Earlier Adjuvant Therapy Is Beneficial in Patients With Breast and Colon Cancer

Two recent studies have highlighted the importance of the timing of treatment in the adjuvant setting for individuals with early-stage colorectal and breast cancer.

Colorectal Cancer
Several previous studies have shown that initiating adjuvant chemotherapy for patients with colorectal cancer within 8 weeks after surgery improves outcomes compared with starting chemotherapy after a longer postoperative interval. Previous studies also have shown that laparoscopic surgery provides outcomes comparable to those of open surgical resection for colorectal cancer. The current study examined the effect of the timing of adjuvant chemotherapy for patients with stage III colon cancer on outcomes with a focus on initiating treatment within 4 weeks of surgery. The study also examined whether laparoscopic surgery allowed earlier adjuvant treatment (J Surg Oncol. 2015;112:538-543).

Researchers obtained data from the Danish Colorectal Cancer Group (DCCG) prospective database, which contains information for 99% of patients diagnosed with colorectal cancer in Denmark. Variables in the database include demographic information and preoperative, intraoperative, and postoperative variables, including postoperative complications and morbidity, mortality, and pathology. Information regarding the administration of adjuvant chemotherapy was included in the DCCG database via the Danish National Patient Registry.

Results
A total of 1827 patients who were treated with adjuvant chemotherapy between 2005 and 2012 and whose data were retrieved from the DCCG were included in the final analysis. Of these, 54% underwent open resections and 46% underwent laparoscopic resections. The majority of these patients (72%) initiated adjuvant treatment 4 to 8 weeks after surgery, and 12% started within 4 weeks.

Adjuvant therapy was initiated longer after open resection compared with laparoscopic resection (43 days vs 39 days; \(P < .001\)). Significantly more patients who underwent laparoscopic resection were able to start adjuvant therapy within 4 weeks compared with those who underwent open resection (9% vs 16%; \(P < .001\)). Furthermore, adjuvant therapy was initiated more than 8 weeks postoperatively in a larger percentage of patients after laparotomy versus laparoscopy (18% vs 13%; \(P = .002\)).

When compared with patients whose adjuvant therapy was initiated within 4 weeks after surgery, those starting later than 8 weeks had an increased risk of death during the follow-up period (hazard ratio [HR], 1.7; \(P = .024\)). In addition, starting therapy 4 to 8 weeks after surgery improved survival significantly when compared with starting therapy after 8 weeks (HR, 1.4; \(P = .013\)), but this difference was not statistically significant compared with starting within 4 weeks (HR, 1.2; \(P = .37\)).

Using a Cox regression analysis with covariates of age, overall disease stage, type of surgical resection (which segments of bowel were removed), tumor size, and lymph node classification, longer time-to-chemotherapy (TTC) (analyzed as 3 groups—fewer than 4 weeks, 4-8 weeks, and greater than 8 weeks) was associated with poorer survival.

The study authors concluded that survival is significantly improved when adjuvant chemotherapy is initiated within 8 weeks of surgery for patients with colon cancer and that there is a nonstatistically significant trend toward a further improvement in survival if it is started within 4 weeks.

- Administering adjuvant chemotherapy to patients with breast cancer fewer than 7 weeks after surgery resulted in a longer overall survival compared with that in the group with a longer time-to-chemotherapy (TTC).
- More research is needed to ascertain whether shorter TTC intervals will further improve outcomes.

KEY POINTS
- Survival is significantly improved when adjuvant chemotherapy is initiated within 8 weeks of surgery for patients with colon cancer and there is a nonstatistically significant trend toward a further improvement in survival if it is started within 4 weeks.
- Administering adjuvant chemotherapy to patients with breast cancer fewer than 7 weeks after surgery resulted in a longer overall survival compared with that in the group with a longer time-to-chemotherapy (TTC).
- More research is needed to ascertain whether shorter TTC intervals will further improve outcomes.
but in multivariate analyses, the surgical approach did not appear to significantly affect survival.

“The main point is that it is crucial to reduce time to adjuvant therapy in stage III colon cancer, and that surgeons, oncologists, and pathologists should work together to optimize logistics and avoid unnecessary delay,” says Mads Klein, MD, PhD, the lead author of the current study and a gastrointestinal surgeon at Copenhagen University in Denmark.

“This issue should be investigated in a larger sample: whether adjuvant chemotherapy within 4 weeks can reduce mortality further. This can possibly best be achieved with minimally invasive surgery, which is proven to shorten convalescence,” says Dr. Klein.

Breast Cancer

A separate study examined the effect of the timing of adjuvant chemotherapy specifically in patients with rapidly proliferating breast cancer (Eur J Cancer. 2015;51:1874-1881). A recent meta-analysis of retrospective data revealed that survival decreased by 15% for every 4-week delay in the initiation of adjuvant chemotherapy for patients with breast cancer (BMC Cancer. 2013;13:240). Another recent retrospective review demonstrated a survival advantage to early adjuvant therapy in patients with breast cancer, especially in high-risk subgroups such as those with triple-negative, human epidermal growth factor receptor 2 (HER2)-positive, and stage III disease (J Clin Oncol. 2014;32:735-744).

The current study was a secondary analysis of a previously published phase 3 study comparing 3 adjuvant chemotherapy regimens in patients with rapidly proliferating early breast cancer (EBC) (Breast Cancer Res Treat. 2011;125:775-784.). Patients included had EBC of any size with 1 to 3 positive axillary lymph nodes or lymph node-negative tumors measuring greater than 1 cm. All tumors were rapidly proliferating EBC, defined by a thymidine labeling index of greater than 3%, histological grade 3, an S-phase greater than 10%, or a Ki-67/MIB-1 labeling index greater than 20%.

