weighed against proven clinical benefits, we were surprised by our observation that nearly half of responding radiation oncologists in the USA recommend ART, with various indications cited by respondents for pursing this approach.

The incremental benefit and potential toxicities of ART are not fully elucidated. The best data exploring ART come from the Egyptian National Cancer Institute. The first trial randomized 236 patients with bladder cancer to either observation, ART using 1.25 Gy three times daily to a total dose of 37.5 Gy or ART using 2 Gy per fraction daily to 50 Gy. Eligibility included what would be today's pT2b-T4, any N-stage patients. The use of adjuvant or neoadjuvant chemotherapy was not specified in the trial, but is unlikely given that adding chemotherapy is a more modern approach. Of note, about 75 percent were N0, two-thirds had pT3/4 disease and two-thirds had squamous cell carcinoma, whereas only about 20 percent had transitional cell carcinoma. Patients receiving either of the ART regimens had improved 5 year local control (87 percent and 93 percent versus 50 percent, $P< 0.0001$) and improved 5 year disease-free survival (49 percent and 44 percent versus 25 percent, $P<0.0001$). Interestingly, the distant metastasis rate was 27 percent in the conventional fractionation ART group, whereas it was <10 percent in the other groups. Acute toxicity was modest, but late small bowel toxicity occurred in 36 percent of the conventional fractionation ART group, with more intestinal fistulas and increased uropathy and deterioration of renal function in this group. An analysis of 78 patients who received a regimen of split preoperative and postoperative radiotherapy using two-dimensional radiotherapy corroborated the potential for gastrointestinal toxicity, with 37 percent of patients who received ART developing bowel obstructions. Thus, despite improvements in local control and disease free survival, ART was not taken up by general practice due to concern for undue toxicity as a result of bowel falling into the pelvis post-cystectomy.

However, the results of a second Egyptian randomized trial, using three-dimensional radiotherapy techniques and a higher proportion of transitional cell patients, were recently presented, but not yet published. This study enrolled 198 patients ≥ 70 years of age and treated with radical cystectomy with negative surgical margins who had high-risk factors (≥pT3b disease, high-grade or involved lymph nodes) and randomized them to either ART, adjuvant sequential chemotherapy and radiotherapy or adjuvant chemotherapy alone. In this study 53 percent had urothelial carcinoma and 41 percent had squamous cell carcinoma, suggesting a population potentially more similar to the population of bladder cancer patients treated in the U.S. today. The two radiotherapy groups had improved three year local recurrence free survival in the ART arms (87 percent and 96 percent versus 69 percent, $P<0.01$). Three year disease-free survival was numerically higher in the ART arms (63 percent and 68 percent versus 56 percent), but this was not statistically significant ($P=0.25$) and there was no difference in distant metastasis-free survival or overall survival. Toxicity was improved compared with the previous

trial, with grade ≥3 gastrointestinal toxicity of 7 and 8 percent in the ART arms, but one could argue that this is still relatively high compared with ART in other diseases. A subsequent presentation focusing on the comparison between the sequential chemoradiotherapy (n =75) and the chemotherapy (n=45) arms revealed dramatically improved two year local recurrence-free survival (96 percent versus 69 percent, P< 0.01), a trend towards improved 2 year disease-free survival (68 percent versus 56 percent, P=0.07) and a numerically but not significantly improved two year overall survival (71 percent versus 60 percent, P= 0.11). The late grade ≥3 gastrointestinal toxicity rate was 7 percent versus 2 percent for the chemoradiotherapy and chemotherapy alone groups, respectively.

To test the benefit of ART in the North American population, NRG-GU001 randomized patients with pT3/4 N0-2 urothelial carcinoma after radical cystectomy to either observation or ART (with neoadjuvant or adjuvant chemotherapy per physician discretion). This study recently closed to accrual and thus it will be up to the other international trials to answer the question of whether ART in bladder cancer improves outcomes with acceptable toxicity. However, accrual to this study has been slow. Interestingly, despite active trials evaluating the benefit, the most recent NCCN bladder cancer guideline has endorsed consideration for ART in some patients with high-risk disease.

It is in this setting that we carried out our survey of U.S. radiation oncologists to further evaluate the patterns of ART use in MIBC patients. Our finding that nearly half of radiation oncologists have used ART in the past suggests that a large proportion of radiation oncologists have used this approach clinically. One could argue, however, that the fact that a co-operative group trial is actively randomizing patients to ART gives credence to this approach and establishes a clear equipoise in this field. This also questions whether ART should be used in routine clinical practice outside of a clinical trial setting. It is important to offer eligible patients an opportunity to be treated on the NRGGU001 trial whenever possible, rather than offering patients treatment off a clinical trial.

We found that respondents who use IMRT in bladder cancer are independently more likely to offer ART to patients than those who do not. IMRT is commonly used in other pelvic malignancies in the ART setting, and thus clinicians are probably applying these same principles to patients with MIBC. In the setting of bladder-preservation therapy, IMRT has been associated with lower normal organ doses and potentially reduced toxicity. The ability of IMRT to spare bowel and the urinary diversion may be even more important in the postoperative setting, and may help to further reduce the 7-8 percent grade ≥3 gastrointestinal toxicity seen in the recent Egyptian trial conducted using three-dimensional radiotherapy. IMRT is the modality chosen in NRG-GU001, and the results of this study will shed light on to any differential toxicity with ART using IMRT.