Results

The TTC was available for 921 of the 1066 study participants. Of these, 93% had stage I or stage II EBC, with 47% having positive lymph nodes. The median TTC was 38 days; 11% of the participants had a TTC that was within 4 weeks, 85% had a TTC between 5 to 8 weeks, and 4% had a TTC that was longer than 8 weeks.

A multivariate Cox regression analysis was performed using TTC as a continuous variable and lymph node involvement, estrogen receptor (ER) status, HER2 status, Ki-67 value, type of adjuvant chemotherapy, menopausal status, and tumor size as covariates. With a median follow-up of 105 months, an increasing TTC was associated with an increased risk of disease relapse (HR, 1.15; P = .019).

A time-dependent receiver operating characteristic (ROC) curve analysis of the data was also performed. This ROC curve was plotted for disease-free survival (DFS) and for overall survival (OS). Researchers found that the best threshold value for TTC was 7 weeks. The patient group receiving chemotherapy within 7 weeks of surgery had a 5-year DFS rate of 81% versus 77% for those with a longer TTC. At 8 years after diagnosis, this difference was more pronounced. The DFS rate was 74% for patients with a TTC within 7 weeks and 62% for the group with a longer TTC. Furthermore, the patients with a TTC of fewer than 7 weeks had a longer OS compared with the longer TTC group, with 8-year OS rates of 88% and 78%, respectively (P = .043).

“Our take-home message is that time matters; the risk of relapse is not related to a prespecified cutoff between surgery and chemotherapy, but increases as time passes,” says Alberto Farolfi, MD, the lead author of the current study and a medical oncologist at the Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS in Meldola, Italy.

The authors note that a main limitation of their data is that only 4% of patients had a TTC that was longer than 8 weeks, and this prompt treatment may not reflect patterns of care in the “real-world” setting.

“The challenge now is to definitively show that time to chemotherapy is an important prognostic factor in luminal B (ER-positive, HER2-negative) breast cancer patients in the real-world setting. We are now evaluating a subgroup of these patients from the case series enrolled in a prospective randomized clinical trial. The data obtained from the analysis of this group will then be validated on an independent series of consecutive patients treated as per normal clinical practice outside of a trial,” says Dr. Farolfi.

Implications of Both Studies

“Both studies find improved survival when adjuvant chemotherapy begins sooner, before 7 weeks for patients with breast cancer and 8 weeks for those with colon cancer,” says Peter Paul Yu, MD, director of cancer research at Palo Alto Medical Foundation and immediate past president of the American Society of Clinical Oncology. “The papers also document that this is already the dominant practice pattern, with only 3.8% of breast
cancer and 16% of colon cancer patients exceeding these time points. The more interesting question is whether it is beneficial to start earlier, such as within 4 to 6 weeks after surgery."

"It is unlikely that most patients could start treatment much before 4 weeks, given the need to recover from surgery and complete the pathologic assessment, which increasingly includes complex biomarker-based studies," adds Dr. Yu. "There is no suggestion that it is deleterious to start sooner rather than later if the patient’s condition allows, so all things being equal, we should strive to start sooner in my opinion."

Dr. Yu also points out that a related operational challenge is how to optimize workflow to permit the earlier initiation of chemotherapy. Improved communication and coordination between multidisciplinary specialists and patient education are essential, he says.

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**Structured Palliative Care Program Found to Be Helpful for Caregivers of Patients With Lung Cancer**

It is recognized that family (or friend) caregivers (FCGs) of patients with cancer undergo significant stress. Multiple past studies have shown that caregivers experience such negative effects as psychological distress, relationship disruptions, erosion of well-being, and even a higher incidence of cardiac diseases. Despite all this, FCGs are largely ignored by support services. For these reasons, a study was initiated to help provide evidence-based models to support FCGs of patients with lung cancer (Cancer. 2015;121:3737-3745).

“Family caregivers are providing the majority of informal care for cancer patients in the community,” says Virginia Sun, RN, PhD, the current study’s lead author and assistant professor in the department of population sciences at the City of Hope Comprehensive Cancer Center in Duarte, California. “There is an urgent need for interventions to support family caregivers in the caregiving role and their own physical, psychological, social, and spiritual needs. Our intervention can serve as an effective and replicable palliative care model for family caregivers of lung cancer patients.”

Dr. Sun and her colleagues performed a 2-group prospective study at their institution. Between November 2009 and December 2010, FCGs were enrolled in the usual-care group. FCGs in the palliative care intervention arm were enrolled between July 2011 and August 2014.

FCG quality of life (QOL) was obtained using a validated tool that measures QOL in the domains of physical, psychological, social, and spiritual well-being. Caregiver burden was assessed using a tool that measures caregiving impact on 3 aspects of burden: objective burden, subjective demand, and subjective stress. A caregiver skills preparedness scale was also employed.

Patients’ QOL and symptoms were measured using the Functional Assessment of Cancer Therapy-Lung tool, which measures physical, social, emotional, and functional well-being. After the baseline assessment, follow-up questionnaires were administered to FCGs at 7 weeks and 12 weeks.

In the intervention arm, a personalized palliative care plan was devised based on the results of the initial comprehensive QOL assessment. These patients and FCGs were also presented at weekly multidisciplinary care meetings at which recommendations were made concerning ways to support them. In addition, these

**KEY POINTS**

- A structured and personalized palliative care intervention is feasible to implement among caregivers of patients with lung cancer.
- A palliative care program for caregivers provided improvements in their social well-being and reduced psychological distress as well as decreased caregiver burden and perceived disruption of their life.
- Further research to broaden the caregiver palliative care program to other tumor types and community settings is needed.