Our exploration of the indications for ART revealed interesting findings. Based on the above studies, there are no subgroups that differentially benefit from ART more than others. However, a three-tiered risk stratification for local failure developed in a University of Pennsylvania cohort and validated in a cohort of patients treated on SWOG 8710 may be helpful for identifying the patients who would probably benefit from ART. Patients were stratified into low risk (≤pT2), intermediate risk (≥pT3 with ≥10 benign or malignant lymph nodes identified and negative surgical margins) and high risk (≥pT3 with <10 benign or malignant lymph nodes identified or positive surgical margins). The five year risk of local failure was 8 percent, 20 percent and 41 percent, for each of the groups, respectively. The rationale for ART in those with positive surgical margins and pT3/4 disease is supported by this. Furthermore, a study validating this risk stratification schema found that lymphovascular invasion aids in identifying a group at higher risk of locoregional recurrence. High-grade disease was also used as an indication in our respondents. There was no interaction between grade and benefit to ART in the older Egyptian trial, thus suggesting that this may not be as effective a selection tool. Many respondents reported using nodal involvement as an indication for ART. Interestingly, there was no disease-free survival benefit for node-positive patients in the original Egyptian randomized trial, although the locoregional control was still improved in this group. Subgroup analysis of the lymph node-positive subgroup in the more recent Egyptian randomized trial is not available. A single institution retrospective patterns of failure study found that patients with nodal involvement had significantly higher

locoregional recurrences. Potentially, modern chemotherapy approaches may magnify the impact of pelvic disease control and make ART even more beneficial.

Limitations to this study include the relatively low response rate. This was probably, at least partially, due to self-selection of participants, as there is frequently specialization within departments with physicians focusing on specific disease sites, and thus those who do not treat bladder cancer may have been less likely to respond. The relative rarity of cases probably also contributed to the response rate. Additionally, we cannot make conclusions regarding the optimal ART field to use, although multiple recent studies have described the patterns of nodal involvement and recurrence after radical cystectomy, and most studies have used a standard 'whole pelvis' field encompassing up to L5/S1. A contouring atlas was created specifically for NRG-GU001 to aid in target delineation. We also cannot comment on the optimal dose/fractionation to use, although NRG-GU001 used 50.4 Gy and the most recent Egyptian trial used 45 Gy twice daily. Additionally, given the inherent limitations of the survey study design, we cannot make conclusions regarding the actual rates of utilization of ART, which are probably low given the emerging nature of the data supporting its use in the modern era. Also, we did not ask about the frequency with which respondents used ART, and cannot identify whether respondents had only used it in the past or currently use it as well.

Conclusions

ART is an unexpectedly commonly utilized treatment modality for patients with MIBC after radical cystectomy. With modern radiotherapy techniques there is renewed interested in this approach for high-risk patients, with the available data suggesting a locoregional control benefit. There are multiple international randomized studies investigating the benefit of ART, and these studies will hopefully elucidate its role in bladder cancer patients.

Appendix A. Supplementary data

Supplementary data related to this article can be found at: http://dx.doi.org/10.1016/j.clon.2017.02.005.

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Glossary of Terms

Accession: The addition of new cancer cases to the Oncology Registry. Each patient is assigned a separate and permanent number.

ACOS: American College of Surgeons

ACS: American Cancer Society

Class of Case: The class of case divides cases recorded in the database of the facility into categories of analytic and non-analytic. Analytic data includes cases diagnosed at the accessioning facility and/or administration of any of the first course of treatment after the *registry's reference date. Non-analytic cases are first diagnosed and receive all of first course of therapy at another institution, or are diagnosed at autopsy or by death certificate only. Non-analytic cases are not usually included in routine treatment or survival statistics. Based on category, the cancer program selects cases to be used by their facility or to be reported to the central registry, as well as, the National Cancer Database (NCDB).

Analytic: A case first diagnosed and/or receiving first course treatment at that facility, or diagnosed at autopsy.

Non-analytic: Any case diagnosed at another facility and receiving all of first course treatment at that facility, then seen at Loyola University Medical Center for subsequent treatment.

Class 0 Diagnosis at accessioning facility and the entire first course of treatment was performed elsewhere or the decision not to treat was made at another facility.

> Patients who elect to be treated elsewhere.

> Patients who are referred elsewhere for treatment for any reason. For example, lack of special equipment; proximity of a patient's residence; financial, social or rehabilitative considerations

Class 1	Diagnosis at the accessioning facility, and all or part of the first course of treatment was performed at the accessioning facility.
	Patients diagnosed at the accessioning facility whose treatment plan is either not to treat or watchful waiting.
	Patients diagnosed at the accessioning facility who refuse treatment.
	Patients diagnosed at the accessioning facility who are not treatable or who were given palliative care only due to age, advanced disease, or other medical conditions.
	Patients diagnosed at the accessioning facility for whom it is unknown whether treatment was recommended or administered.
	Patients diagnosed at the accessioning facility for whom treatment was recommended, but it is unknown whether it was administered.
	Patients diagnosed at a staff physician's office who receive their first course of treatment at the accessioning facility. "Staff physician" refers to any medical staff with admitting privileges at the accessioning facility.
	Patients diagnosed at the accessioning facility who received all or part of their first course of treatment in a staff physician's office.
Class 2	Diagnosis elsewhere, and all or part of the first course of treatment was performed at the accessioning facility.
	Patient provided palliative care in lieu of first course treatment, or as part of the first course of treatment, at the accessioning facility.
Class 3	Diagnosis and all of first course treatment done elsewhere.
	Patient treated or managed at the accessioning facility, but first course of treatment information is unknown.
	Patient for whom the accessioning facility developed a treatment plan or provided "second opinion" services, but the diagnosis and treatment was provided elsewhere.
	Patient treated for a recurrence or progression for a previously diagnosed malignancy.

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